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Effectiveness of Assisted Reproductive Technology

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The National Institutes of Health (NIH) Office of Research on Women's Health (ORWH) requested and provided funding for this report. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to **epc@ahrq.gov.**

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Structured Abstract

Objectives: We reviewed the evidence regarding the outcomes of interventions used in ovulation induction, superovulation, and in vitro fertilization (IVF) for the treatment of infertility. Short-term outcomes included pregnancy, live birth, multiple gestation, and complications. Long-term outcomes included pregnancy and post-pregnancy complications for both mothers and infants.

Data Sources: MEDLINE® and Cochrane Collaboration resources.

Review Methods: We included studies published in English from January 2000 through January 2008. For short-term outcomes, we excluded non-randomized studies and studies where a pregnancy or live birth rate per subject could not be calculated. For long-term outcomes, we excluded studies with fewer than 100 subjects and those without a control group. Articles were abstracted for relevant details, and relative risks or odds ratios, with 95 percent confidence intervals, were calculated for outcomes of interest for each study.

Results: We identified 5294 abstracts and (for the three questions discussed in this draft report) reviewed 1210 full-text articles and included 478 articles for abstraction. Approximately 80 percent of the included studies were performed outside the United States.

The majority of randomized trials were not designed to detect differences in pregnancy and live birth rates; reporting of delivery rates and obstetric outcomes was unusual. Most did not have sufficient power to detect clinically meaningful differences in live birth rates, and had still lower power to detect differences in less frequent outcomes such as multiple births and complications.

Interventions for which there was sufficient evidence to demonstrate improved pregnancy or live birth rates included: (a) administration of clomiphene citrate in women with polycystic ovarian syndrome, (b) metformin plus clomiphene in women who fail to respond to clomiphene alone; (c) ultrasound-guided embryo transfer, and transfer on day 5 post-fertilization, in couples with a good prognosis; and (d) assisted hatching in couples with previous IVF failure. There was insufficient evidence regarding other interventions.

Infertility itself is associated with most of the adverse longer-term outcomes. Consistently, infants born after infertility treatments are at risk for complications associated with abnormal implantation or placentation; the degree to which this is due to the underlying infertility, treatment, or both is unclear. Infertility, but not infertility treatment, is associated with an increased risk of breast and ovarian cancer.

Conclusions: Despite the large emotional and economic burden resulting from infertility, there is relatively little high-quality evidence to support the choice of specific interventions. Removing barriers to conducting appropriately designed studies should be a major policy goal.

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Executive Summary

Background

In the United States, approximately seven percent of married couples report at least 12 months of unprotected intercourse without conception, the most commonly used definition of infertility, while two percent of all women report an infertility-related clinic visit within the past year. Infertility causes significant emotional distress and its treatment costs well over $3 billion annually.

For many couples, treatment for infertility will ultimately include in vitro fertilization (IVF). The number of IVF cycles performed in the United States has increased from approximately 30,000 in 1996 to over 130,000 in 2005; during that time, the proportion of all U.S. births that resulted from IVF increased from 0.3 percent to almost 1 percent.

IVF and its variations are classified as "assisted reproductive technologies" (ART), which generally include any procedure that involves handling of both sperm and eggs outside of the body. This report covers not only ART, but two other types of infertility treatment – ovulation induction in women who do not ovulate frequently enough to conceive, most commonly as part of polycystic ovarian syndrome (PCOS); and superovulation, where women who do ovulate normally are given extra doses of hormones to stimulate the production of extra eggs.

Although all of these treatments improve the chances that a given couple will ultimately become parents, they also all carry the risk of multiple gestations. All multiple gestations, even twins, are at increased risk of preterm delivery, which carries increased risk of neonatal mortality, prolonged hospitalization, and long-term complications. This report reviews the evidence on the short- and long-term safety and effectiveness of interventions used for ovulation induction, superovulation, and ART.

Methods

We searched MEDLINE® for English-language studies published from January 2000 through January 2008. The search was supplemented by a hand search of reviews published by the Cochrane Menstrual Disorders and Subfertility Review Group. Primary research articles whose abstracts met inclusion criteria were subsequently reviewed by two independent reviewers; agreement by both reviewers was required for inclusion. For short-term outcomes (complications of treatment, pregnancy, live birth, multiples), we excluded non-randomized studies and studies where a pregnancy or live birth rate per subject could not be calculated. For long-term outcomes (pregnancy and long-term maternal complications, neonatal and childhood complications), we excluded studies with fewer than 100 subjects and those without a control group. Articles were abstracted for relevant details, and relative risks or odds ratios, with 95 percent confidence intervals, were calculated for the outcomes of interest for each study. Abstractions were read by a second reviewer as a check for accuracy. Quantitative synthesis with meta-analyses was outside of the scope of the review.

The review and evidence synthesis are structured around three key questions, involving (a) outcomes (including pregnancy, live birth, multiple gestation, and complications) after different interventions used in the treatment of anovulatory infertility and PCOS, and in superovulation;

(b) the same outcomes after different interventions used in ART; and (c) longer-term outcomes for both the fetus/child (including spontaneous abortion, ectopic pregnancy, preterm delivery, low birth weight, neonatal and infant complications, and longer-term physical and developmental problems), and the mother (including pregnancy complications, cancer, and psychological/emotional problems).

Results

We reviewed 5294 abstracts relevant to ART. For the three key questions discussed in this report, we reviewed 1210 full-text articles and included 478 articles. There were several consistent methodologic shortcomings, particularly with clinical studies. The number of randomized trials was small relative to the number of articles identified in the initial search. The majority of randomized trials that were included provided data only on pregnancy rates, not live birth or obstetric outcomes. Few studies were adequately powered to detect differences in pregnancy rates, let alone less frequent outcomes such as live birth, multiple gestations, or severe complications. Few studies of ART randomized couples to treatment for more than one cycle.

Ovulation Induction

Clomiphene is an effective first-line therapy for women with PCOS. Metformin is, at best, no more effective, and, based on a large multi-center trial, less effective than clomiphene alone.

Although a statistically significant effect is not observed in individual studies, meta-analyses do demonstrate a significant increase in pregnancy rates in clomiphene-resistant women treated with metformin, a finding which should be confirmed in large studies. There is insufficient evidence to draw conclusions about the relative efficacy of aromatase inhibitors.

Use of laparoscopic cauterization of the ovaries, followed by ovulation induction if necessary, results in similar pregnancy and live birth rates, with significantly lower multiple gestation rates, compared to immediate gonadotropin use in clomiphene-resistant women; these rates may be further improved by the addition of metformin, although there are no data on possible long-term adverse outcomes of cautery.

Superovulation in Ovulatory Women

Pooled data show significantly higher pregnancy rates with gonadotropins compared to clomiphene or aromatase inhibitors; there are trends toward higher rates of live birth, multiple pregnancy and hyperstimulation with gonadotropins, but study sizes are too small to draw definite conclusions regarding relative efficacies of these ovulation-inducing therapies.

There do not appear to be substantial differences in pregnancy rates between different gonadotropin preparations. Higher doses increase the risk of multiples and hyperstimulation without significant improvement in pregnancy rates. The addition of gonadotropin-releasing hormone (GnRH) antagonists to superovulation protocols may increase both pregnancy rates and twin gestation rates. Further studies adequately powered for the outcome of live birth per couple are needed.

ART–the Female Partner

No clear superiority of any specific protocol for pituitary down-regulation with GnRH agonists was identified.

Although only one individual study comparing GnRH agonists to antagonists found a significant difference in pregnancy or live birth rates (in favor of agonists), published meta-analyses show significantly higher pregnancy and live birth rate with the use of agonists. Antagonists do result in significant decreases in gonadotropin requirements, and a significant decrease in the risk of ovarian hyperstimulation syndrome (OHSS).

Pooled results of individual trials of gonadotropin preparations suggest that human menopausal gonadotropins are superior in terms of pregnancy and live birth rates compared to recombinant follicle stimulating hormone (rFSH) in long protocol GnRH agonist regimens, with higher multiple pregnancy rates, and that the addition of recombinant luteinizing hormone (rLH) to rFSH improves live birth rates in poor responders. Based on differences in the amount of gonadotropin required, there may be economic advantages to some formulations.

Timing of human chorionic gonadotropin (hCG) administration for triggering oocyte maturation is important for optimizing live birth rates, but the optimal timing and threshold relative to follicular growth have not been determined. There does not appear to be any difference in pregnancy or live birth rates, or other major outcomes, between recombinant hCG and urinary hCG, although injection site reactions are more common with urinary hCG. In cycles using a GnRH antagonist for pituitary down-regulation, use of hCG is superior to use of a GnRH agonist.

There is insufficient evidence to determine the optimal method for endometrial preparation for frozen-thawed embryo transfer.

Ultrasound-guided embryo transfer consistently results in substantially improved (40 percent relative increase) pregnancy and live birth rates compared to various “clinical touch” methods. The consistency of this finding and the size of the effect are striking considering that the majority of interventions evaluated in this review do not show significant differences.

Some form of luteal support is necessary with ART, since both progesterone and hCG result in improved pregnancy rates compared to no treatment. Although there is no detectable difference between oral progesterone and the various formulations of vaginal progesterone, both result in lower pregnancy and live birth rates compared to intramuscular progesterone. The addition of estrogen to progesterone may improve outcomes, although additional larger studies are needed to confirm these findings.

The non-steroidal anti-inflammatory drug (NSAID) piroxicam significantly improved pregnancy and live birth rates in a general ART population, and further studies of NSAIDs are warranted. Randomized trials of intercessory prayer and acupuncture showed benefit, but there are remaining methodological questions (particularly the most appropriate control intervention) which need to be addressed.

ART–the Embryo

ART results in much higher birth rates within 90 days than watchful waiting in eligible patients, although cumulative pregnancy rates were similar in one trial comparing ART to intrauterine insemination (IUI) and IUI after ovarian stimulation. There is no evidence of benefit for intracytoplasmic sperm injection (ICSI) compared to ART in patients with non-male factor

infertility. Laboratory procedures used during fertilization, such as media and equipment used, may have significant impact on outcomes.

Assisted hatching improves pregnancy and live birth rates in couples with previous ART failure, but there is insufficient evidence to draw inferences about benefits in other groups.

Blastocyst transfer results in better live birth rates than day 3 transfer, especially in patients with a good prognosis. The disadvantage of delaying transfer is a reduction in the number of embryos available for transfer and for cryopreservation, and an increased risk of monozygotic twinning.

Although double embryo transfer results in higher pregnancy and live birth rates compared to single embryo transfer, multiple rates – almost all twins – are consistently higher. Strategies involving alternative methods for pituitary down-regulation, or involving multiple cycles with fewer embryo transfers per cycle, appear to result in similar live birth rates with fewer multiples.

Long-Term Outcomes

Review of the literature on this topic included the inherent limitations of observational studies compared to randomized trials, difficulty in identifying appropriate controls, changes in clinical practice which may make findings about older treatments obsolete, and issues relating to generalizability of findings between countries.

Loss of the entire pregnancy is more common for singleton pregnancies than for twins after ART, suggesting that factors associated with successful implantation and placentation contribute to the likelihood of both multiple gestation and a successful pregnancy outcome.

False positive results for maternal testing for chromosomal abnormalities after assisted reproduction are more likely for second trimester serum screening, resulting in an increased false positive rate with combined screening strategies that incorporate both modalities.

Preterm delivery is approximately twice as likely in women pregnant with singleton pregnancies after infertility treatment compared to spontaneous singleton pregnancies. The evidence is most consistent for ART, but the risk was also increased in a large study of women pregnant after ovulation induction alone. The proportion of preterm deliveries that are indicated due to maternal/fetal complications versus those due to spontaneous preterm labor is unclear. Conversely, the risk of preterm birth in ART twins compared to spontaneous twins is either not elevated, or elevated to a lesser extent than in singletons, in the majority of studies.

Much of the elevated risk of low birth weight is due to the increased risk of preterm birth. However, studies that examined gestational age-specific weights found an increased risk of small-for-gestational age (SGA) infants among singleton, but not twin, pregnancies after infertility treatment.

Women pregnant after infertility treatment are at increased risk for disorders potentially related to abnormal implantation, including preeclampsia, placenta previa, and placental abruption. The extent to which specific treatments or underlying maternal/embryonic characteristics contribute to this risk is unclear.

Risks for major congenital anomalies are increased after infertility treatment, but much of this risk appears to be related to maternal and/or paternal characteristics, including a history of subfertility or infertility. Given the relative rarity of specific birth defects or syndromes, identifying an association between a specific exposure and subsequent risk is difficult.

In the neonatal period, although there is evidence of an increased risk for adverse outcomes, especially among singletons, it is unclear to what extent this is due to the observed increased

preterm delivery rate. Large-scale studies that control for gestational age and birth weight are needed. In later infancy, there is a significantly increased hospitalization rate among children born after ART compared to the general population, but rates are similar when compared to children born to couples with a history of treated and untreated subfertility.

Children born after assisted reproduction have an increased risk of hospitalization and surgery compared to general population controls. There does not appear to be an increased risk of childhood cancers in children conceived after infertility treatments.

The available evidence suggests that there is not an increase in the risk of adverse neurodevelopmental outcomes in children born after infertility treatment that is not associated with the underlying condition of infertility or the well-established increased risk of prematurity and SGA. The available evidence on learning and other developmental outcomes is reassuring, but larger studies across a wider population are needed.

In general, infertility treatments involving ovarian stimulation do not appear to be associated with an increased risk of breast cancer, although non-significantly elevated risks were seen 20 years after exposure in one study, suggesting that continued monitoring is warranted.

Ovarian cancers are strongly associated with an infertility diagnosis; use of ovulation stimulating drugs does not appear to increase the risk above baseline levels in this patient population. As with breast cancer, increasing risk with increased duration with treatment cannot be ruled out with confidence.

Based on the available literature, there are no differences in psychological outcomes, including parenting skills, when comparing singleton pregnancies resulting from ART to spontaneous conceptions. If anything, mothers of infants resulting from ART have better outcomes, although there is some evidence that fathers may do worse on some scales. Multiple gestations significantly increase stress and depressive symptoms, especially for mothers of infants with chronic disabilities; to the extent that women undergoing ART are more likely to experience multiples, especially preterm multiples, they are more likely to experience these symptoms.

Discussion

Limitations of this report include the restriction of studies to English language, the potential for missing relevant studies, and, perhaps, the lack of formal meta-analysis.

Future research considerations include attention to ameliorating some of the most common problems identified, including the use of multi-center trials to ensure adequate sample size; consensus on a minimally significant clinical difference to aid sample size estimates; development of standard data sets to facilitate meta-analysis, especially for less common outcomes; and study treatment durations that reflect clinical practice. Attention should also be paid to some of the political, regulatory, and financial barriers to high-quality research in infertility.

Research areas for prioritization for clinical research include almost all interventions currently in use, studies of effectiveness and long-term outcomes in male partners, and prevention of preterm birth. One area of great potential is further investigation of the potential link between infertility, infertility treatments, and pregnancy outcomes associated with implantation and placentation; these pregnancy outcomes are associated with long-term cardiovascular risk in the mother, suggesting yet another avenue for potential research. Finally,

health services research into patient decisionmaking and methods for valuing the impact of infertility and its treatment on mother, father, and infant are crucial to helping design reasonable policy.

Evidence Report

Chapter 1. Introduction

Normal Reproduction

Normal spontaneous reproduction is a complex process that involves a series of steps.[1] For women, these include:

- Coordination between the hypothalamus, pituitary, and ovary to allow development of (usually) a single dominant egg (oocyte);
- Preparation of the lining of the uterus (the endometrium) to receive an embryo;
- Release of the egg (ovulation) from the ovary;
- "Capture" of the egg by the fallopian tube;
- Interaction with sperm within the tube resulting in fertilization;
- Transport of the fertilized egg (zygote) through the tube and into the uterine cavity, as the zygote divides and becomes a multi-cell embryo; and
- Implantation of the embryo into the endometrium, and development of the placenta.

For men, the steps include:

- Production of sperm in sufficient number and of sufficient motility to allow enough travel from the vagina through the cervix and uterus into the fallopian tube; and
- Fertilization itself, which involves a complex chemical interaction between sperm and egg.

Conditions that affect any of these processes reduce the chances of conception in a given cycle; if the condition is chronic, it can lead to the clinical condition of infertility.

Infertility

The most commonly used definition of infertility is at least 12 months of unprotected intercourse without conception, used in everything from population-based surveys[2] to clinical practice recommendations.[3] Approximately 10 to 15 percent of couples will meet this definition, based on observational studies.[4,5] Up to half of those couples reaching the 12-month threshold may conceive within the next 36 months,[4] a finding borne out in clinical trials, where four to five percent of subjects may conceive spontaneously between enrollment and the beginning of treatment.[6,7] Because a large number of couples meeting the definition of infertility are actually

capable of conceiving and simply represent one end of the distribution of fecundity, many, particularly in Europe, prefer the term "subfertility."[5,8] This is the term preferred, for example, by the Cochrane Collaboration, where the relevant review group is the Cochrane Menstrual Disorders and Subfertility Group. The use of "subfertility" has, however, not been widely accepted in the United States; therefore, this report will use the more common U.S. term "infertility" throughout the text.

Assisted Reproductive Technologies

The 1992 Fertility Clinic Success Rate and Certification Act mandates that all clinics providing assisted reproductive services report results annually to the Centers for Disease Control and Prevention (CDC).[9,10] The Act defines "assisted reproduction technologies" as those that involve the handling of both sperm and eggs. The vast majority of these involve in vitro fertilization (IVF), a process that involves direct removal of oocytes from the mother's body, combining sperm and oocytes in the laboratory, and returning the embryo to the woman's body. Fertilization of the oocyte occurs either through co-incubation of sperm and oocytes (classic IVF) or through direct injection of a single sperm into the oocyte under microscopic visualization (intracytoplasmic sperm injection, or ICSI); ICSI is particularly effective for couples where there are problems with number and/or function of sperm.[11] This report covers these techniques, as well as those that involve stimulation of the ovary, either to induce ovulation in women who do not ovulate at all, or only very irregularly, or to stimulate production of extra oocytes (superovulation) to increase the chances of conception. We do not address other treatments for specific conditions that cause infertility, such as surgical procedures for tubal infertility or endometriosis. Although specific interventions used in men also fall into this framework, there were only a few relevant studies; this report thus focuses on interventions in the female patient and the embryo and identifies further studies in men as a research priority. We also focus on treatments using the couple's own sperm and oocytes, and in which the embryos are returned to the female patient's body. While the use of donor gametes and gestational surrogates provides another set of options for infertile couples, the scientific, ethical, and policy issues are complex enough to warrant a separate report.

Prevalence and Burden of Disease

World-wide, an estimated nine percent of couples meet the definition of infertility, with 50 to 60 percent of them seeking care.[12] In the United States, approximately seven percent of married couples reported at least 12 months of unprotected intercourse without conception, while two percent of women reported an infertility-related clinic visit within the past year, based on estimates from the National Survey of Family Growth.[2]

Although there is some controversy about whether the proportion of the population with self-reported infertility is increasing, stable, or decreasing,[10,13] there has clearly been increasing utilization of assisted reproductive technology (ART; Figure 1).

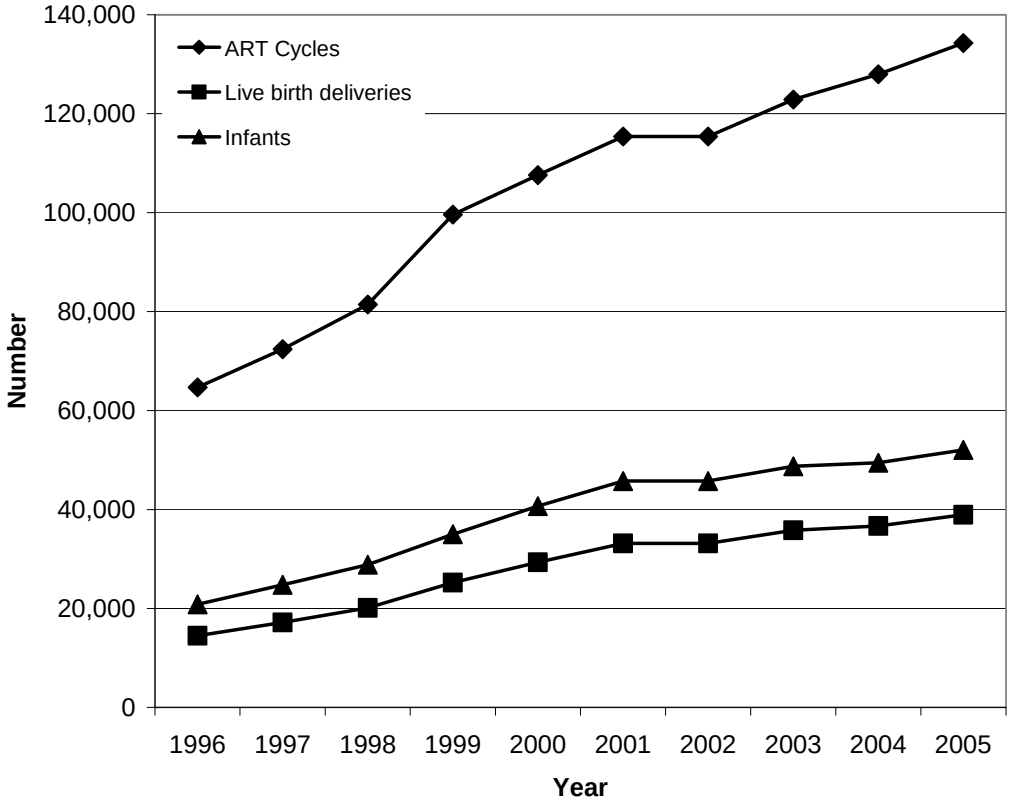

Figure 1. Growth in numbers of ART cycles, deliveries, and infants in the United States, 1996-2005. From Centers for Disease Control and Prevention, American Society for Reproductive Medicine, Society for Assisted Reproductive Technology. 2005 Assisted Reproductive Technology Success Rates: National Summary and Fertility Clinic Reports, Atlanta: Centers for Disease Control and Prevention; 2007.[14]

Over this time, the proportion of deliveries in the United States resulting from ART has increased from 0.37 percent in 1996 to 0.94 percent in 2005.[14] There is no similar registry for ovulation induction/superovulation.

Measuring the "burden of disease" of infertility is difficult. Some conditions associated with infertility, such as endometriosis, uterine leiomyomata, or polycystic ovary syndrome (PCOS), have other symptoms such as painful or unusually heavy menstrual periods, lack of periods altogether (amenorrhea), or hirsutism which lead to interactions with the health system. These symptoms have a significant impact on health-related quality of life (HRQOL) as measured by standard instruments.[15,16]

In the absence of symptoms, however, quantifying the "health" burden of infertility is difficult. In the National Survey of Family Growth, 40 percent of women aged 25-29 and 24 percent of women aged 30-44 who were childless would be bothered "a great deal" if they would never be able to have children; the corresponding numbers for men were 32 percent of men 25-29 and 18 percent of men 30-44.[17] Infertility clearly has an emotional impact on couples,[18] some of which is measurable using generic instruments,[19-21] but there are no population-based data in the United States

What is clear, however, is that there is a substantial economic burden associated with infertility. The diagnostic and treatment modalities used, especially for assisted reproduction,

are expensive, with one estimate for total U.S. costs of almost $3 billion.[22] Many ART treatments result in multiple pregnancies, and complications of multiple pregnancy, including preterm delivery, contribute significantly to the overall costs[23-25] It is these costs, with the measurable morbidity associated with preterm delivery, that drive the search for ART interventions that maximize pregnancy rates while minimizing multiple birth rates.[10,26]

Evidence and Practice

In many ways, infertility practice in the United States is highly regulated. Professional societies require certain credentials for membership, states require licensure for professionals, and there is a Federal requirement for central reporting of outcomes (albeit without penalty for failure to report), which is highly unusual for medical procedures. Laboratories used in assisted reproductive techniques, which handle human tissues, are subject to inspection by the U.S. Food and Drug Administration (FDA). However, as in other areas of medicine where much of the practice involves procedures, such as surgery, there is no explicit regulatory mechanism requiring evidence of safety and efficacy as there is for new drugs.[27,28] Medical devices, such as embryo transfer catheters, while subject to approval by the FDA, have much less stringent approval requirements.[29] Variations in regimens for the use of drugs already approved for one indication do not require FDA approval under most circumstances and so do not undergo formal regulatory review. Many insurance companies do not cover infertility services,[30,31] so there is no third-party payer demand for rigorous evidence. Infertility treatment may be one of the closest approximations of a true market between providers and patients; although lack of insurance coverage means that infertility patients tend to be wealthier and better educated,[32] there is no evidence that this translates into an ability to judge the evidence on the comparative safety and efficacy of different options for treatment.[33] In this setting, practice patterns may change rapidly without a clear rationale; for example, although ICSI is highly effective for treatment of male infertility, the proportion of ART procedures performed using ICSI increased from 11 to 57 percent between 1995 and 2004, despite no change in the prevalence of male factor infertility or evidence that ICSI was superior to traditional IVF in couples with other causes[34] (although this change has also been observed in Europe, where there are stricter regulatory controls[35]). There has been consistent criticism of the methodological quality of much of the clinical literature, for both immediate outcomes of treatment (such as pregnancy, live birth, and complication rates) and especially for longer term outcomes (such as neonatal and childhood outcomes in children conceived after infertility treatment.[36,37]

Uses of This Report

This report summarizes the results of our review of the evidence regarding the outcomes of interventions for ovulation induction, superovulation, and assisted reproduction on pregancy, live birth, and short- and long-term complications of treatment for both mothers and children – the lack of data on men is a clear research need. The report may be used by professional societies, patient advocacy groups, payers, and policymakers to help with practice guidelines, identifying areas for promising research, and setting research priorities. The report may also be used by

clinicians as a guide to the available evidence, and, although not primarily intended for patients, may assist some couples in making decisions about available treatment options.

Chapter 2. Methods

This section describes the basic methodology used to develop the evidence report, including topic assessment and refinement, the analytic framework, literature search strategies and results, literature screening, quality assessment, data abstraction methods, and quality control procedures.

Topic Assessment and Refinement

The National Institutes of Health (NIH) Office of Research on Women's Health (ORWH) and the Agency for Healthcare Research and Quality (AHRQ), sponsors of this report, and the other partners, the American College of Obstetrics and Gynecology (ACOG) and the Society for Assisted Reproductive Technology (SART), originally identified four key questions to be addressed by the report, which is intended to assess the evidence for the effectiveness and efficiency of assisted reproductive technology (ART). The Duke research team clarified and refined the overall research objectives and key questions by first consulting with AHRQ and the study partners, and then convening a national panel of technical experts to serve as advisors to the project. These experts were selected to represent relevant specialties. Members of the technical expert panel were:

- Kurt T. Barnhart, M.D., M.S.C.E.; Penn Fertility Care and Department of Obstetrics and Gynecology; University of Pennsylvania Health System; Philadelphia, PA
- Lisa Begg, Dr.P.H., R.N.; NIH Office of Research on Women's Health; Bethesda, MD
- David A. Grainger, M.D.; Center for Reproductive Medicine, Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology; University of Kansas School of Medicine; Wichita, KS (representing SART)
- Joseph C. Isaacs; Resolve: The National Infertility Association; Bethesda, MD
- Julia V. Johnson, M.D.; Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology; University of Vermont and Fletcher Allen Health Care; Burlington, VT
- Richard E. Leach, M.D.; Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology; University of Illinois at Chicago; Chicago, IL
- Richard S. Legro, M.D.; Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology; Milton S. Hershey Medical Center at Penn State; Hershey, PA
- Nancy O'Reilly, ACOG Committee for Practice Bulletins; Washington, DC

- Catherine Racowsky, Ph.D.; Center for Reproductive Medicine, Department of Obstetrics and Gynecology; Brigham and Women's Hospital; Boston, MA

- Robert W. Rebar, M.D.; American Society for Reproductive Medicine; Birmingham, AL

- Uma M. Reddy, M.D., M.P.H.; Pregnancy and Perinatology Branch, NIH National Institute of Child Health and Human Development; Bethesda, MD

- Laura E. Riley, M.D.; Vincent Obstetrics and Gynecology Services; Massachusetts General Hospital; Boston, MA

As a result of an initial conference call with the technical experts, AHRQ, ORWH, ACOG, and SART, the Duke research team finalized the key research questions to be included in the report and the approach that would be used to address them. The key questions are:

- **Question 1:** Among women of reproductive age (12-44), what factors identify couples with a low probability of spontaneously conceiving? Factors to be considered could include: age of mother, age of father, presence of endometriosis, prior conception history, body size, alcohol use, smoking, history of previous sexually transmitted infection, and results of infertility testing (hysterosalpingogram, diagnostic laparoscopy, blood tests for ovulatory function). In terms of our analytic framework, this question can be further refined into three separate broad questions:

    - **Question 1a:** What biological, environmental, or other factors increase the likelihood that a given couple will present with infertility or subfertility?

    - **Question 1b:** What biological, environmental, or other factors affect the likelihood of different outcomes of ovulation induction or ART?

    - **Question 1c:** What diagnostic tests are useful in helping predict the likelihood of different outcomes of ovulation induction or ART?

- **Question 2:** Among women of reproductive age, what are the benefits and risks of Clomid® and Pergonal® (or other injectable super-ovulatory drugs) and Glucophage®, and how do they vary in different patient populations?

    - Different patient populations include racial/ethnic groups and age by decade (or age groups comparable to those in the Centers for Disease Control (CDC)-SART national ART success rates reports[14]).

    - Risks include high rates of higher order multiples and ovarian hyperstimulation syndrome.

    - Benefits include reduced time to achieve pregnancy, correction of ovulatory dysfunction, possible decreased miscarriage rates, and decreased gestational diabetes risk with Glucophage®.

- **Question 3:** Among women of reproductive age, which laboratory, clinical, and other practice approaches result in the highest successful singleton pregnancy (or live-born) rates, and what practices lead to high multiple rates?

    - Laboratory practices include intracytoplasmic sperm injection (ICSI), different types of embryo culture, fresh versus frozen embryo transfer, and day 2 to 3 versus day 5 to 6 transfer.

    - Clinical practices include number of embryos transferred and selection criteria for eligible patients, as well as using the implantation rates from previous unsuccessful cycles to inform subsequent embryo transfer.

    - Other practices include insurance coverage strategies.

- **Question 4:** What are the adverse outcomes of ovulatory drug-induced pregnancies and of pregnancies achieved with in vitro fertilization (IVF)? Is there evidence to link these adverse outcomes with the treatments and not the underlying maternal health or gestational age problems?

    - For the mother, outcomes include preeclampsia, cesarean delivery, gestational diabetes, abruption, placenta previa, and breast and ovarian cancer.

    - For the infant, outcomes include birth defects, prematurity, low birth weight, and long-term outcomes as available.

After further discussion with the technical experts, AHRQ, ORWH, ACOG, and SART, it was agreed that we would not attempt a formal review of the literature pertaining to Question 1a. This was based on several factors. First, in our initial search of the recent literature, the majority of potentially relevant studies focused on environmental or occupational exposures. While identifying possible causal links between such exposures and subsequent infertility is clearly an important public health question, the state of the science does not allow immediately relevant clinical recommendations. For some exposures, there is substantial ongoing basic and clinical research (for example, in men and women exposed to cancer therapies as children or young adults), but these examples do not represent "typical" infertility practice, and warrant separate systematic review. Second, many of the best quality studies, particularly with respect to ascertainment of exposure, were performed outside the United States; for many exposures, this would limit their potential relevance to a U.S. population. Finally, in the United States, one of the most important factors that "increases the likelihood that a given couple will present with infertility or subfertility" is the availability of adequate insurance coverage or sufficient financial resources to cover diagnosis and treatment; wide variations in this availability could substantially affect risk estimates for the general population, especially in case-control studies

Given the large volume of the literature, the methodological complexities involved in interpreting the literature (in particular, the results of non-randomized studies of outcomes in subgroups and diagnostic tests), and the recent publication of several large relevant trials, the timeline for producing this draft report was extended. In order to expedite dissemination of the

most immediately relevant results for clinical care, research, and policy, and after discussion with AHRQ, this initial draft is limited to Questions 2, 3, and 4 (those questions that focus on immediate and longer term outcomes); Questions 1b (subgroup analyses) and 1c (diagnostic and predictive testing) will be covered in a supplement to this draft.

For the sake of coherence, the sections below on the "Analytic Framework" and the "Literature Search and Review" include material relevant to all five of the final key questions (1b, 1c, 2, 3, and 4), while the sections on "Data Abstraction and Development of Evidence Tables" and "Quality Assessment Criteria" focus on Questions 2-4.

Analytic Framework

We developed a simplified project-specific analytic framework to address the key questions within the context of a standardized evidence report (Figure 2). This framework incorporates etiologic causes, diagnostic evaluation, and treatment outcomes. Numbers refer to the research questions. The diagnostic classes of (a) ovulatory dysfunction, (b) unexplained subfertility/infertility, and (c) tubal factor and some male factor are not meant to be comprehensive or mutually exclusive, but represent broad diagnostic classes where ovulation induction and/or ART are generally considered appropriate therapy.

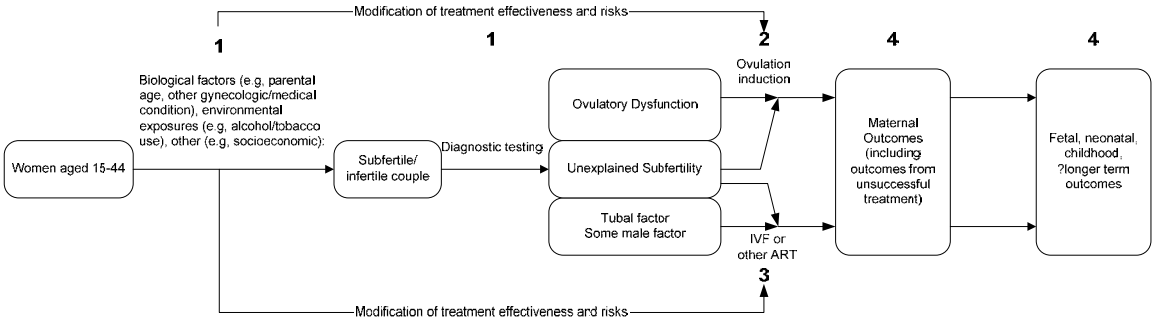

Figure 2. Analytic framework for evidence report. Numbers refer to key questions.

Briefly, Question 1 addresses etiology and patient-specific characteristics that affect the likelihood of different treatment outcomes, Question 2 addresses short-term treatment outcomes after therapy with ovulation-inducing therapies, Question 3 addresses short-term treatment outcomes with ART, and Question 4 addresses longer term outcomes for both mothers and infants after both ovulation induction and ART.

Literature Search and Review

I. Sources

The primary source of literature was MEDLINE® (1966-January Week 4 2008). Searches of this database were supplemented by a search of the Cochrane Database of Systematic Reviews, and by a review of the reference lists of included articles and relevant review articles and meta-analyses.

II. Search Strategies

The basic MEDLINE® search strategy used the National Library of Medicine's Medical Subject Headings (MeSH) key word nomenclature. Searches were limited to articles published in English. The exact search string used is given in Appendix A.* Relevant reviews in the Cochrane Database of Systematic Reviews were identified by hand searching the list of reviews published by the Menstrual Disorders and Subfertility Group, which covers all topics relevant to this report. All search strategies combined yielded a total of 5294 citations, whose records are maintained in a ProCite (Thompson ISI ResearchSoft, Berkeley, CA) database.

III. Screening of Abstracts

Paired clinicians from the Duke research team independently reviewed abstracts and classified each as included or excluded according to project-specific criteria, which they also developed. An abstract was included for full-text review if at least one of the paired reviewers recommended that it be included.

The ***inclusion*** criteria applied at the abstract screening stage were:

- N ≥ 50 if not a randomized controlled trial (RCT; smaller RCTs were acceptable); *and*
- Female age ≤ 45; *and*
- Study relevant to at least one of the key questions, as follows:
    - Compares outcomes of ovulation induction or ART based on presence/absence or differing levels of biological, environmental, or other factors (Question 1b); *and/or*
    - Reports sensitivity/specificity of diagnostic tests for predicting the likelihood of different outcomes of ovulation induction or ART; *or* study reports "associations" or "correlations" between test results and outcomes (Question 1c); *and/or*
    - Reports benefits and risks of treatment with Clomid®, Pergonal®, other injectable super-ovulatory drugs, or Glucophage® in various populations (Question 2); *and/or*
    - Reports pregnancy and/or live birth rates of ART (Question 3); *and/or*
    - Reports adverse outcomes (including quality-of-life measures) of ovulatory drug-induced pregnancies and of pregnancies achieved with IVF based on either (i) history of infertility or (ii) treatment (Question 4).

*Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/reprotech/reprotech.pdf

When these screening criteria were applied, a total of 2712 citations were included for further review at the full-text stage.

IV. Screening of Full Texts

At the full-text screening stage, paired researchers independently reviewed the articles that had passed the abstract screening and indicated a decision to include or exclude them for data abstraction for one or more of the key questions. When the two reviewers arrived at different decisions about inclusion/exclusion or about question assignment for a given article, they were asked to reconcile their differences. The question-specific screening criteria applied at the full-text stage are described in Table 1.

Table 1. Full-text screening criteria by question

Question 1b (biological, environmental, and other factors affecting the likelihood of different outcomes of ovulation induction or ART):

Include when:

- Article published from 2000-present; *and*
- N ≥ 100; *and*
- Female age ≤ 45; *and*
- Study compares outcomes of ovulation induction/ART based on presence/absence or differing levels of factor; *and*
- Outcomes include (a) pregnancy and/or live birth; (b) multiple pregnancy; and/or (c) adverse outcomes; *and*
- Outcomes are reported or calculable on a per-patient or per-couple basis; *and*
- Able to construct 2-by-2 table for outcomes based on data provided in the paper.
- Include donor egg if (and only if) an explicit comparison to non-donor egg pregnancies is made.

Notes:

- Factors to be considered include:
  - Age of mother
  - Age of father
  - Presence of endometriosis
  - Prior conception history
  - Body size
  - Alcohol use
  - Smoking
  - History of previous sexually transmitted infection

Question 1c (diagnostic tests for predicting the likelihood of different outcomes of ovulation induction or ART):

Include when:

- Article published from 2000-present; *and*
- N ≥ 100; *and*
- Female age ≤ 45; *and*
- Study reports sensitivity/specificity of diagnostic test in predicting outcome of ovulation induction/ART; or study reports "associations" or "correlations" between test results and outcomes; *and*
- Outcomes include pregnancy and/or live birth; *and*
- Outcomes are reported/calculable on a per-patient or per-couple basis, or outcomes are reported/calculable on a per-cycle basis if test is repeated each cycle (e.g., embryo quality score prior to implantation would be repeated each cycle, and analysis on a per-cycle basis would be appropriate; maternal blood tests performed only prior to treatment should have results presented/calculable per-patient/couple, rather than per-cycle); *and*
- Able to construct 2-by-2 table for outcomes based on data provided in the paper.

Exclude when study uses donor egg or sperm.

Notes:

- Diagnostic tests include:
  - Hysterosalpingogram
  - Diagnostic laparoscopy
  - Blood tests for ovulatory function

Question 2 (benefits and risks of Clomid Glucophage®, Pergonal®, other injectable super-ovulatory drugs, and Glucophage® in various populations):

Include when:

- Article published from 2000-present; *and*
- Study design = RCT; *and*
- Female age ≤ 45; *and*
- Study reports outcomes of treatment with drugs for ovulation induction, including:
  - Clomiphene
  - Tamoxifen
  - Human menopausal gonadotropins
  - GnRH agonists; *and*
- Outcomes include pregnancy and/or live birth, and data are reported or calculable on a per-patient or per-couple basis.

Exclude when study uses donor egg or sperm.

Notes:

- Different patient populations include:

- Racial/ethnic groups
- Age by decade (or age groups comparable to CDC-SART national ART success rates reports[14])

- Risks include high rates of higher order multiples and ovarian hyperstimulation syndrome
- Benefits include:
  - Reduced time to achieve pregnancy
  - Correction of ovulatory dysfunction
  - Possible decreased miscarriage rates
  - Decreased gestational diabetes risk with Glucophage®

Question 3 (laboratory, clinical, and other practices resulting in the highest successful singleton pregnancy (or live-born) rates, and practices leading to high multiple rates):

Include when:

- Article published from 2000-present; *and*
- Study design = RCT; *and*
- Female age ≤ 45; *and*
- Study reports pregnancy and/or live birth rates of ART, and data are reported or calculable on a per-patient basis or per-couple basis.

Exclude when study uses donor egg or sperm.

Notes:

- Laboratory practices include:
  - Intracytoplasmic sperm injection (ICSI)
  - Different types of embryo culture
  - Fresh versus frozen embryo transfer
  - Day 2-3 versus day 5-6 transfer
- Clinical practices include:
  - Number of embryos transferred
  - Selection criteria for eligible patients
  - Using the implantation rates from previous unsuccessful cycles to inform subsequent embryo transfer
- Other practices include insurance coverage strategies

Question 4 (adverse outcomes of ovulatory drug-induced pregnancies and of pregnancies achieved with IVF):

Include when:

- Article published from 2000-present; *and*
- If not an RCT, N ≥ 100 (this refers to the total number of patients, not the number of cases, which may be < 100); *and*

- Female age ≤ 45; *and*
- Study reports pregnancy-related outcomes based on either (a) history of infertility or (b) treatment (note that such outcomes can include quality-of-life measures); *and*
- Study reports short- or long-term neonatal and maternal outcomes (listed below) on a per-patient, per-pregnancy, or per-birth basis.
- Include donor egg if (and only if) explicit comparison made to non-donor egg pregnancies.

Exclude non-U.S. studies that do not report base rates of incidence for comparison group.

Notes:

- For the mother, outcomes include:
  - Preeclampsia
  - Cesarean delivery
  - Gestational diabetes
  - Abruption
  - Placenta previa
  - Breast, ovarian, and other cancers
  - Quality-of-life measures
- For the infant, outcomes include:
  - Birth defects
  - Prematurity
  - Low birth weight
  - Long-term outcomes as available
  - Quality-of-life measures

Summaries of the results of the abstract screening and full-text review are provided in Tables 2 and 3. A list of excluded articles, with reasons for exclusion, is provided in Appendix B.

Table 2. Results of abstract and full-text screening

Articles identified	5294
Abstracts screened	5294
Included	2712
Excluded	2582
Full-text articles screened	2712
Included for at least one question	818
Excluded for at least one question	1942
Included for at least one question and excluded for at least one other question	48

Table 3. Included full-text articles by question

Question	Number of articles
Question 1b: Biological, environmental, and other factors affecting outcomes of ovulation induction/ART	131
Question 1c: Diagnostic tests	229
Question 2: Ovulation induction with assisted conception	63
Question 3: Assisted conception: IVF and ICSI	237
Question 4: Longer-term outcomes	178
Total number of articles included for data abstraction[†]	818

[†] Some articles were included for more than one question.

Data Abstraction and Development of Evidence Tables

The Duke research team developed data abstraction forms/evidence table templates for abstracting data for each of the key questions; the forms used for Questions 2-4 are provided in Appendix C. Based on clinical expertise, a pair of researchers was assigned to each key question to abstract data from the eligible articles. One of the pair abstracted the data, and the other over-read the article and the accompanying abstraction to check for accuracy and completeness. At this stage of the review, included articles were also assigned to specific topics within each key question. The completed evidence tables for Questions 2-4 are provided in Appendix D.

The evidence tables include estimates of appropriate summary measures. For Questions 2 and 3, which were limited to RCTs, we calculated the relative risk of clinical pregnancy, live birth, or both, associated with treatment, along with 95 percent confidence intervals, using a Microsoft Excel® spreadsheet incorporating the appropriate formulas. When possible, no treatment or placebo was used as the reference; if an active control was used, we attempted to use those therapies that reflected "standard of care," as defined by the study authors or based on input from the clinicians on the Duke team. Whenever possible, the denominator for these ratios was the number of women or couples randomized.

For Question 4, we similarly estimated the relative risk (for RCTs and cohort studies) or the odds ratio (for case-control studies), along with 95 percent confidence intervals.

Relevant meta-analyses identified by our search (including all relevant Cochrane reviews) were not abstracted, but results are summarized in the text.

Quality Assessment Criteria

At the data abstraction stage, abstractors were asked to evaluate each included article for factors affecting internal and external validity. The quality assessment criteria used for this purpose were developed by the Tufts-New England Medical Center Evidence-based Practice Center (EPC) for an evidence report on "Effects of Omega-3 Fatty Acids on Cardiovascular Disease."[38] Abstractors were instructed to assign a "+" or "-" to each item and provide a brief rationale for their decisions.

The quality criteria assessed for Questions 1b and 1c will be described in a supplement to this report. For Questions 2-4, the criteria were:

For Questions 2 and 3:

- Randomization method
- Blinding
- Dropout rate < 20%
- Adequacy of randomization concealment

For Question 4:

For RCTs:

- Randomization method
- Blinding
- Dropout rate < 20%
- Adequacy of randomization concealment

For cohort studies:

- Unbiased selection of the cohort (prospective recruitment of subjects)
- Large sample size
- Adequate description of the cohort
- Use of validated method for ascertaining exposure
- Use of validated method for ascertaining clinical outcomes
- Adequate followup period
- Completeness of followup
- Analysis (multivariate adjustments) and reporting of results

For case-control study:

- Valid ascertainment of cases

- Unbiased selection of cases
- Appropriateness of the control population
- Comparability of cases and controls with respect to potential confounders
- Appropriateness of statistical analyses

After some deliberation, we decided not to assign individual studies a summary quality score (*see*, e.g., the "A, B, C" scale used in previous evidence reports by the Tufts-New England Medical Center EPC, including in the report cited above[38]). First, there is no evidence that the use of any particular quality scoring system has a substantial impact on the results of systematic reviews.[39] Second, our experience has been that it is more helpful to identify consistent and specific quality issues that affect the majority of the literature (concerning, e.g., sample size, analytic methods, or ascertainment bias) in order to guide future research, rather than relying on a global quality score.

Peer Review Process

We employed internal and external quality-monitoring checks through every phase of the project to reduce bias, enhance consistency, and verify accuracy. Examples of internal monitoring procedures include: three progressively stricter screening opportunities for each article (abstract screening, full-text screening, and data abstraction); involvement of three individuals (two clinicians and a copy-editor) in each data abstraction; and agreement of at least two clinicians on all included studies.

Our principle external quality-monitoring device is the peer-review process. Nominations for peer reviewers were solicited from several sources, including the technical expert panel (who also served as reviewers) and interested Federal agencies. The list of nominees was forwarded to AHRQ for vetting and approval. A list of reviewers submitting comments on this draft is included in Appendix E.

Chapter 3. Results

Ovulation Induction without Assisted Conception (Question 2)

I. Research Question

Among women of reproductive age, what are the benefits and risks of Clomid® and Pergonal® (or other injectable super-ovulatory drugs) and Glucophage®, and how do they vary in different patient populations? Different patient populations include racial/ethnic groups and age by decade (or age groups comparable to those in the Centers for Disease Control and Prevention [CDC]-Society for Assisted Reproductive Technology [SART] national assisted reproductive technology [ART] success rates reports[14]). Risks include high rates of higher order multiples and ovarian hyperstimulation syndrome. Benefits include reduced time to achieve pregnancy, correction of ovulatory dysfunction, possible decreased miscarriage rates, and decreased gestational diabetes risk with Glucophage®.

II. Approach

Agents that promote ovulation are used in two specific subgroups of infertile patients. First, the single most common etiology for infertility in the United States is anovulation or oligo-ovulation, most commonly as part of the polycystic ovarian syndrome (PCOS).[40] Without ovulation, conception and pregnancy cannot occur; in these patients, use of techniques that stimulate ovulation is oriented towards correcting the primary etiology of infertility. We focused on treatment of anovulation solely in women seeking pregnancy: correction of endocrine abnormalities, including anovulation, in women not seeking pregnancy is clearly an important therapeutic goal, but the considerations in deciding on optimal therapy may be quite different.[41] We did not include studies of women with anovulation due to hypothalamic amenorrhea or premature ovarian failure.

A second group of patients includes couples with unexplained infertility, mild male factor infertility, or other non-tubal etiologies. In theory, given patent fallopian tubes, normal uterine anatomy, and functional tubes, increasing the number of eggs produced in a given cycle increases the probability of conception. In these patients, use of ovulation-inducing agents is aimed at producing multiple eggs in a given cycle (superovulation), in order to increase the chances of conception. Given these very different patient populations and therapeutic goals, we began our review by separating included studies between those which specifically corrected anovulation in women with PCOS and those which involved superovulation in women with normal ovulatory function.

For each category of patient, we further divided studies by the types of intervention used. For anovulatory women, these were: (a) inhibitors of estrogen action (including anti-estrogens such as clomiphene citrate, e.g., Clomid®, and aromatase inhibitors such as letrozole; as a group, we refer to these as estrogen inhibitors); (b) insulin sensitizers (such as metformin, or Glucophage®); (c) gonadotropins (such as human menopausal gonadotropins, e.g., Pergonal®); (d) combination therapies; and (e) surgical therapies. For ovulatory women, we used the same

categories, with the exception of insulin sensitizers. Since intrauterine insemination (IUI) is often included as part of the ovulation induction or superovulation regimen, we also included studies which addressed specific aspects of IUI in each group.

As described in the Methods chapter, we excluded all non-randomized studies, as well as "quasi-randomized" studies (such as those where treatment assignment was based on alternate history numbers or clinic days). For this topic, the primary outcome of interest was the cumulative number of clinical pregnancies or, preferably, live births per couple; wherever possible, we used the number of women/couples randomized as the denominator. We excluded any study where these outcomes were not reported or calculable from the presented results. Some studies used crossover designs. Because a crossover design requires the assumption that all cycles are equivalent, and ignores the implications of different pregnancy rates in the first cycle on the subjects in the second cycle, interpretation of the results of crossover studies of infertility treatments is extremely problematic.[36] Therefore, we included crossover studies only if the results for the first cycle were presented separately.

For the primary outcomes, relative risks (RRs) with 95 percent confidence intervals (CIs) were calculated from the presented results. Because of substantial clinical heterogeneity in the studies in terms of patient characteristics (such as body mass index [BMI] in studies of PCOS) and treatment regimens, we did not perform formal meta-analyses.

Results for other outcomes, such as multiple pregnancy or spontaneous abortion rates, are summarized in the text. The majority of included studies were extremely limited in power to detect differences in the primary outcomes, let alone any differences in other less common outcomes. Outcomes related to later pregnancy and longer term maternal and child outcomes are discussed under Question 4.

Please note that in the summary tables throughout this chapter, estimates of relative effect with CIs that do not cross 1 (i.e., estimates that are statistically significant) are bolded for emphasis.

III. Search Results

The flow of articles on this topic through the literature search and screening process is depicted in Figure 3.

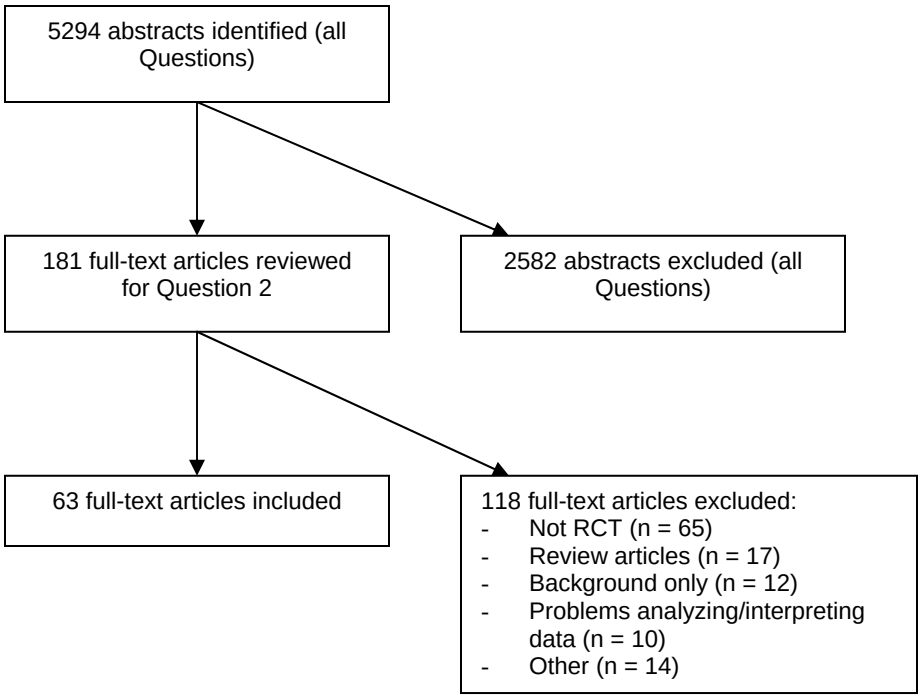

Figure 3. Literature flow diagram – Question 2

IV. Induction of Ovulation in Anovulatory Women

A. Drugs for inducing ovulation–estrogen inhibitors. PCOS is a condition marked by anovulation, hyperandrogenism, and insulin resistance. Common clinical manifestations include oligo- or amenorrhea, acne, hirsutism, and obesity.[42] The mainstay of treatment for many years has been clomiphene citrate (CC); clomiphene is a non-steroid which chemically resembles tamoxifen, and, like tamoxifen, it has both estrogen agonist and antagonist effects at the level of the estrogen receptor; it promotes the release of follicle-stimulating hormone (FSH) from the pituitary, with subsequent follicular development and ovulation in the ovary.[43] Trials prior to 2000 demonstrated that clomiphene is superior to placebo in achieving pregnancy in anovulatory women.[44]

Recently, another class of estrogen inhibitors, aromatase inhibitors, has been explored as an alternative for ovulation induction. These agents, which have been shown to have efficacy in breast cancer patients, work by preventing the conversion of testosterone to estrogen via the enzyme aromatase.

This section reviews studies where estrogen inhibitors were the sole treatments for infertile women with PCOS. Studies where they are compared to other classes of agents, or studies with combination therapies, are described below.

1. Included studies. Five studies met our inclusion criteria (Table 4). All five had fewer than 50 subjects per arm, only two followed subjects for more than one cycle, and none reported live births.

In direct comparisons of estrogen inhibitors, the small sample sizes of comparisons of clomiphene to tamoxifen,[45] anastrozole,[46] and letrozole[47] result in wide confidence intervals for treatment efficacy.

Based on one small study, administration of clomiphene on cycle days 1-5 results in a significantly higher cumulative pregnancy rate than administration on cycle days 5-9 (RR 2.08; 95 percent CI 1.00-4.33).[48]

None of the studies had sufficient numbers to draw any conclusions regarding other outcomes such as spontaneous abortion or multiple pregnancies.

Table 4. Estrogen inhibitors alone in anovulation

Study	Interventions		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Clomiphene vs. other estrogen inhibitors									
Boostan-far et al., 2001[45]	Reference	Clomiphene	40						
		Tamoxifen	46	1.30	0.51	3.35	-	-	-
			Cycles/patient: 2.4						
Wu et al., 2007[46]	Reference	Clomiphene	19						
		Anastrozole	14	5.68	0.27	119	-	-	-
			Cycles/patient: 1.0						
Bayar et al., 2006[47]	Reference	Clomiphene	36						
		Letrozole	38	1.45	0.60	3.53	-	-	-
			Cycles/patient: 2.7						
Timing of clomiphene administration									
Dehbashi et al., 2006[48]	Reference	Clomiphene days 5-9	41						
		Clomiphene days 1-5	37	**2.08**	**1.00**	**4.33**	-	-	-
			Cycles/patient: 1.9						

2. Other published systematic reviews. In one published systematic review of clomiphene versus tamoxifen[49] involving four studies (three pre-2000) with a total of 243 subjects and 743 cycles, there was no significant difference in pregnancy rate per cycle (RR 1.06; 95 percent CI 0.58-1.91); pregnancy or live birth per couple were not calculable.

3. Cochrane reviews. The most recent Cochrane update was in November 2004.[44] Other than showing superiority of clomiphene to placebo, no comparison (tamoxifen vs. clomiphene, clomiphene plus tamoxifen vs. clomiphene alone, or letrozole vs. anastrozole) had sufficient numbers of patients to be able to reach any conclusions regarding relative efficacy in achieving pregnancy (Table 5).

Table 5. Cochrane review, estrogen inhibitors alone in anovulation[44]

Interventions		N	Efficacy					
			Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
			Relative Effect	Lower 95% CI	Upper 95% CI	Relative Effect	Lower 95% CI	Upper 95% CI
Clomiphene vs. placebo								
Reference	Placebo	63						
	Clomiphene	70	**5.77**	**1.55**	**21.5**	-	-	-
	3 studies, all pre-2000							
Clomiphene vs. tamoxifen								
Reference	Tamoxifen	91						
	Clomiphene	90	1.00	0.48	2.09	-	-	-
	2 studies, 1 post-2000							
Clomiphene + tamoxifen vs. clomiphene								
Reference	Clomiphene	10						
	Clomiphene + tamoxifen	10	3.32	0.12	91.6	-	-	-
	1 study, pre-2000							
Letrozole vs. anastrozole								
Reference	Anastrozole	18						
	Letrozole	22	1.88	0.40	8.88	-	-	-
	1 study, post-2000							

4. Conclusions. Clomiphene citrate is superior to placebo in achieving pregnancy in anovulatory women; as such, it is a reasonable reference treatment for evaluation of other methods for induction of ovulation in this patient population. There is insufficient evidence to allow any inferences regarding the relative efficacy of other estrogen inhibitors compared to clomiphene.

B. Drugs for inducing ovulation – insulin-sensitizers. Interventions that improve insulin resistance, such as weight loss or treatment with specific drugs in women with PCOS can also lead to decreases in circulating androgens and ovulation. The most commonly used agent has been metformin; the most recent Cochrane review found significantly increased rates of ovulation with metformin compared to placebo (odds ratio [OR] 3.88; 95 percent CI 2.26-6.69).[50] A different class of insulin sensitizers, the thiazolidinediones, have also been investigated, although one agent that increased ovulation rates in PCOS patients in a randomized controlled trial (RCT), troglitazone,[51] has subsequently been removed from the market due to hepatic toxicity. Potential advantages of insulin sensitizers for induction of ovulation compared to estrogen inhibitors or gonadotropins include correction of underlying metabolic abnormalities which may have adverse longer term cardiovascular consequences[52] and reduced rates of multiple gestation. Although neither class of drugs is approved for use in pregnancy, there are enough data available for metformin to be placed in the U.S. Food and Drug Administration (FDA) Pregnancy Category B (human data reassuring), while thiazoledinediones are in Category C (insufficient data).[53]

Although efficacy in establishing ovulation has been established, at least for metformin, the evidence available at the time of the Cochrane review was limited for pregnancy and live birth.[50] This section reviews the literature meeting our search criteria that provided data on pregnancy and live birth rates.

1. Included Studies. The following sections describe studies comparing metformin to placebo, metformin to other insulin sensitizers, and metformin to clomiphene. Studies that

compared metformin in combination with other agents are described in the section on combination therapy.

We identified three studies[54-56] comparing metformin to placebo that met our search criteria (Table 6). All three studies were small, ranging in size from 20 to 56 subjects. Two studies, one in new patients[54] and one in patients who had previously failed to ovulate with clomiphene treatment,[55] had non-significant increases in pregnancy rates; the third trial[56] had only three pregnancies in 20 subjects.

Two small studies compared metformin to rosiglitazone[57] or pioglitazone[58] (Table 6). Neither study had sufficient power to demonstrate any difference in pregnancy or live birth rates, and the study by Ortega-Gonzalez and colleagues[58] was not designed as an infertility trial.

Two RCTs provided data which allowed direct comparison of metformin to clomiphene[6,59] (Table 6). Both studies used a double-blind, double-dummy design, where women received either clomiphene plus placebo "metformin," or metformin plus placebo "clomiphene," and continued treatment for up to 6 months.

In a single center study, Palomba and colleagues randomized 50 women to each arm. The primary outcome was pregnancy rate, and the study was powered to detect a 30 percent absolute difference. Both ovulation and pregnancy rates were higher in the first two cycles with clomiphene, but higher with metformin in subsequent cycles.[59] Cumulative ovulation rates were similar (62.9 percent with metformin vs. 67 percent for clomiphene), but cumulative and ongoing pregnancy rates were significantly higher with metformin (RR for cumulative pregnancy rates 3.10; 95 percent CI 1.71-5.62; for ongoing pregnancy, RR 2.80; 1.53-5.13). Spontaneous abortion rates were higher in the clomiphene group. There were no multiple pregnancies in either arm, and no clear difference in pregnancy complications.

Contrasting results were found in a larger multi-center trial, the Pregnancy in Polycystic Ovary Syndrome (PPCOS) study, conducted by Legro and colleagues.[6] This trial also included a third arm of active clomiphene plus metformin; these results are discussed separately in the combination therapy section. Randomization was stratified by center and history of prior therapy with either metformin or clomiphene (approximately 60 percent of subjects had previously received at least one of the experimental treatments, with 18 percent having received both). The primary outcome was live birth, powered to detect an absolute difference of 15 percent. Six hundred twenty-six women were randomized. Ovulation rates were significantly higher in the clomiphene only group compared to metformin (49 percent vs. 29 percent), and both pregnancy and live birth rates were substantially higher in the clomiphene only group (RR for live birth 0.33; 95 percent CI 0.19-0.57). There were three multiple pregnancies in the clomiphene-only group, none in the metformin group, with a non-significant trend towards higher pregnancy loss rates in the metformin group; there were no clear differences in pregnancy complications. Overall side effects were similar, with hot flashes and vaginal symptoms more common with clomiphene, and gastrointestinal symptoms more common with metformin.

From the published data, there is no clear explanation for the discrepant results of these two similarly designed studies. The main differences in the subject populations were prior treatment (none in the Palomba study, 60 percent in PPCOS) and BMI (restricted to less than 30 kg/m^2 in the Palomba study, while almost 20 percent of the PPCOS subjects had a BMI between 30 and 34 kg/m^2, and almost 50 percent had a BMI of 35 kg/m^2 or above). However, because of the large sample size and randomized design, these factors were equally distributed between treatment arms. In addition, post-hoc analyses based on BMI and history of prior treatment showed similar results for the comparison of metformin to clomiphene alone. Given the single

center European setting versus the multi-center U.S. setting, and subsequent findings of genetic variability in response to metformin,[60] it is possible that variations in the distribution of relevant genes in different patient populations contributed to some of the difference.

Table 6. Insulin sensitizers in anovulation

Study	Interventions		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Metformin vs. placebo									
Fleming et al., 2002[54]	Reference	Placebo	19						
		Metformin	23	3.30	0.40	27.1			
				Subgroup of patients actively seeking pregnancy; cycles/patient: > 1					
Kocak et al., 2002[55]	Reference	Placebo	28						
		Metformin	28	6.00	0.31	114			
		Clomiphene-resistant		*Cycles/patient: > 1*					
Ng et al., 2001[56]	Reference	Placebo	10						
		Metformin	10	0.50	0.05	4.67			
		Clomiphene-resistant		*Cycles/patient: > 1*					
Metformin vs. other sensitizers									
Rouzi and Ardawi, 2006[57]	Reference	Metformin	13						
		Rosiglitazone	12	1.30	0.53	3.17	1.35	0.47	3.89
				Cycles/patient: > 1					
Ortega-Gonzalez et al., 2005[58]	Reference	Metformin	27						
		Pioglitazaone	25				1.80	0.48	6.76
				Cycles/patient: 6 months; not designed as infertility study					
Metformin vs. clomiphene									
Palomba et al., 2005[59]	Reference	Clomiphene + placebo	50						
		Metformin + placebo	50	**3.10**	**1.71**	**5.62**	**2.80**	**1.53**	**5.13**
				Cycles/patient 4.2					
Legro et al., 2007[6]	Reference:	Clomiphene + placebo	209						
		Metformin + placebo	203	**0.36**	**0.22**	**0.60**	**0.33**	**0.19**	**0.57**
		Clomiphene + metformin	209	1.30	0.95	1.78	1.19	0.85	1.67
				Cycles/patient: 4.7; multiples only in clomiphene arms					

2. Other published systematic reviews. We identified one published non-Cochrane review by Kashyap and colleagues.[61] This review identified two studies with a total of 65 subjects comparing metformin to placebo, with a summary odds ratio of 1.07 (95 percent CI 0.20-5.74).

3. Cochrane reviews. The most recent Cochrane update was in December 2002.[50] Based on five studies with a total of 172 subjects, pregnancy rates were increased non-significantly with metformin compared to no treatment or placebo (OR 2.76; 95 percent CI 0.85-8.98); only two of these studies (n = 50) reported live birth rates (OR 1.00; 0.13-7.79).

4. Conclusions. Although the majority of randomized studies suggest that pregnancy rates are increased with metformin compared to placebo, the small number of trials, along with the

small size of the trials, means that the results are non-significant for both individual studies and meta-analyses performed to date.

There is insufficient evidence to compare the efficacy of available thiazolidinediones to placebo, metformin, or any other currently used agent for induction of ovulation in women with PCOS.

Results of the two direct randomized comparisons of metformin to clomiphene are contradictory. The smaller single center study found metformin superior to clomiphene in achieving pregnancy, while a much larger multi-center study found clomiphene superior to metformin in achieving both pregnancy and live birth, results that were consistent regardless of BMI or history of prior therapy. Results for spontaneous abortion rates were similarly discrepant. Multiple pregnancies were only observed in women treated with clomiphene. Based on this evidence, we conclude that metformin is, at best, not superior to clomiphene in achieving pregnancy and live birth, and, based on the largest study, is inferior. Sample sizes are too small in the randomized trials to draw conclusions about spontaneous abortion or other pregnancy-related outcomes.

C. Drugs for inducing ovulation – gonadotropins. Approximately 20-40 percent of women with PCOS will fail to conceive in response to clomiphene.[62,63] One option for treating these women is stimulation with exogenous gonadotropins. Although effective in achieving pregnancy, there is an increased risk of both multiple pregnancies and ovarian hyperstimulation syndrome (OHSS).[64] The purpose of studies of variation in the type and/or dosing of gonadotropin is to determine optimal pregnancy and live births while minimizing multiple births and OHSS. This section reviews the existing evidence on the efficacy of various approaches to ovulation induction using gonadotropins in PCOS patients.

1. Included studies. The six identified studies are shown in Table 7. None of the studies had adequate power to detect differences in pregnancy rate. Because multiples and OHSS will be even less frequent than pregnancy, these studies were not able to provide any conclusive evidence regarding any gonadotropin-based method.

Table 7. Gonadotropins alone in PCOS

Study	Interventions		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Dosage									
Balasch et al., 2001[65]	Reference	rFSH step-down	14						
		rFSH step-up	15	1.87	0.19	18.4			
		Clomiphene-resistant		*Cross-over design – 1st cycle only*					
Christin-Maitre et al., 2003[66]	Reference	rFSH step-down	39						
		rFSH step-up	44	1.26	0.69	2.29			
		Clomiphene-resistant		*Cycles/patient: 1.9; multiple gestations 0.59 (010, 3.35)*					
Leader and Monofol-licular Ovulation Induction Study Group, 2006 [67]	Reference	25 IU rFSH step-up	83						
		50 IU rFSH step-up	78	0.67	0.32	1.38			
		Clomiphene-resistant		*Cycles/patient: 1.0; multiples 0.26 (0.01, 5.8); ovarian hyperresponse 4.26 (1.49, 12.2)*					
Type of gonadotropin									
Gerli et al., 2004[68]	Reference:	rFSH	88						
		Urinary FSH	82	1.03	0.62	1.69			
				Cycles/patient: 2.23; multiples 0.91 (0.21, 4.00)					
Revelli et al., 2006[69]	Reference:	rFSH	35						
		Highly purified urinary FSH	39				0.51	0.16	1.63
		Clomiphene-resistant		*Cycles/patient: 1.0; fewer vials of rFSH used – lower cost*					
Timmer-man-van Kessel et al., 2000[70]	Reference:	Clomiphene	12						
		Pulsatile GnRH	16	0.75	0.23	2.41			
		Clomiphene-resistant		*Cycles/patient: 2.1*					

2. Other systematic reviews. We did not identify any other non-Cochrane published reviews.

3. Cochrane reviews. There are three relevant Cochrane reviews. The first[71] was most recently updated in May 2000 and reviewed studies of gonadotropin therapy in PCOS. All studies were published prior to 2000, and neither pregnancy nor live birth per couple was reported or calculable. In five studies, FSH alone resulted in lower OHSS compared to human menopausal gonadotropins (hMG) when no gonadotropin-releasing hormone (GnRH) analog was used (OR 0.20; 95 percent CI 0.08-0.46); when GnRH agonists were used, overstimulation requiring cycle cancellation was significantly more frequent. OHSS was increased, but the confidence intervals for the OR include 1.0.

The second review[72] was most recently updated in February 2001 and compared recombinant (rFSH) versus urinary FSH (uFSH) preparations. Using urinary FSH as the reference, there was no significant difference in pregnancy rate (OR 0.95; 95 percent CI 0.64-1.41), multiple gestations (0.44; 0.16, 1.21), or OHSS (1.55; 0.50, 4.84). Only one study (pre-2000) of different dosing regimens was included in the review. It compared a conventional regimen guided by

ovarian response versus chronic low-dose rFSH and found non-significant differences in pregnancy rates (OR 1.62; 95 percent CI 0.65-4.07).

The third review of pulsatile GnRH administration[73] included only the study of Timmerman et al.;[70] with only 30 subjects, this study, like the majority of the others, was not powered to detect meaningful differences in pregnancy rates.

4. Conclusions. Based on pre-2000 studies included in the Cochrane review,[71] use of FSH results in a lower incidence of OHSS compared with hMG, particularly if there is no concomitant pituitary suppression. There is insufficient evidence to determine the most effective form or regimen for administration of FSH for ovulation induction in women with PCOS who do not respond to clomiphene.

D. Drugs for inducing ovulation – combinations. Combinations of all three of the major classes of medical treatments for PCOS have been tested, along with other adjunctive therapies, both as primary treatment for PCOS and in women who fail to respond to a trial of clomiphene. This section describes studies that tested combinations of medical therapies, divided broadly by studies of first-line treatment and treatments in clomiphene-resistant women.

1. Included studies: first-line treatment. Summary RRs for included studies are shown in Table 8. Two studies compared metformin plus clomiphene to monotherapy in patients receiving initial therapy for infertility associated with PCOS. Moll and colleagues[74] randomized 225 women to clomiphene plus placebo or clomiphene plus metformin and found no difference in pregnancy rates (RR 0.87; 95 percent CI 0.64-1.18). In the previously described PPCOS study,[6] clomiphene plus metformin was significantly more effective in achieving both pregnancy and live birth than metformin alone; live birth rates were increased, but not significantly, compared to clomiphene alone (RR 1.19; 0.85-1.67). This effect was seen in women with and without prior therapy. In another subgroup analysis, any benefit of adding metformin to clomiphene was limited to women with a BMI greater than or equal to 35, although the sample size was not sufficient to show statistical significance.

Two studies compared clomiphene alone to clomiphene with ultrasound monitoring of the ovaries and triggering of ovulation with human chorionic gonadotropin (hCG), followed by intercourse.[75,76] Pregnancy rates were increased in both, but not significantly (Table 8).

In one small study, the addition of ketoconazole to clomiphene resulted in significantly more live births (RR 2.24; 95 percent CI 1.01-4.95), with a trend towards reduced multiple pregnancies. This study was published in 2001, and we did not identify any subsequent similar studies in our search.

Because clomiphene has both agonist and antagonist effects on the estrogen receptor, depending on the target tissue, failure to conceive or early pregnancy loss in some women receiving clomiphene may be due to estrogen inhibiting effects in other sites in the reproductive tract. Two studies evaluating the addition of estrogens, either ethinyl estradiol[77] or phytoestrogens,[78] found significantly increased live birth rates compared to clomiphene alone (RRs of 4.6 and 6.0), with decreased spontaneous abortion rates. Again, we did not identify any other studies that would confirm these results.

Table 8. Combination therapy as first-line-treatment in anovulation

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Clomiphene + metformin									
Moll et al., 2006[74]	Reference	Clomiphene + placebo	114						
		Clomiphene + metformin	111	0.87	0.64	1.18	-	-	-
				Cycles/patient: > 1.0					
Legro et al., 2007[6]	Reference	Clomiphene + placebo	209						
		Metformin + placebo	203	0.36	0.22	0.60	0.33	0.19	0.57
		Clomiphene + metformin	209	1.30	0.95	1.78	1.19	0.85	1.67
				Cycles/patient: 4.7; multiples only in clomiphene arms					
Clomiphene + hCG trigger									
George et al., 2007[75]	Reference	Clomiphene	90						
		Clomiphene + hCG trigger	90	1.67	0.63	4.39	1.60	0.54	4.70
				Cycles/patient: 1.0??					
Yilmaz et al., 2006[76]	Reference	Clomiphene citrate	60						
		Clomiphene + hCG as trigger	65	1.20	0.71	2.05	-	-	-
				Cycles/patient: 1.0; multiples 2.17 (0.20, 23.3)					
Clomiphene + ketoconazole									
Ali Hassan et al., 2001[79]	Reference	Clomiphene	48						
		Clomiphene + ketoconazole	49	2.08	0.99	4.36	**2.24**	**1.01**	**4.95**
				Cycles/patient: 3.3; multiples 0.63 (0.33, 1.19); more dropouts in clomiphene-only group					
Clomiphene + estrogens									
Unfer et al., 2004[78]	Reference	Clomiphene	69						
		Clomiphene + phytoestrogen	65	1.77	0.83	3.76	**4.60**	**1.37**	**15.4**
				Cycles/patient: 1.0; spontaneous abortion rate lower in CC + estrogen group					
Gerli et al., 2000[77]	Reference	Clomiphene	32						
		Clomiphene + estradiol	32	**1.75**	**0.85**	**3.59**	**6.00**	**1.46**	**24.6**
				Cycles/patient: 1.0; spontaneous abortion rates lower in clomiphene + estradiol group (0.33; 95% CI 0.07, 1.53)					

2. Included studies: second-line treatment after initial failure with clomiphene. Summaries of study size and RRs are presented in Table 9.

Two small studies[80,81] suggest an improvement in pregnancy rates with the addition of metformin in women who have previously failed clomiphene treatment, although individual differences were not statistically significant. Another small study failed to show a significant difference with the addition of rosiglitazone.[82]

Metformin also non-significantly increased pregnancy rates in two studies of gonadotropin use.[83,84]

Three studies of different adjunct therapies demonstrated large and statistically significant improvements in pregnancy rates in clomiphene-resistant women compared to clomiphene alone: pre-treatment with oral contraceptives[85] (RR 13.0; 95 percent CI 1.84-97.0); co-administration of n-acetyl-cysteine[86] (RR 28.0; 1.7-488); and co-administration of dexamethasone[87] (RR 8.00; 1.97-32.5). Of note, multiple gestation rates were increased with all three approaches. As is evident from the width of the confidence intervals, the combination of relatively small study size and lower event rates prevents precise estimates of efficacy, but the effect size for all suggests that further studies of each of these approaches with a focus on minimizing multiple gestation risk are warranted.

Table 9. Combination therapy in women who fail initial treatment with clomiphene

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Clomiphene + insulin sensitizers									
George et al., 2003[88]	Reference	Metformin x 6 months, followed by clomiphene	30						
		hMG	30	1.40	0.50	3.92	3.00	0.66	13.7
		Clomiphene-resistant		*Cycles/patient: > 1.0*					
Ghazeeri et al., 2003[82]	Reference	Rosiglitazone + placebo	12						
		Rosiglitazone + clomiphene	13	1.85	0.19	17.9	0.92	0.06	13.2
		Clomiphene-resistant							
Malkawi et al., 2002[80]	Reference	Clomiphene + placebo	12						
		Clomiphene + metformin	16	3.30	0.89	12.8	-	-	-
		Clomiphene-resistant		*Cycles/patient: 2.7*					
Vander-molen et al., 2001[81]	Reference	CC + placebo	15						
		CC + metformin	12	**7.50**	**1.04**	**54.1**	-	-	-
		Clomiphene-resistant							
Gonadotropins + insulin sensitizers									
Yarali et al., 2002[83]	Reference	FSH + placebo	15						
		FSH + metformin	16	4.69	0.62	35.6	-	-	-
				Cycles/patient: 1.0					
		Clomiphene-resistant							
Palomba et al., 2005[84]	Reference	COH only	35						
		COH + metformin	35	1.29	0.77	2.16	1.42	0.80	2.51
		Non-obese; insulin-resistant; clomiphene-resistant		*Cycles/patient: 2.45; multiples 0.51 (0.02, 15.0); OHSS 0.31 (0.07, 1.37)*					

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Clomiphene + oral contraceptive pre-treatment									
Branigan and Estes, 2003[85]	Reference	Clomiphene + hCG trigger	24						
		Pre-treatment with OCP + clomiphene + hCG trigger	24	**13.0**	**1.84**	**91.7**	-	-	-
		Clomiphene-resistant		*Cycles/patient: 1.9; multiples increased with OCPs*					
Clomiphene + hCG trigger									
Branigan and Estes, 2005[89]	Reference	Clomiphene 100 mg	36						
		Clomphene 50 mg + hCG ovulation trigger	35	6.38	0.35	126	-	-	-
		Clomiphene-resistant		*Cycles/patient: 1.0*					
Clomiphene + other agents									
Rizk et al., 2005[86]	Reference	Clomiphene + placebo	75						
		Clomiphene + n-acetyl-cysteine	75	**28.8**	**1.7**	**488**	-	-	-
		Clomiphene-resistant		*Cycles/patient: 1.0; multiple gestation 10.3 (0.6, 189.8)*					
Elnashar et al., 2006[87]	Reference	Clomiphene + placebo	40						
		Clomiphene + dexametha-sone	40	**8.00**	**1.97**	**32.5**	-	-	-
		Clomiphene-resistant		*Cycles/patient: 1.0*					

3. Other systematic reviews. One published non-Cochrane systematic review[61] found an increased pregnancy rate with clomiphene plus metformin compared to clomiphene plus placebo in clomiphene-resistant women (OR 3.65; 95 percent CI 1.11-12.0).

The relevant Cochrane review[44] (Table 10) showed significantly increased pregnancy rates with use of clomiphene plus dexamethasone (OR 11.3; 95% CI 5.33-24.1) and clomiphene after pre-treatment with oral contraceptives (OR 26.7; 4.91-145); both of these treatments also had substantial increases in multiple pregnancy rates, although confidence intervals included 1.0. The addition of metformin to gonadotropins was also superior to gonadotropins alone for pregnancy (OR 4.88; 2.46-9.67).

Table 10. Cochrane review, combination therapies in clomiphene-resistant women[44]

Interventions		N	Efficacy					
			Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
			Rel Effect	Lower 95% CI	Upper 95% CI	Rel Effect	Lower 95% CI	Upper 95% CI
Clomiphene + bromocryptine vs. clomiphene								
Reference	Clomiphene	53						
	Clomiphene + bromocryptine	47	0.98	0.33	2.96	-	-	-
	1 study, post-2000							
Clomiphene + dexamethasone vs. clomiphene								
Reference	Clomiphene	141						
	CC + dexamethasone	134	**11.3**	**5.33**	**24.1**	-	-	-
	2 studies, 1 post-2000		*Multiples (1 study), 7.68 (0.37, 157)*					
Clomiphene + ketoconazole vs. clomiphene								
Reference	Clomiphene	37						
	CC + ketonazole	43	2.37	0.88	6.40	-	-	-
	1 study, post-2000							
Clomiphene + OCPs vs. clomiphene								
Reference	Clomiphene	24						
	Clomiphene + OCPs	24	**26.7**	**4.91**	**145**	-	-	-
	1 study, post-2000		*Multiples 7.98 (0.39, 163)*					
Metformin + ovulation induction vs. ovulation induction alone								
Reference	Ovulation induction	109						
	Metformin + induction	110	**4.88**	**2.46**	**9.67**	5.48*	0.81	37.3
	5 studies, all post-2000		**1 study, post-2000, n = 27*					

4. Conclusions. Based on two large randomized trials, the addition of metformin to clomiphene as first-line therapy does not appear to significantly increase pregnancy or live birth rates, although a subgroup analysis of the largest trials suggests that there may be benefit in women with a BMI greater than or equal to 35, a finding which should be confirmed in a larger study.

The addition of ketoconazole (one study) and estrogens (two studies) to clomiphene in first-line therapy resulted in significantly increased live birth rates due to decreased spontaneous abortion rates, findings which should be confirmed in larger trials.

Although a statistically significant effect is not observed in individual studies, meta-analyses do demonstrate a significant increase in pregnancy rates in clomiphene-resistant women treated with metformin. Whether these results translate into improved live birth rates should be confirmed in larger studies, although the lower overall birth rate in this population will require large studies.

Pre-treatment with oral contraceptives, co-treatment with n-acetyl-cysteine, and co-treatment with dexamethasone all resulted in large and statistically significant increases in pregnancy rates in combination with clomiphene in clomiphene-resistant anovulatory women, along with increased multiple gestation rates. These findings warrant further investigation, particularly if multiple gestation can be avoided.

E. Surgical procedures for inducing ovulation. One of the earliest treatments for PCOS was wedge resection of the ovary, which, while effective in inducing ovulation, had attendant

surgical risks, as well as the risk of developing adhesions.[90] With the advent of laparoscopic surgical procedures, both short- and long-term risks are theoretically lower. Several studies have investigated the role of laparoscopic "drilling" of the ovary using electrocautery.

1. Identified studies. Identified studies are summarized in Table 11. The largest study, by Bayram and colleagues,[91] compared a strategy of immediate gonadotropins to laparoscopic electrocautery, followed by ovulation induction agents only if pregnancy did not occur. The electrocautery strategy resulted in similar pregnancy and live birth rates (live birth RR 1.14; 95 percent CI 0.94-1.39) with significantly lower multiple gestation rates (RR 0.11; 0.01-0.88). In another study in a similar population, Palomba and colleagues found significantly higher pregnancy and live birth rates with the addition of metformin after laparoscopic cautery.[92] None of the studies had sufficient followup to assess the risk of longer term complications such as adhesions or premature ovarian failure.

Table 11. Surgical interventions for anovulatory infertility

Study	Interventions		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Bayram et al., 2004[91]	Reference	rFSH	85						
		Electrocautery followed by ovulation induction if necessary	83	1.14	0.94	1.39	1.14	0.94	1.39
		Clomiphene-resistant		*Multiples 0.11 (0.01, 0.88)*					
Palomba et al., 2005[93]	Reference	Laparoscopic drilling + clomiphene	20						
		Metformin x 6 months + clomiphene	8	1.25	0.73	2.98	1.43	0.54	3.57
		Clomiphene-resistant; anovulatory after metformin or drilling		*Cycles/patient: 3.9*					
Palomba et al., 2005[93]	Reference	Laparoscopic drilling + clomiphene	20						
		Metformin x 6 months + clomiphene	8	1.25	0.73	2.98	1.43	0.54	3.57
		Clomiphene-resistant; anovulatory after metformin or drilling		*Cycles/patient: 3.9*					
Palomba et al., 2004[92]	Reference	Laparoscopic ovarian dia-thermy + placebo	60						
		Laparoscopic ovarian dia-thermy + metformin	60	**1.60**	**1.04**	**2.46**	**1.60**	**1.04**	**2.46**

Study	Interventions		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Farquhar et al., 2002[94]	Reference	Gonadotropins	21						
		Laparoscopic drilling	29	0.83	0.36	1.93	0.72	0.20	2.57
Sharma et al., 2006[95]	Reference	Unilateral drilling	10						
		Bilateral drilling	10	1.40	0.67	2.94	-	-	-

2. Other systematic reviews. We did not identify any non-Cochrane published reviews.

3. Cochrane reviews. The relevant Cochrane review[96] concluded that laparoscopic drilling, with or without stimulation, resulted in essentially equivalent pregnancy (OR 1.08; 95 percent CI 0.69-1.71) and live birth rates (OR 1.04; 0.59-1.85), with a significantly reduced risk of multiple gestation (OR 0.13; 0.03-0.52).

4. Conclusions. Use of laparoscopic cautery, followed by ovulation induction if necessary, results in similar pregnancy and live birth rates, with significantly lower multiple gestation rates, compared to immediate gonadotropin use in clomiphene-resistant women. The addition of metformin may result in further improvements in pregnancy and live birth rates. There are no data on the long-term sequelae of laparoscopic ovarian cautery.

F. Aspects of intrauterine insemination in anovulatory women. Intrauterine insemination (IUI) may be used as an adjunct to ovulation induction in women with PCOS, although we did not identify any recent randomized trials that directly compared ovulation induction with and without IUI.

1. Identified studies. We identified one study that addressed aspects of IUI in this population. Lewis and colleagues[97] compared two methods for the timing of IUI – one with home monitoring of urinary luteinizing hormone (LH), with IUI after detection of the LH surge, versus ultrasound monitoring of follicular development and triggered ovulation using hCG, followed by IUI. Pregnancy rates were increased with hCG triggering, but not significantly (RR 1.73; 95 percent CI 0.88-3.38).

2. Other systematic reviews. Kosmas and colleagues,[98] in a systematic review of timing of IUI based on LH monitoring versus hCG triggering, found non-significantly increased pregnancy rates with hCG triggering after clomiphene treatment in anovulatory patients (OR 2.00; 95 percent CI 0.84-4.77)

3. Cochrane reviews. There were no relevant Cochrane reviews.

4. Conclusions. Although the available studies suggest an increase in pregnancy rates with hCG triggering for IUI after ovulation induction with clomiphene in women with PCOS, sample sizes have been too small to demonstrate statistically significant differences. Given the large differences in cost, patient convenience, and the fairly high relative rates (1.7-2.0) observed between these two treatments, definitive determination of superiority should be a research priority.

V. Superovulation in Ovulatory Women

For couples where the female partner has normal ovulatory function and at least one patent fallopian tube, and the male partner has motile sperm, superovulation (use of gonadotropins to induce development of more than one follicle in a given cycle), followed by IUI, is the most

efficient method of treatment, resulting in 2-3 times higher pregnancy and live birth rates within 6 months of treatment compared to IUI alone, intracervical insemination (ICI) alone, or superovulation with ICI.[99] However, this increased probability is associated with an increased risk of multiple gestations, which are at risk of multiple complications, including preterm birth and its sequelae; in the trial cited above, 16 percent of the live births in the two superovulation arms were preterm, compared to 6 percent of those in the other two arms (RR 2.60; 95 percent CI 0.79-8.61).

This section reviews publications subsequent to this study that address methods for superovulation, largely with IUI, as therapy in infertile couples where the female partner has normal ovulatory function and tubal patency, and where the male partner has motile sperm.

A. Drugs for superovulation–estrogen inhibitors. In theory, estrogen inhibitors should produce similar hypothalamic and pituitary responses in ovulatory women as they do in anovulatory women, leading to the development of multiple follicles and an increased probability of conception. Because estrogen inhibitors are oral agents with a lower risk of higher order multiples than the injectable gonadotropins, and cost significantly less, they are a potentially attractive candidate for superovulation. This section reviews the evidence on the efficacy of estrogen inhibitors and aromatase inhibitors compared to no treatment, to each other, and to gonadotropins.

1. Identified studies. Table 12 summarizes the identified studies. In general, significant differences were not observed in pregnancy rates for any comparison, with the exception of 2.5 mg versus 5.0 mg of letrozole, where the higher dose resulted in large and significant increase in pregnancy rate (RR 4.47; 95 percent CI 1.05-19.0). Although no differences were observed in rates of multiple pregnancy or OHSS, the number of these events in individual studies was small.

Table 12. Estrogen inhibitors, alone and in combination, for superovulation

Study	Interventions		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Clomiphene vs. aromatase inhibitors									
Al-Fozan et al., 2004[100]	Reference	Clomiphene	80						
		Letrozole	74	1.26	0.61	2.67	-	-	-
		All unexplained infertility		*Cycles/patient: 1.8; 25% of all pregnancies ectopic*					
Fatemi et al., 2003[101]	Reference	Clomiphene	8						
		Letrozole	7	0.76	0.17	3.33	-	-	-
				Cycles/patient: 1.0					
Clomiphene plus adjunctive therapy									
Badawy et al., 2006[102]	Reference	Clomiphene + placebo	400						
		Clomiphene + n-acetyl-cysteine	404	0.83	0.65	1.05	-	-	-
				Cycles/patient: 1.0; multiples 0.66 (0.27,1.60)					
Estrogen inhibitor dosing									
Al-Fadhli et al., 2006[103]	Reference	2.5 mg letrozole	34						
		5 mg letrozole	38	4.47	1.05	19.0	-	-	-
				Cycles./patient: 1.0					

Study	Interventions		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Estrogen inhibitors vs. gonadotropins									
Baysoy et al., 2006[104]	Reference	hMG	40						
		Letrozole	40	1.17	0.43	3.17	-	-	-
		Unexplained infertility							
				Cycles/patient: ?1.0; multiples 1.00 (0.06, 15.4)					
Dankert et al., 2007[105]	Reference	Clomiphene	71						
		Low-dose rFSH	67	0.90	0.58	1.41	0.95	0.55	1.64
				Cycles/patient: 2.94; multiples and OHSS identical					

2. Other systematic reviews. We did not identify any non-Cochrane reviews.

3. Cochrane reviews. There are three relevant Cochrane reviews. The first,[106] most recently updated in November 2006, reviewed studies of clomiphene versus placebo or no treatment in couples with unexplained infertility; statistically significant differences were not observed, but the overall sample sizes were small, and there was a trend towards higher pregnancy rates when clomiphene was used with IUI (OR 2.40; 95 percent CI 0.70-8.19) or with hCG triggering (OR 1.66; 0.48-4.80). Multiple pregnancy rates were similar (OR 0.99; 0.14-7.12).

The second review,[107] updated in May 2002, compared clomiphene to gonadotropins. In three studies with a total of 200 subjects, clomiphene had a significantly lower pregnancy rate (OR 0.44; 95 percent CI 0.19-0.99) and a trend towards lower live births (OR 0.51; 0.18-1.47). There was also a trend towards fewer multiple gestations (OR 0.37; 0.06-2.43).

Finally, a review updated in January 2007 compared a variety of protocols for superovulation combined with IUI.[108] Compared to estrogen inhibitors, gonadotropins resulted in higher pregnancy rates (OR 1.76; 95 percent CI 1.16-2.66) based on seven studies, but there was no difference in live birth rates in the single study that allowed estimation of live birth rates (OR 0.94; 0.44-1.98). Both multiple pregnancy (OR 1.85; 0.53-6.44) and OHSS (OR 4.44; 0.48, 41.3) were more likely with gonadotropins, but, again, because of the relatively low number of these events, confidence intervals include 1.0. In five studies comparing aromatase inhibitors to clomiphene, there was no significant difference in pregnancy rates (OR 0.15; 95 percent CI 0.64-2.08).

4. Conclusions. The available literature does not allow any conclusions about the relative efficacy of different estrogen inhibitors, although 5 mg of letrozole appears to be superior to 2.5 mg. Pooled data show significantly higher pregnancy rates with gonadotropins compared to estrogen inhibitors, but data are too limited to draw conclusions about live birth rates. There is a trend towards higher rates of multiple pregnancies and OHSS with gonadotropins compared to estrogen inhibitors, but the number of events, even in pooled studies, prevents definite conclusions.

B. Drugs for superovulation – gonadotropins. Given the finding that superovulation with gonadotropins plus IUI results in the highest pregnancy rates along with higher multiple pregnancy rates, the obvious next step is to identify a protocol that optimizes the chances of a live birth while minimizing the multiple gestation risk. This section summarizes studies that address this issue.

1. Identified studies. Identified studies that met our inclusion criteria are summarized in Table 13. Individual studies show no significant difference between urinary and recombinant

FSH, although fewer vials are used with rFSH, which may result in reduced treatment costs. Significant differences were not observed between lower and higher dose protocols, although hyper-response, a potential surrogate for OHSS, was higher. Pregnancy rates were consistently higher when GnRH antagonists were used in conjunction with gonadotropins in four studies (significantly in one[109]), while twin rates were 4- to 5-fold higher in three of the four studies.

Table 13. Gonadotropin protocols for superovulation

Study	Interventions		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Recombinant vs. urinary FSH									
Revelli et al., 2006[69]	Reference	rFSH	93						
		Highly purified urinary FSH	91	-	-	-	0.92	0.39	2.16
				Fewer vials with rFSH, lower cost; cycles/patient: 1.0					
Gerli et al., 2004[68]	Reference	rFSH	88						
		uFSH	82	1.03	0.62	1.69	-	-	-
				Cycles/patient: 2.23					
Demirol and Gurgan, 2007[110]	Reference	rFSH	81						
		uFSH	80	0.53	0.27	1.03	-	-	-
		hMG	80	0.48	0.24	0.96	-	-	-
				Cycles/patient: 1.0					
Matorras et al., 2000[111]	Reference	rFSH	45						
		uFSH	46	0.94	0.64	1.37	-	-	-
				Cycles/patient: 3.79					
FSH vs. hMG									
Filicori et al., 2003[112]	Reference	rFSH	25						
		hMG	25	1.75	0.58	1.24	-	-	-
				Cycles/patient: 1.0					
Gomes et al., 2007[113]	Reference	rFSH	17						
		hCG	17	2.25	0.86	5.92	-	-	-
		hMG	17	1.25	0.40	3.87	-	-	-
				Cycles/patient: 1.0					
Dosing protocols									
Leader and Monofol-licular Ovulation Induction Study Group, 2006[67]	Reference	25 IU	78						
		50 IU	83	0.67	0.32	1.38		-	-
		Step-up protocols with different incremental increase if no follicle at least 12 mm by 7 days		*Cycles/patient: 1.0 (dropout rate 27%); ovarian hyper-response 4.26 (1.49, 12.2)*					
Christin-Maitre, et al., 2003[66]	Reference	Step down	39						
		Step up	44	1.26	0.69	2.29	-	-	-
				Cycles/patient: 1.9; multiple gestations 0.59 (0.10, 3.35)					
Ovulation trigger									
Intl. rhCG Study Group, 2001[114]	Reference	uhCG	99						
		rhCG	99	0.76	0.47	1.22	0.70	0.38	1.31
				Cycles/patient: 1.0					

Study	Interventions		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Sakhel et al., 2007[115]	Reference	uhCG	144						
		rhCG	140	0.95	0.66	1.39	0.89	0.58	1.35
				Cycles/patient: 1.0					
Gondaotropins + GnRH agonists									
Karlstrom et al., 2000[116]	Reference	hMG	80						
		hMG + GnRH agonist (buserelin)	81	1.23	0.50	3.07	0.99	0.38	2.59
				Cycles/patient: 1.0; no difference in multiple rates					
Gonadotropins + GnRH antagonists									
Gomez-Palomares et al., 2005[117]	Reference	FSH	42						
		FSH + GnRH antagonist (cetrorelix)	40	**2.63**	**1.13**	**6.09**	-	-	-
				Cycles/patient: 1.0					
Allegra et al., 2007[109]	Reference	rFSH only	52						
		rFSH + Cetrorelix	52	**1.75**	**1.08**	**2.83**	-	-	-
				Cycles/patient: 2.9; twins 4.00 (0.46, 34.6)					
Checa et al., 2006[118]	Reference	rFSH only	32						
		rFSH + Cetrorelix	35	1.60	0.52	4.96	-	-	-
				Cycles/patient: 1.0; twins 5.68 (0.29, 112.1)					
Crosignani et al., 2007[119]	Reference	rFSH only	151						
		rFSH + Ganirelix	148	0.96	0.49	1.86	-	-	-
				Cycles/patient: 1.0; twins 5.10 (1.51, 17.3)					

2. Other systematic reviews. We did not identify any non-Cochrane published reviews.

3. Cochrane reviews. Results of the relevant Cochrane review,[108] updated in January 2007, are summarized in Table 14. As has been seen with all of the study reviews, live birth is rarely reported and overall study numbers are small, with no consistent difference in pregnancy rates. Elevated pooled estimates for the risk of multiples and OHSS were observed with higher doses compared to lower doses (multiples 3.11; 95 percent CI 0.48-20.13; OHSS 5.52; 1.85-16.5), and with gonadotropins and GnRH agonists compared to gonadotropins alone (multiples 2.86; 95 percent CI 1.03-7.94; OHSS 2.02; 0.70-5.87). Pooled estimates of multiple pregnancy rates were not elevated with gonadotropins plus GnRH antagonists, but two of the studies noted above which did observe a significant increase in twins were published after this review.

Table 14. Cochrane review, gonadotropins for superovulation[108]

Interventions		N	Efficacy					
			Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
			Relative Effect	Lower 95% CI	Upper 95% CI	Relative Effect	Lower 95% CI	Upper 95% CI
hMG vs. FSH								
Reference	FSH	228						
	hMG	145	1.02	0.59	1.75	-	-	-
	5 studies, 4 post-2000							
rFSH vs. uFSH								
Reference	uFSH	301						
	rFSH	304	1.36	0.95	1.94	-	-	-
	5 studies, all post-2000							
Gonadotropins alone vs. gonadotropins + GnRHa								
Reference	Gonadotropins	190						
	Gonadotropins + GnRHa	201	0.98	0.60	1.59	-	-	-
	4 studies, 2 post-2000							
Gonadotropins alone vs. gonadotropins + GnRH antagonist								
Reference	Gonadotropins	148						
	Gonadotropins + GnRH antagonist	151	1.51	0.83	2.76	***3.04**	**1.07**	**8.57**
	3 studies, all post-2000		**1 study, n = 80*					
Timing of dosing								
Reference	Alternate	33						
	Daily	30	-	-	-	**13.71**	**1.62**	**116.3**
	1 study, post-2000							
High dose vs. low dose								
Reference	Low dose	149						
	High dose	148	1.15	0.69	1.92	-	-	**-**
	2 studies, 1 post-2000							
Ultralong vs. long protocol GnRHa								
Reference	Ultra-long	41						
	Long	39	**2.59**	**1.02**	**6.59**	-	-	**-**
	1 study, pre-2000							

4. Conclusions. There do not appear to be substantial differences in pregnancy rates between different gonadotropin preparations. Higher doses increase the risk of multiples and OHSS without significant improvement in pregnancy rates. The addition of GnRH antagonists to superovulation protocols may increase both pregnancy rates and twin gestation rates. Further studies adequately powered for the outcome of live birth per couple are needed.

C. Surgical adjuncts. Surgical procedures to address minor abnormalities detected during the infertility evaluation may result in improved outcomes for those couples who go on to superovulation and IUI.

1. Identified studies. We identified one study[120] that assessed the utility of diagnosis and treatment of minor abnormalities. Women who were candidates for superovulation and IUI who had small endometrial polyps (mean diameter 16 mm) detected on ultrasound were randomized to hysteroscopy with either biopsy (to rule out malignancy) or resection of the polyps. Polypectomy resulted in significantly higher pregnancy rates (RR 2.23; 95 percent CI 1.57-3.15); data on live birth rates were not presented. Time to pregnancy was substantially shorter in the

polypectomy group; of note, 65 percent of the pregnancies in this group occurred before the first IUI.

2. Other systematic reviews. We did not identify any other published or relevant Cochrane reviews.

3. Conclusions. Hysteroscopic resection of ultrasound-detected endometrial polyps results in improved pregnancy rates for women undergoing superovulation and may even obviate the need for further treatment; this would likely result in a decrease in multiple pregnancy rates.

D. Aspects of intrauterine insemination after superovulation. Finally, we reviewed studies that addressed various aspects of IUI after superovulation.

1. Identified studies. We did not identify any studies that met our inclusion criteria.

2. Other systematic reviews. One published systematic review of hCG triggering of ovulation versus urinary LH monitoring for timing of IUI after clomiphene found no significant differences in pregnancy rates in couples with male factor infertility (OR 0.66; 95 percent CI 0.35-1.21) or unexplained fertility (OR 0.79; 0.38-1.64), although hCG triggering did significantly increase rates in anovulatory women, as noted above.

3. Cochrane reviews. In a review updated in July 2007,[121] three studies published prior to 2000, with a total of 202 subjects, suggest a higher pregnancy rate with IUI compared to timed intercourse with superovulation, but confidence intervals cross 1.0 (OR 1.67; 95 percent CI 0.83-3.37). A review updated in July 2007 found no evidence for superiority of any semen preparation techniques, but the number of subjects was small.[122] Finally, in a review updated in November 2002,[123] no differences were observed when comparing single versus double IUI (total number of subjects 355, OR 1.45; 95 percent CI 0.78-2.68).

4. Conclusions. There is insufficient evidence to identify any aspect of IUI that significantly affects pregnancy rates, let alone live birth rates or other less common outcomes.

Assisted Conception: IVF and ICSI (Question 3)

I. Research Question

Among women of reproductive age, which laboratory, clinical, and other practice approaches result in the highest successful singleton pregnancy (or live-born) rates, and what practices lead to high multiple rates? Laboratory practices include intracytoplasmic sperm injection (ICSI), different types of embryo culture, fresh versus frozen embryo transfer, and day 2 to 3 versus day 5 to 6 transfer. Clinical practices include number of embryos transferred and selection criteria for eligible patients, as well as using the implantation rates from previous unsuccessful cycles to inform subsequent embryo transfer. Other practices include insurance coverage strategies.

II. Approach

Some infertile couples are either not candidates for the interventions described in the preceding section (because of tubal disease, for example) or have failed a trial of ovulation induction or superovulation. In all of the interventions described in the previous section, the ovaries are exposed to increased levels of endogenous or exogenous gonadotropins, and may or

may not receive additional agents to trigger ovulation (the extrusion of the egg[s] from the ovary), but the individual steps of ovulation, exposure to sperm, fertilization, and initial development of the embryo all take place within the patient's body. The interventions described in this section involve direct intervention with at least one, and most commonly all, of these individual steps.

The review is organized around interventions applied to the individual steps in the process, based on the most commonly used protocols. Interventions are divided into those used in the female partner, in the male partner, and in the embryo.

For the female partner, interventions include:

a) Suppression of endogenous pituitary gonadotropin secretion (pituitary down-regulation);

b) Stimulation of follicular development with exogenous agents (controlled ovarian hyperstimulation);

c) Triggering of ovulation;

d) Retrieval of oocytes;

e) Replacement of gametes (relevant only for gamete intrafallopian transfer [GIFT]);

f) Transfer of the embryo;

g) Luteal support;

h) Other adjunctive therapies; and

i) Strategies for prevention of ovarian hyperstimulation syndrome (OHSS).

For the male partner, interventions include:

a) Methods for sperm retrieval; and

b) Methods for sperm preparation.

For the embryo, interventions include:

a) Methods for fertilization;

b) Methods to support early embryonic growth;

c) Methods for preparation for transfer;

d) Methods for embryo storage for future transfers;

e) Selection of embryos for transfer;

f) Timing of embryo transfer;

g) Number of embryos to transfer.

Our focus here is on interventions that can feasibly be evaluated using randomized trials; as mentioned in the Introduction, there was almost no literature on the male partner, so this section focuses on interventions focusing on the female partner and the embryo. The effect of broader interventions, such as insurance coverage for specific procedures, is more difficult to evaluate. Although there are some data on the effects of varying insurance policies on outcomes, the evaluation of the effectiveness of these policies involves completely different methods. The available data, and their implications for clinical care and policy, are discussed in the final chapter of this report.

Our general approach to study inclusion and summarization was similar to the one used for studies of ovulation induction and superovulation. As described in the Methods chapter, we excluded all non-randomized studies, as well as "quasi-randomized" studies (such as those where treatment assignment was based on alternate history numbers or clinic days). For this topic, the primary outcome of interest was the cumulative number of clinical pregnancies or, preferably, live births per couple; wherever possible, we used the number of women/couples randomized as the denominator. We excluded any study where these outcomes were not reported or calculable from the presented results.

For the primary outcomes, relative risks (RRs) with 95 percent CIs were calculated from the presented results. Because of substantial clinical heterogeneity in the studies in terms of patient characteristics (such as BMI in studies of PCOS) and treatment regimens, we did not perform formal meta-analyses.

Results for other outcomes, such as multiple pregnancy or spontaneous abortion rates, are summarized in the text. The majority of included studies were extremely limited in power to detect differences in the primary outcomes, let alone any differences in other less common outcomes. Outcomes related to later pregnancy and longer term maternal and child outcomes are discussed under Question 4.

III. Search Results

The flow of articles on this topic through the literature search and screening process is depicted in Figure 4.

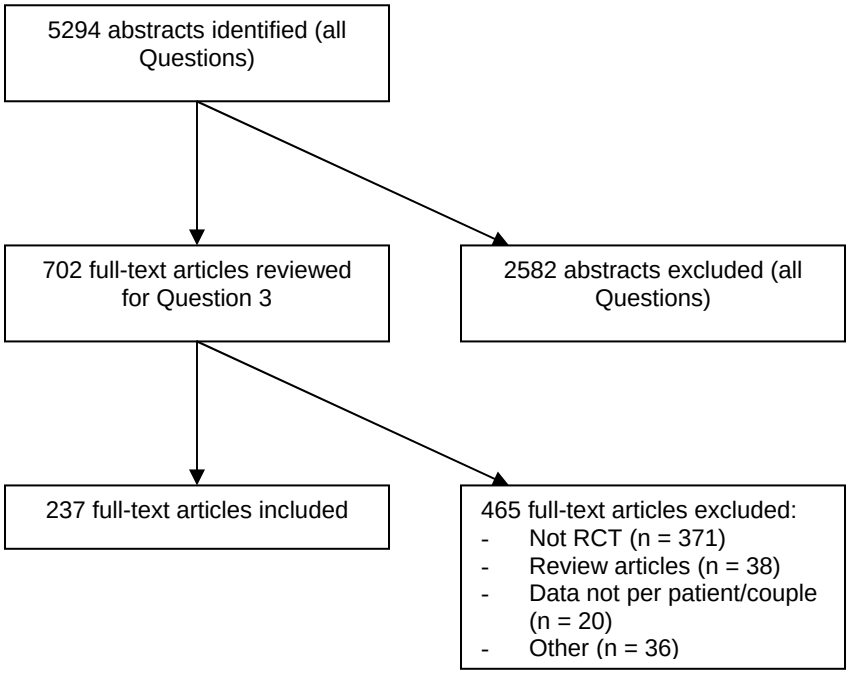

Figure 4. Literature flow diagram – Question 3

IV. The Female Partner

Up to and including embryo transfer, the overall immediate short-term goal of each step in the IVF process is to maximize the probability of success at the next step, with the ultimate goal of maximizing the likelihood of a healthy live birth. This is usually achieved by maximizing the number of "units" available for the subsequent step. Thus, controlled ovarian hyperstimulation aims at maximizing the number of follicles suitable for oocyte retrieval, where as many eggs as possible are retrieved, after which as many embryos as possible are cultured. All other things being equal, increasing the number of embryos improves the likelihood that at least one will develop and progress to a live birth.

Unfortunately, this "maximization" strategy increases the risk of multiple pregnancies, as well as the risk of OHSS. As a rule, the ultimate goal for comparative trials of these steps is to identify interventions that maximize the chances of a healthy live birth while minimizing the risks of multiple pregnancy and complications such as OHSS.

A. Methods for pituitary down-regulation. In the normal menstrual cycle, ovulation is triggered by a surge of luteinizing hormone (LH) in response to feedback mechanisms involving ovarian hormones at the level of the hypothalamus and pituitary. Hyperstimulation of the ovaries with exogenous gonadotropins in women with a normal hypothalamic/pituitary/ovarian axis alters these feedback mechanisms and, potentially, the timing of the LH surge. Since the goal of hyperstimulation in the setting of IVF is to have as many eggs as possible to retrieve through the development of as many follicles as possible, a premature spontaneous LH surge may lead to ovulation prior to retrieval, forcing the cancellation of the entire IVF cycle.[124]

Two general approaches have been used. The "classic" technique involves the use of a gonadotropin-releasing hormone (GnRH) agonist, given beginning 2 to 3 weeks before the IVF cycle. More recently, direct antagonists of the GnRH receptor, which do not require pre-treatment, have been introduced.

1. Included studies. We identified nine studies comparing different aspects of GnRH agonist administration that met our inclusion criteria (Table 15). In general, none of the comparisons of timing, dose, or type of agonist showed significant improvements in pregnancy or, when reported, live birth rates. The one exception was a comparison of a reduced dose of triptorelin compared to the standard dose, which showed significant improvement in both cycle-specific pregnancy rates and cumulative rates when using subsequent frozen embryo transfer.[125]

Table 15. Methods for pituitary down-regulation – GnRH agonists alone†

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
GnRH agonist: dosing/timing/type									
Dal Prato et al., 2004[125]	Reference	3.50 mg triptorelin	90						
		1.87 mg triptorelin	90	**1.65**	**1.03**	**2.65**	-	-	-
				*Cumulative pregnancy rate with frozen transfer **1.69 (1.19, 2.41)**; intent-to-treat outcomes better than reported results*					
Yim et al., 2001[126]	Reference	3.50 mg triptorelin	30						
		1.87 mg triptorelin	30	0.67	0.27	1.64	-	-	-
Dal Prato et al., 2001[127]	Reference	Depot triptorelin (3.50 mg)	66						
		Daily triptorelin (100 ug until menses, then 50 ug)	66	0.92	0.57	1.46	-	-	-
Fabregues et al., 2005[128]	Reference	0.1 mg triptorelin daily	68						
		0.1 mg triptorelin daily, then 0.5 mg	69	1.02	0.68	1.54	-	-	-
Garcia-Velasco et al., 2000[129]	Reference	Long protocol (leuprolide)	34						
		Stop protocol (stop with onset menses)	36	0.79	0.26	2.34	-	-	-
Simons et al., 2005[130]	Reference	Long protocol	58						
		Short protocol (triptorelin) (stop on day of gonadotropin start)	58	1.31	0.70	2.44	1.33	0.69	2.56
		Medium protocol (triptorelin) (stop day 4 gonadotropins)	62	1.41	0.78	2.57	1.17	0.60	2.28

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Orvieto et al., 2002[131]	Reference	Depot agonist (leuprolide)	26						
		Depot agonist (triptorelin)	26	0.42	0.17	1.02	-	-	-
Dor et al., 2000[132]	Reference	hMG only	26						
		Intranasal GnRH agonist (buserelin)	24	1.30	0.46	3.71	-	-	-
		IM GnRH agonist (triptorelin)	24	1.52	0.56	4.14	-	-	-
Isikoglu et al., 2007[133]	Reference	GnRH agonist stop with hCG administration	91						
		GnRH agonist through day 12 post-transfer	90	0.99	0.74	1.33	1.07	0.73	1.58

† All studies had 1.0 cycles/patient unless otherwise noted.

We identified 14 studies directly comparing GnRH agonists and antagonists (Table 16). Pregnancy rates did not differ significantly in any of the individual studies, although none were adequately powered or designed as equivalency studies. In studies where relative OHSS rates were calculable, rates were consistently lower with antagonists, although this was statistically significant in only one.[134]

Table 16. Methods for pituitary down-regulation – GnRH agonists versus antagonists†

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
GnRH agonists vs GnRH antagonists									
Albano et al., 2000[135] and Ludwig et al., 2000[134] (OHSS results)	Reference	Agonist (buserelin)	88						
		Antagonist (ganirelix)	188	0.89	0.57	1.40	0.84	0.51	1.38
				Multiples (twins) 2.10 (0.49, 1.38); ***OHSS 0.18 (0.04, 0.91)***					
Bahceci et al., 2005[136]	Reference	Agonist (leuprolide)	59						
		Antagonist (cetrorelix)	70	1.02	0.76	1.36	-	-	-
				Equivalent multiples					
Barmat et al., 2005[137]	Reference	Agonist (leuprolide)	41						
		Antagonist (ganirelix)	38	0.82	0.47	1.41	0.76	0.42	1.38

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Check et al., 2004[138]	Reference	Agonist (leuprolide)	28						
		Antagonist (ganirelix)	19	0.74	0.34	1.62	0.98	0.42	2.31
European and Middle East Orgalutran Study Group, 2001[139]	Reference	Agonist (triptorelin)	111						
		Antagonist (ganirelix)	226	0.93	0.67	1.29	-	-	-
				Multiples not reported; OHSS 0.12 (0.01, 1.09)					
Hohmann et al., 2003[140]	Reference	Agonist (triptorelin) long protocol	45						
		Antagonist (cetrorelix) day 2	48	0.94	0.43	2.04	-	-	-
		Antagonist (cetrorelix) day 5	49	0.92	0.42	2.00	-	-	-
Lee et al., 2005[141]	Reference	Agonist (buserelin)	20						
		Daily antagonist (cetrorelix) beginning day 5	20	1.11	0.58	2.14	-	-	-
		Single dose antagonist (cetrorelix) day 7	20	0.56	0.23	1.37	-	-	-
Olivennes et al., 2000[142]	Reference	Agonist (triptorelin)	39						
		Antagonist (cetrorelix)	115	0.80	0.44	1.47	-	-	-
Sauer et al., 2004[143]	Reference	Agonist (leuprolide)	25						
		Antagonist (cetrorelix)	25	1.00	0.54	1.87	-	-	-
		Antagonist + midcycle rLH	24	0.95	0.50	1.81	-	-	-
Vlaisav-ljevic et al., 2003[144]	Reference	Agonist (goserelin)	226						
		Antagonist (cetrorelix)	236	1.08	0.83	1.40	1.06	0.80	1.41
				Multiples 0.66 (0.33, 1.33); severe OHSS 0.55 (0.16, 1.84)					
Borme and Man-naerts, 2000[145]	Reference	Agonist (buserelin)	238						
		Antagonist (ganirelix)	463	**0.76**	**0.59**	**0.99**	0.81	0.61	1.07
				Multiples 0.69 (0.38, 1.24) ; OHSS 0.65 (0.30, 1.65)					
Loutradis et al., 2004[146]	Reference	Agonist (triptorelin)	58						
		Antagonist (cetrorelix)	58	0.79	0.39	1.58	-	-	-
Zikopou-los et al., 2005[147]	Reference	Agonist (buserelin)	29						
		Antagonist (cetrorelix)	36	0.99	0.58	1.71	0.72	0.29	1.81
				Multiples 1.21 (0.38, 3.88)					

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Fluker et al., 2001[148]	Reference	Agonist (leuprolide)	105						
		Antagonist (ganirelix)	208	0.93	0.68	1.28	0.86	0.61	1.20
				OHSS 3.03 (0.69, 13.2)					

[†] All studies had 1.0 cycles/patient unless otherwise noted.

We identified one other randomized trial comparing a GnRH long agonist protocol to a protocol of pre-treatment with oral contraceptives, clomiphene citrate plus rFSH, and rLH plus prednisolone in 194 subjects;[149] pregnancy rates were not significantly different (RR 1.20; 95% CI 0.86-1.67), and OHSS rates were lower with the clomiphene-based regimen (RR 0.23; 0.07-0.79). We did not find any additional studies evaluating this regimen.

Studies that compared different dosing, timing, or types of GnRH antagonists did not show significant differences in pregnancy rates (Table 17). However, three studies of pre-treatment with oral contraceptives (in order to allow scheduling of the beginning of the stimulation cycle) followed by an antagonist suggest, at best, no benefit and possibly worse outcomes with this regimen. Oral contraceptives followed by an antagonist had similar pregnancy rates compared with long protocol GnRH agonist in a small study of PCOS patients who had previously failed clomiphene,[150] and non-significantly lower rates in a larger trial (which excluded PCOS subjects).[151] In the Rombauts study[151] and two others comparing the addition of pre-treatment with OCPs to GnRH antagonists alone,[152,153] pregnancy rates were lower, significantly so in one.[152]

Table 17. Methods for pituitary down-regulation – GnRH antagonist regimens

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
GnRH antagonists: dosing/timing /type									
Wilcox et al., 2005[154]	Reference	Cetrorelix	87						
		Ganirelix	88	0.94	0.67	1.31	-	-	-
Escudero et al., 2004[155]	Reference	GnRH antagonist when lead follicle > 14 mm	51						
		GnRH antagonist on day 6 after gonadotropins	45	1.15	0.75	1.75	-	-	-
Mochtar and the Dutch Banirelix Study Group, 2004[156]	Reference	GnRH antagonist when lead follicle > 14 mm	101						
		GnRH antagonist on day 6 after gonadotropins	103	1.45	0.92	2.28	1.43	0.89	2.28

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
GnRH antagonist + OCPs									
Hwang et al., 2004[150]	Reference	Long agonist (buserelin)	29						
	PCOS patients	OCP pre-treatment + antagonist (ganirelix)	27	1.07	0.53	2.17	-	-	-
Huirne et al., 2006[152]		*Gonadotropin + antagonist (Antide)*	32						
		OCP pre-treatment + antagonist (antid)	32	**0.34**	**0.12**	**0.95**	0.52	0.17	1.54
Kolibianakis et al., 2006[153]	Reference	Gonadotropin + antagonist (ganirelix)	250						
		OCPs cycle prior to COH + Gonadotropin + antagonist	254	-	-	-	0.86	0.62	1.20
				Pregnancy loss 1.73 (0.92, 3.29)					
Rombauts et al., 2006[151]	Reference	Agonist (naferelin)	111						
		Antagonist (ganirelix)	110	-	-	-	0.89	0.54	1.46
		OCP + ganirelix	111	-	-	-	0.69	0.40	1.19

We identified six studies in patients with either a history of a poor response to standard hyperstimulation protocols,[157-159] a low likelihood of a good response based on age or basal FSH levels,[160,161] or endometriosis[162] (Table 18). The five studies comparing antagonists to agonists did not show significant differences or a consistent pattern of one type of agent being superior to the other. In the one study comparing two GnRH agonist protocols, a short protocol was significantly inferior to a long protocol.

Table 18. Down-regulation protocols in patients at risk of poor response

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
History of poor response									
Cheung et al., 2005[157]	Reference	Agonist (buserelin)	32						
		Antagonist (cetrorelix)	31	1.72	0.45	6.59	-	-	-
		Poor responders							
Malmusi et al., 2005[158]	Reference	Agonist (triptorelin) flare	30						
		Antagonist (ganirelix)	25	0.60	0.17	2.16	-	-	-
		Poor responders							
Marci et al., 2005[159]	Reference	Agonist (leuprolide)	30						
		Antagonist (cetrorelix)	30	2.50	0.53	11.89	8.00	0.44	144.8
		Poor responders							
Likely to have poor response									
De Placido et al., 2006[160]	Reference	Agonist (triptorelin) +LH	66						
		Antagonist (ganirelix)	67	0.81	0.44	1.51	-	-	-
		High risk for poor response based on age or basal FSH							
Sbracia et al., 2005[161]	Reference	Long protocol (buserelin)	110						
		Short protocol (buserelin)	110	**0.48**	**0.25**	**0.91**	-	-	-
		Age ≥ 40							
Endometriosis									
Pabuccu et al., 2007[162]	Reference	Agonist (triptorelin)	122						
		Antagonist (cetrorelix)	124	0.83	0.56	1.23	-	-	-
				Results similar for different subgroups (Stage I-II, resected endometrioma, active endometrioma)					

2. Other systematic reviews. We did not identify any relevant non-Cochrane reviews.

3. Cochrane reviews. There are three relevant Cochrane reviews, which are summarized in Table 19. The first, updated in September 2004, focuses on comparisons of a long-acting depot form of a GnRH agonist to daily administration.[163] No significant differences in pregnancy or live birth rate were found, although the gonadotropin requirement was lower with daily administration.

The second review[124] performed a meta-analysis of studies comparing GnRH agonists to antagonists. Pooled data showed a significant reduction in both pregnancy (OR 0.83; 95 percent CI 0.72-0.95) and live birth (OR 0.82; 0.68-0.97), multiple pregnancy rates were not significantly different (OR 0.82; 0.57-1.18). Antagonists significantly lowered the risk of severe OHSS (OR 0.61; 0.42-0.89), as well as the dosage and duration of gonadotropin required.

Finally, a review of interventions for poor responders[164] did not find sufficient evidence to draw conclusions about efficacy for any of the regimens reviewed.

Table 19. Cochrane reviews, pituitary down-regulation

Interventions		N	Efficacy					
			Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
			Relative Effect	Lower 95% CI	Upper 95% CI	Relative Effect	Lower 95% CI	Upper 95% CI
GnRH agonist – daily vs. depot[163]								
Reference	Daily	289						
	Depot	263	0.94	0.65	1.37	0.85	0.54	1.36
	6 studies, 1 post-2000					*4 studies, 1 post-2000, n = 392*		
GnRH agonists vs. antagonists[124]								
Reference	GnRH agonist	1804						
	GnRH antagonist	2554	**0.83**	**0.72**	**0.95**	**0.82**	**0.68**	**0.97**
						15 studies, all post-2000, n = 2973		
Poor responders[164]								
GnRH agonist – long vs. stop protocol								
Reference	Stop protocol	74						
	Long protocol	74	0.86	0.31	2.37	0.51	0.04	5.91
	2 studies, 1 post-2000, outcomes per cycle					*1study, pre-2000, n = 78, ongoing pregnancy/cycle*		
GnRH agonist vs. antagonist								
Reference	Long protocol	30						
	Antagonist	30	2.80	0.50	15.7	-	-	-
	1 study, post-2000		*Significantly fewer units gonadotropin required with antagonist*					
GnRH agonist vs. bromocrytine								
Reference	Long protocol	31	**5.60**	**1.40**	**22.5**	3.65	0.88	15.1
	Bromocrytine	32						
	1 study, pre-2000							

4. Conclusions. Only a few of the studies we identified had adequate power to detect differences in pregnancy or live birth rates, let alone less common outcomes such as multiple pregnancy or OHSS. We did not identify clear evidence of the superiority of any specific protocol involving GnRH agonists. In the setting of endometrial preparation for frozen-thawed embryo transfer, two relatively large studies had conflicting results regarding the benefit of adding an agonist; further research is needed.

Although only one individual study comparing GnRH agonists to antagonists found a significant difference in pregnancy or live birth rates (in favor of agonists), formal meta-analysis shows a significantly lower pregnancy and live birth rate with the use of antagonists; antagonists do result in significant decreases in gonadotropin requirements, and a significant decrease in the risk of OHSS.

Pre-treatment with an oral contraceptive to assist with scheduling GnRH antagonist cycles resulted in decreases in pregnancy rates in all three identified studies; this reduction was statistically significant in one.

Finally, although there is no clear evidence for superiority of any strategy for improving outcomes in patients with a history of poor response, a long GnRH agonist protocol was superior to a short GnRH protocol in women over 40 in one trial.

B. Methods for ovarian stimulation. Once endogenous gonadotropin down-regulation has occurred, exogenous gonadotropins need to be administered in order to stimulate follicular development. A variety of preparations are available. The classic method uses human menopausal gonadotropin (hMG), which contains both LH and FSH; in addition to hMG, pure FSH, derived either from urine (uFSH) or as a recombinant form (rFSH), is also available. All three of these can stimulate follicular development alone. Because LH is part of normal follicular development in ovulating women, adding recombinant LH (rLH) to protocols using rFSH theoretically may improve outcomes.[165] In addition, some women do not produce multiple follicles (usually defined as three or more) in response to standard stimulation protocols and are classified as "poor responders;" women who are above age 35, or who have elevated levels of FSH early in a spontaneous cycle, are at increased risk of poor response.[164]

1. Included studies. We identified 38 studies meeting inclusion criteria. Results are summarized in tables for comparisons of rFSH versus hMG, rFSH versus uFSH, and different rFSH preparations (Table 20); rFSH alone versus rFSH plus rLH (Table 21); various gonadotropin dosing regimens (Table 22); methods of administering gonadotropins (Table 23); and protocols for stimulation in poor responders (Table 24). Of all the studies, only two individual studies showed a significant improvement in pregnancy rates: individualized dosing protocol based on a nomogram was superior to a fixed dose regimen,[166] and a regimen of urinary FSH for 6 days followed by rFSH was superior to FSH alone.[167] Only one study[168] was explicitly designed as an equivalence trial. From both a statistical and regulatory perspective, demonstrating equivalence or non-inferiority requires specific a priori hypotheses about the degree of difference in efficacy, and in general requires a larger sample size than studies designed to demonstrate superiority.[36] This means that, in spite of a lack of demonstrable superiority of one preparation or another, it is not possible to conclude that the preparations are in fact equivalent in efficacy.

Table 20. Ovarian stimulation – different gonadotropin preparations

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Single gonadotropin: rFSH vs. HMG									
Andersen et al., 2006[169]	Reference	rFSH	368						
		hMG	363	1.20	0.93	1.55	1.19	0.92	1.53
European and Israeli Study Group, 2002[168]	Reference	rFSH	354						
		Highly purified hMG	373	1.19	0.92	1.55	1.13	0.86	1.49
				Multiple gestation 0.89 (0.58, 1.36)					

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Wester-gaard et al., 2001[170]	Reference	Subcutaneous agonist + rFSH	92						
	GnRH agonist: buserelin	Subcutaneous agonist +hMG	89	-	-	-	1.16	0.74	1.82
		Intranasal agonist + hMG	100	-	-	-	1.44	0.95	2.17
		Intranasal agonist + rFSH	98	-	-	-	1.05	0.66	1.66
Gordon et al., 2001[171]	Reference	rSH (0 LH)	39						
		uFSH (0.1 IU LH)	30	0.47	0.17	1.34	0.24	0.06	0.99
		hMG 25 IU LH	30	0.95	0.43	2.06	0.71	0.30	1.70
		hMG 75 IU LH	29	1.34	0.68	2.66	1.10	0.53	2.30
Ng et al., 2001[172]	Reference	rFSH	20						
		hMG	20	1.25	0.39	3.99	-	-	-
				Multiples 1.34 (0.62, 1.89)					
Strehler et al., 2001[173]	Reference	rFSH	296						
		hMG	282	1.08	0.83	1.40	-	-	-
Dickey et al., 2003[174]	Reference	Follitropin-β	118						
		Highly purified FSH	120	1.11	082	1.52	1.09	0.76	1.55
Kilani et al., 2003[175]	Reference	rFSH	50						
		Highly purified hMG	50	0.93	0.51	1.72	0.92	0.45	1.88
rFSH vs. urinary FSH									
Schats et al., 2000[176]	Reference	rFSH	247						
		Highly purified urinary FSH	249	0.76	0.53	1.09	-	-	-
Selman et al., 2002[177]	Reference	rFSH							
		Highly purified urinary FSH		1.26	0.95	1.69	1.29	0.93	1.79
Frydman et al., 2000[178]	Reference	rFSH	139						
		Urinary FSH	139	1.00	0.61	1.65	0.97	0.65	1.45
				OHSS 0.43 (0.11, 1.62)					
Mohamed et al., 2006[179]	Reference	rFSH	128						
		uFSH	129	-	-	-	1.09	0.63	1.86
Pacchia-rotti et al., 2007[167]	Reference	rFSH only	61						
		uFSH for 6 days, followed by rFSH	58	**2.02**	**1.15**	**3.56**	-	-	-
Different recombinant FSHs									
Moon et al., 2007[180]	Reference	rFSH (follitropin	48						
		DA-3801	49	0.73	0.34	1.58	0.80	0.37	1.76

Table 21. Ovarian stimulation – rFSH alone versus rFSH + rLH

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
FSH vs. FSH + LH									
Humaidan et al., 2004[181]	Reference	rFSH	115						
		rFSH + rLH	116	1.19	0.82	1.72	-	-	-
Marrs et al., 2004[182]	Reference	rFSH	219						
		rFSH + rLH	212	1.02	0.82	1.28	-	-	-
Tarlatzis et al., 2006[183]	Reference	rFSH	59						
		rFSH +rLH	55	0.69	0.32	1.46	0.64	0.25	1.65
Koicihi et al., 2006[184]	Reference	GnRH agonist + uFSH	66						
		GnRH antagonist + uFSH	63	0.67	0.44	1.02	-	-	-
		GnRH antagonist + uFSH + hCG	63	0.73	0.49	1.10	-	-	-
Griesinger et al., 2005[185]	Reference	rFSH	65						
	GnRH antagonist	rFSH + rLH	62	0.70	0.31	1.59	-	-	-
Levi-Setti et al., 2006[186]	Reference	rFSH	20						
		rFSH + rLH	20	1.17	0.48	2.86	-	-	-
		Antagonist							
Serafini et al., 2006[187]	Reference	GnRH agonist + uFSH	98						
		GnRH antagonist + uFSH	96	0.93	0.67	1.30	-	-	-
		GnRH antagonist + uFSH + hCG	103	1.25	0.94	1.66	-	-	-
Drakakis et al., 2005[188]	Reference	rFSH	22						
		rFSH + hMG	24	0.76	0.27	2.15	-	-	-
		1st 4 days of stimulation							
Balasch et al., 2001[189]	Reference	rFSH	14						
		rFSH +LH	16	0.21	0.01	4.33	-	-	-

Table 22. Ovarian stimulation – gonadotropin dosing regimens

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Aboulghar et al., 2004[190]	Reference	Standard dose gonadotropins	72						
		↑ by 75 IU from time of GnRH antagonist	79	1.15	0.74	1.79	-	-	-
		GnRH antagonist		*Multiples 0.97 (0.49, 1.93)*					
Klinkert et al., 2005[191]	Reference	150 IU rFSH	26						
		300 IU rFSH	26	0.30	0.04	3.00	0.50	0.05	5.18
		Low antral follicle count							
Out et al., 2004[192]	Reference	150 IU rFSH	132						
		200 IU rFSH	132	-	-	-	0.78	0.53	1.16
Popovic-Todorovic et al., 2003[166]	Reference	Standard step-up FSH	131						
		Individualized dose based on nomogram	131	**1.50**	**1.03**	**2.18**	-	-	-
Hoomans et al., 2002[193] and Ng et al., 2000[194]	Reference	200 IU rFSH	166						
		100 IU rFSH	163	1.12	0.72	1.75	1.10	0.67	1.81
Latin-American Puregon IVF Study Group, 2001[195]	Reference	150 IU rFSH	201						
		250 IU rFSH	203	0.99	0.64	1.53	-	-	-
Hugues et al., 2003[196]	Reference	rFSH dose prepared by bioassay	65						
		rFSH dose prepared by mass	66	1.16	0.67	2.01	-	-	-
Propst et al., 2006[197]	Reference	Constant dose rFSH	30						
		Step-up protocol	30	0.86	0.59	1.25	1.06	0.69	1.62
Scholtes et al., 2004[198]	Reference	150 IU rFSH daily	51						
		450 IU rFSH every 3 days	51	1.86	0.81	4.27	0.83	0.27	2.56

Table 23. Ovarian stimulation – methods of administering gonadotropins

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Greco et al., 2005[199]	Reference	rFSH via syringe	152						
		rFSH via injector	148	1.17	0.89	1.53	-	-	-
Platteau et al., 2003[200]	Reference	rFSH via syringe	104						
		rFSH via injector	96	1.02	0.70	1.49	0.99	0.66	1.47

Table 24. Protocols for stimulation in poor responders

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Gomez-Palomares et al., 2005[201]	Reference	rFSH + rLH 1st 5 days stimulation	36						
		rFSH + hMG 1st 5 days stimulation	58	**0.47**	**0.25**	**0.87**	-	-	-
		Women > 38 years							
De Placido et al., 2005[202]	Reference	rFSH step-up	65						
		rFSH + rLH	65	1.46	0.79	2.71	-	-	-
		Poor responders							
De Placido et al., 2001[203]	Reference	rFSH step-up	23						
		hMG	20	1.44	0.71	2.93	-	-	-
		Initial poor ovarian response							
Fabregues et al., 2006[204]	Reference	rFSH	60						
		rFSH + LH	60	1.04	0.68	1.60	-	-	-

2. Other systematic reviews. We did not identify any relevant non-Cochrane reviews.
3. Cochrane reviews. There are two relevant Cochrane reviews[165,205] (Table 25). In the review of hMG versus rFSH, last updated in August 2002,[205] hMG was significantly superior to rFSH in terms of pregnancy rates (OR 1.28; 95 percent CI 1.11-1.54), and nearly so for live birth rates (OR 1.27; 0.98-1.64). hMG required significantly more medication, however, and the rate of multiple gestations was higher (OR 1.48; 0.98-2.16). In the review of rFSH versus rFSH plus rLH,[165] the addition of rLH to rFSH significantly increased live birth rates in previous poor responders (OR 1.85; 95 percent CI 1.10-3.11).

Table 25. Cochrane reviews, ovarian stimulation

Interventions	N	Efficacy					
		Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
		Relative Effect	Lower 95% CI	Upper 95% CI	Relative Effect	Lower 95% CI	Upper 95% CI
hMG vs. rFSH[205]							
No down-regulation							
Reference rFSH	54						
hMG	35	0.94	0.35	2.53	0.73	0.26	8.20
1 study, pre-2000							
Short protocol GnRH agonist							
Reference rFSH	296						
hMG	288	1.11	0.77	1.60	-	-	-
1 study, post-2000							
Long protocol GnRH agonist							
Reference rFSH	603						
hMG	611	**1.28**	**1.11**	**1.54**	1.27	0.98	1.64
4 studies, all post-2000		*Multiples 1.48 (0.98-2.16), significant increase in gonadotropin dose with hMG*					
rLH + rFSH vs. rFSH alone[165]							
rLH + rFSH vs. rFSH alone, GnRH agonist down-regulation							
Reference rFSH only	630						
rFSH + rLH	626	1.15	0.91	1.45	1.51	0.79	2.87
7 studies, all post-2000					*2 studies, n = 22;*		
rLH + rFSH vs. rFSH alone, GnRH antagonist down-regulation							
Reference rFSH only	24						
rFSH + rLH	25	0.79	0.26	2.43	0.83	0.39	1.80
					2 studies, both post-2000, n = 166		
rLH + rFSH vs. rFSH alone, GnRH agonist down-regulation, poor responders							
Reference rFSH only	155						
rFSH + rLH	155	-	-	-	**1.85**	**1.10**	**3.11**
3 studies							

4. Conclusions. Trials of methods for ovarian stimulation in the setting of IVF, like those of methods for pituitary down-regulation, are consistently underpowered to detect differences in pregnancy rates or live birth rates, and few are specifically designed to demonstrate equivalence in these outcomes. Power to detect less common outcomes such as multiple pregnancy or OHSS is even lower. There is evidence from one trial that pregnancy rates are superior with an individualized dosing regimen of rFSH compared to fixed dosing. Pooled results of individual trials suggest that hMG is superior to rFSH in long protocol GnRH agonist regimens, with higher multiple pregnancy rates, and that the addition of rLH to rFSH improves live birth rates in poor responders.

C. Methods for follicular maturation. In a spontaneous ovulatory cycle, final maturation and rupture of the follicle, resulting in release of the ovum, is triggered by a surge in LH; this surge also promotes luteinization, resulting in production of the progesterone necessary for endometrial preparation for implantation and early placentation.[206] In controlled hyperstimulation, although ovum release is not needed (or desirable), human chorionic

gonadotropin (hCG), which has biological activity similar to LH, has traditionally been given to induce final maturation prior to oocyte retrieval. Recent developments that might theoretically improve outcomes are the development of recombinant hCG (rhCG), which would provide a purer, more consistent product than urinary LH (uLH), and recombinant LH (rLH), which, because of a shorter duration of action, might reduce the risk of OHSS. An alternative approach in patients treated with a short-acting GnRH antagonist could be induction of an endogenous LH surge through administration of a GnRH agonist.

1. Included studies. Studies meeting inclusion criteria are shown in Table 26. One study evaluated two different protocols for timing of administration of hCG.[207] Under ultrasound monitoring beginning on day 6 of stimulation, subjects were randomized to administration of hCG as soon as at least three follicles had reached at least 17 mm in diameter, or 2 days after this point. Live birth rates were significantly lower in the late hCG group (RR 0.72; 95 percent CI 0.53-0.98); including biochemical pregnancies and miscarriages, early pregnancy loss was two-fold greater in the late hCG group.

Three studies randomizing women to urinary versus recombinant hCG showed no difference in pregnancy or live birth rates,[208-210] although minor adverse events, especially injection site reactions, were more common with urinary hCG. In the one study that included two different doses of rhCG, there was a trend towards an increased rate of OHSS at the higher dose (RR 2.93; 95 percent CI 0.75-11.4).[210]

Two studies comparing uhCG to rLH did not demonstrate significant differences in pregnancy or live birth rate.[211,212]

Finally, four studies compared hCG to a GnRH agonist in women receiving a GnRH antagonist for down-regulation.[213-216] Three showed significantly decreased pregnancy rates with the use of the agonist, with significantly higher early loss rates. A fourth, conducted in women considered at high risk of OHSS because of PCOS or prior response to stimulation, showed no difference in pregnancy rates, but significantly lower OHSS rates; this study used a different GnRH agonist and included suppression with oral contraceptives and GnRH agonist before beginning GnRH antagonists.

Table 26. Methods for inducing final follicular maturation

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
hCG timing									
Kolibi-anakis et al., 2004[207]	Reference	hCG when at least 3 follicles at least 17 mm	208						
		hCG 2 days later	205	0.87	0.68	1.13	**0.72**	**0.53**	**0.98**
		Down-regulation with antagonist		*Cycles/patient 1.0; multiples 0.52 (0.24, 1.14); higher early loss rate with late hCG*					
uhCG vs. rhCG									
Euorpean rhCG Study Group, 2000[208]	Reference	uhCG	93						
		rhCG	97	1.50	0.80	2.82	1.26	0.65	2.43
				Multiples 0.95 (0.36, 2.52); OHSS 1.13 (0.36, 3.49)					
Driscoll et al., 2000[209]	Reference	uhCG	40						
		rhCG	44	0.89	0.26	3.04	1.42	0.37	5.45

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Chang et al., 2001[210]	Reference	uhCG	92						
		rhCG 250 IU	94	0.97	0.53	1.76	1.02	0.55	1.90
		rhCG 500 IU	89	1.00	0.55	1.84	1.00	0.53	1.88
				250 IU : Multiples 0.59 (0.24, 1.44); OHSS 0.98 (0.19, 4.98) 500 IU: Multiples 0.71 (0.30, 1.68); OHSS 2.93 (0.75, 11.4)					
hCG vs. LH									
European Recombinant LH Study Group, 2001[211]	Reference	uHCG	121						
		rLH (various doses)	129	0.73	0.42	1.29	0.82	0.42	1.61
				No moderate/severe OHSS in single dose rLH, 12% in uHCG, but individual groups all < 55					
Manau et al., 2002[212]	Reference	uhCG	15						
		rLH	15	1.00	0.23	4.31	-	-	-
				Multiples 0.22 (0.01, 5.25); OHSS 4.62 (0.19, 111)					
hCG vs. GnRH agonist after down-regulation with GnRh antagonist									
Humaidan et al., 2005[213]	Reference	hCG	67						
		GnRH agonist (buserelin)	55	**0.15**	**0.05**	**0.48**	-	-	-
		Down-regulation with antagonist		*Early loss **16.5 (2.06, 139)***					
Humaidan et al., 2006[214]	Reference	hCG	15						
		Buserelin + hCG 12 hours later	17	**0.22**	**0.06**	**0.88**	-	-	-
		Buserelin + hCG 35 hours later	13	0.87	0.41	1.84	-	-	-
		Down-regulation with antagonist							
Kolibianakis et al., 2005[215]	Reference	hCG	54						
		GnRH agonist (triptorelin)	52	**0.14**	**0.03**	**0.58**	-	-	-
		Down-regulation with antagonist		*Early loss **6.61 (1.72, 25.4)***					
Engmann et al., 2008[216]	Reference	hCG	32						
		GnRH agonist (leuprolide)	33	1.10	0.67	1.80	1.11	0.65	1.88
		Down-regulation with antagonist after OCP/agonist treatment		*OHSS signfifcantly lower 0.05 (0.001, 0.76); all subjects high risk for OHSS*					

2. Other systematic reviews. We did not identify any other non-Cochrane reviews.

3. Cochrane reviews. The relevant Cochrane review (Table 27),[206] updated February 2005, quantitatively found no difference in pregnancy or live birth rates between uhCG or rHCG, with a significant decrease in any adverse event, particularly injection site reactions (OR 0.47; 95 percent CI 0.32-0.70). Similarly, there was no difference in pregnancy or live birth rates between uhCG and rLH; an unpublished trial showed that doses of rLH required to prevent OHSS led to decreased pregnancy rate, and further development of the product for this indication was halted.

Table 27. Cochrane review, methods for follicular maturation[206]

Interventions		N	Efficacy					
			Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
			Relative Effect	Lower 95% CI	Upper 95% CI	Relative Effect	Lower 95% CI	Upper 95% CI
uhCG vs. rhCG								
Reference	uhCG	324						
	rhCG	423	0.98	0.71	1.36	0.98	0.69	1.39
	4 studies, all post-2000					*Severe OHSS 1.89 (0.74, 4.82); any adverse event **0.47 (0.32, 0.70)***		
uhCG vs. rLH								
Reference	uhCG	136						
	rLH	144	0.93	0.53	1.63	0.94	0.50	1.76
	2 studies, both post-2000					*Severe OHSS 0.82 (0.39,1.62)*		

4. Conclusions. Timing of hCG administration for follicular maturation is important for optimizing live birth rates – delays of 48 hours after one ultrasound threshold (at least three follicles of at least 17 mm) resulted in significant decreases in live births. The optimal time and threshold have not been determined. There does not appear to be any difference in pregnancy or live birth rates, or other major outcomes, between rhCG and uhCG, although injection site reactions are more common with uhCG. In cycles using a GnRH antagonist for pituitary down-regulation, use of hCG is superior to use of a GnRH agonist in most women, although agonists significantly lowered the risk of OHSS without affecting pregnancy rate in one trial of high-risk women.

D. Methods for oocyte retrieval. The current standard of care for oocyte retrieval is transvaginal aspiration under ultrasound guidance.

1. Included studies. We identified one trial of different techniques for retrieval in PCOS patients, and seven trials comparing different methods for analgesia (Table 28). Branigan and colleagues[217] compared a standard protocol, where only follicles with a diameter of at least 10 mm (those believed to have the greatest likelihood of a fertilizable ovum) were aspirated, to a "thorough" protocol, where any "possible" follicle, down to 4 mm, was aspirated, in women with PCOS scheduled for IVF; those women who did not conceive after IVF were followed. The "thorough" protocol resulted in a higher pregnancy rate (RR 15.1; 95 percent CI 0.91-250) subsequent to the IVF cycle. Results for the entire randomized group, which includes 31 women who conceived during the IVF cycle, were not presented. Cumulative pregnancy and live birth rates for both the IVF and non-IVF cycles would be preferable.

Choice of analgesia did not significantly affect pregnancy rates in any of the studies. In general, overall pain scores were similar between the interventions, although variations in the scales, as well as types and dosing of analgesic agents and doses used, prevent any between-study comparisons. In studies where one arm did not include some kind of sedation,[218,219] or used a lower level of sedation,[220] peri-procedural pain was significantly higher, although this did not appear to have any impact on overall patient preferences.

Table 28. Methods for oocyte retrieval

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Methods for retrieval									
Branigan et al., 2006[217]	Reference	Standard retrieval	30						
		"Thorough" retrieval	34	15.1	0.91	250	-	-	-
		PCOS patients; pregnancy after IVF		*0 pregnancies in standard group*					
Analgesia									
Cerne et al., 2006[221]	Reference	Paracervical block	87						
		Pre-ovarian block	91	0.92	0.56	1.50	-	-	-
				No difference in pain scores					
Humaidan et al., 2006[222]	Reference	Fixed frequency acupuncture	76						
		Mixed frequency electro-acupuncture	76	0.91	0.61	1.34	-	-	-
				No difference in pain scores					
Stener-Victorin et al., 2003[223]	Reference	Alfentanyl + paracervical block (no sedation)	138						
		Electro-acupuncture + paracervical block	136	0.89	0.64	1.24	-	-	-
				No difference in pain scores					
Humaidan et al., 2004[218]	Reference	Alfentanyl + paracervical block (with sedation)	100						
		Electro-acupuncture + paracervical block	100	0.85	0.49	1.48	-	-	-
				Higher peri-procedural pain in electroacupuncture group, shorter hospital times and costs					
Ng et al., 2001[219]	Reference	Paracervical block + placebo	75						
		Paracervical block + conscious sedation	75	0.93	0.44	1.96	-	-	-
				Peri-procedural pain significantly higher with block alone					
Lok et al., 2002[220]	Reference	Physician-controlled sedation	55						
		Patient - controlled sedation	55	0.55	0.21	1.46	-	-	-
				Peri-procedural pain scores higher with patient-controlled, but patient preferences higher					

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Thompson et al., 2000[224]	Reference	IV analgesia	55						
		Inhalational analgesia	57	1.46	0.51	4.15	-	-	-
				No differences in pain scores					

2. Other systematic reviews. We did not identify any non-Cochrane reviews.

3. Cochrane reviews. The relevant Cochrane review[225] found no difference in pregnancy rates. Intraoperative pain scores by visual analog scale were significantly higher with electroacupuncture compared to standard treatment, as well as with patient controlled sedation compared to physician controlled sedation.

4. Conclusions. Choice of analgesia for oocyte retrieval does not appear to affect pregnancy rates. Techniques involving some form of sedation result in lower intraoperative pain, but this does not appear to adversely affect overall patient perceptions and satisfaction.

E. Methods for endometrial preparation in frozen-thawed transfer. In the setting of transfer of frozen-thawed embryos from previous cycles, controlled ovarian hyperstimulation is obviously not necessary, but methods to improve preparation of the endometrium for implantation are frequently used. Since frozen embryo transfer from previous cycles is one potential way to maximize cumulative pregnancy rates while minimizing the risk of multiple gestations (see the section on the number of embryos transferred [section G under "The Embryo"], below), identifying the optimal method for preparation should be a high priority.

1. Included studies. Two studies compared the use of estrogen with and without a GnRH agonist (Table 29). Both were relatively large. In one,[226] the GnRH agonist used did not significantly improve pregnancy rates; in the other,[227] both pregnancy and live birth rates were significantly improved with the use of the agonist (RR for live birth 2.30; 95 percent CI 1.15-4.62). Both the type of agonist and the estrogen formulation used differed between the two studies. A third, smaller study[228] compared regimens in women with unsuppressed cycles and found no difference in rates with oral estradiol followed by vaginal progesterone when endometrial thickness reached 7 mm compared with FSH on cycle days 6, 8, and 10 plus hCG to trigger ovulation.

Table 29. Methods for pituitary down-regulation – endometrial preparation for frozen-thawed embryo transfer

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
GnRH agonist vs. none with artificial endometrial preparation									
Dal Prato et al., 2002[226]	Reference	No agonist + transdermal estradiol	150						
		Agonist (triptorelin) + transdermal estradiol	146	0.85	0.54	1.32	-	-	-
El-Toukhy et al., 2004[227]	Reference	No agonist + oral estrogen	117						
		Agonist (buserelin) + oral estrogen	117	**1.57**	**1.05**	**2.34**	**2.30**	**1.15**	**4.62**
Estradiol + progesterone vs. FSH in unsuppressed cycles									
Wright et al., 2006[228]	Reference	No agonist + estrogen	99						
		No agonist + FSH	100	0.91	0.42	1.96	-	-	-

2. Other systematic reviews. We did not identify any other systematic reviews.

3. Cochrane reviews. The most recent Cochrane review, published in January 2008,[229] is summarized in Table 30. The effectiveness of no intervention (natural cycle) transfer compared to endometrial preparation was evaluated in only one small trial, with subsequent wide confidence intervals. There was insufficient evidence to draw conclusions about other regimens, although there was an overall trend to higher pregnancy rates with the addition of GnRH agonists to estradiol/progesterone.

Table 30. Cochrane review, endometrial preparation for frozen-thawed embryo transfer[229]

Interventions		N	Efficacy					
			Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
			Relative Effect	Lower 95% CI	Upper 95% CI	Relative Effect	Lower 95% CI	Upper 95% CI
Estrogen /progesterone vs. natural cycle								
Reference	Natural	44						
	Estrogen/ progesterone	56	1.06	0.40	2.80			
	1 study, pre-2000							
Estrogen/ progesterone vs. GnRH agonist + estrogen/progesterone								
Reference	GnRH agonist + E/P	353						
	Estrogen/progesterone	372	0.76	0.52	1.10	**0.38**	**0.17**	**0.84**
	4 studies, 3 post-2000					*1 study, post-2000,, n=234*		
Estrogen/progesterone vs. FSH								
Reference	Estrogen/progesterone	94						
	FSH	100	0.84	0.35	2.02			
	2 studies, 1 post-2000							

Interventions		N	Efficacy					
			Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
			Relative Effect	Lower 95% CI	Upper 95% CI	Relative Effect	Lower 95% CI	Upper 95% CI
GnRH agonist + estrogen/ progesterone vs. clomiphene								
Reference	GnRH a + E/P	37						
	Clomiphene	67	0.42	0.12	1.47			
	1 study, post-2000							
Estrogen/progesterone vs. clomiphene								
Reference	Estrogen/progesterone	52						
	Clomiphene	67	0.76	0.21	2.77			
	1 study, post-2000							
hMG vs. clomiphene								
Reference	hMG	102						
	Clomiphene	107	0.46	0.23	0.92			
	1 study, pre-2000							

4. Conclusions. There is insufficient evidence to determine the optimal method for endometrial preparation for frozen-thawed embryo transfer.

F. Methods for embryo transfer. Methods for fertilization, embryo culture, selection and timing of transfer are discussed below. In the majority of procedures in the United States, embryos are transferred back into the uterus using a thin transcervical catheter.

1. Included studies. Studies meeting inclusion criteria are shown in Table 31. Berkkanoglu and colleagues randomized patients to either standard transfer protocol or irrigation with embryo culture media.[230] Although reported rates were similar for the two arms, a much larger number of randomized subjects were excluded from the flushing arm (48 vs. 12) in the analysis, a difference that seems unlikely to be random. When analyzed by intention-to-treat, pregnancy and live birth rates were significantly lower in the flushing group (live birth RR 0.67; 95 percent CI 0.47-0.95).

A Swedish study found no differences in pregnancy rates after ultrasound-guided transfer by a trained midwife or physician.[231]

A study of prophylactic antibiotics found no difference in pregnancy rates, despite a significantly reduced rate of bacterial contamination of the catheter.[232]

Two studies of different catheter types detected no difference in pregnancy rates.[233,234] The third, comparing a catheter with a fixed metal obturator to a soft catheter where use of a metal obturator was optional, found significantly higher pregnancy rates with the soft catheter (RR 1.32; 95 percent CI 1.08-1.60).[235]

Timing of catheter withdrawal did not affect pregnancy rates.[236]

Three studies of embryo transfer media containing hyaluronic acid compared to standard media[237-239] all showed improved pregnancy rates with media containing hyaluronic acid, with one[237] showing significantly increased rates.

Table 31. Methods for embryo transfer

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Pre-transfer irrigation									
Berk-kanoglu et al., 2006[230]	Reference	No treatment	120						
		Irrigation of endometrial cavity prior to embryo transfer	120	**0.59**	**0.42**	**0.83**	**0.67**	**0.47**	**0.95**
Type of provider									
Bjuresten et al., 2003[231]	Reference	Gynecologist	51						
		Midwife	51	1.07	0.59	1.92	-	-	-
Prophylactic antibiotics									
Brook et al., 2006[232]	Reference	No treatment	130						
		Antibiotic (750 mg co-amoxiclav 12 + 2 hours prior to transfer	154	1.01	0.77	1.34	-	-	-
				Bacterial contamination significantly reduced with antibiotic ***0.79 (0.64, 0.98)***					
Transfer catheter type									
Rhodes et al., 2007[233]	Reference:	Cook catheter	49						
		Edwards-Wallace	50	0.92	0.67	1.26	-	-	-
Van Weering et al., 2002[235]	Reference	TDT catheter	657						
		Cook catheter	632	1.32	1.08	1.60	-	-	-
McIlveen et al., 2005[234]	Reference	Cooke	75						
		Wallace	75	0.96	0.59	1.56	-	-	-
Timing of catheter withdrawal									
Martinez et al., 2001[236]	Reference	Withdrawal 30 sec after transfer	49						
		Immediate withdrawal	51	0.88	0.66	1.17	-	-	-
Transfer media									
Friedler, et al., 2007[237]	Reference	No hyaluronic acid	50						
		Hyaluronic acid	51	**3.53**	**1.42**	**8.78**	**9.76**	**2.38**	**39.99**
Korosec, et al., 2007[238]	Reference	No hyaluronic acid	37						
		Hyaluronic acid	28	1.44	0.75	2.77	-	-	-
				Similar results in 214 subjects undergoing frozen-thawed transfer 1.10 (0.59, 2.03)					
Mahani and Davar, 2007[239]	Reference	No hyaluronic acid	30						
		Hyaluronic acid	30	1.57	0.71	3.50	1.80	0.68	4.74

Ultrasound guidance of the transfer resulted in higher pregnancy rates in all but one of the studies identified (Table 32); this difference was significant in five of the eight studies. The one study which did not show any difference[240] varied from the others in several ways. First, a single operator performed all of the procedures – an overall benefit of ultrasound guidance among multiple practitioners does not rule out the possibility of no difference for individuals. Second, there were two unplanned interim analyses involving the investigators rather than a separate statistical or data and safety monitoring board, a process which is somewhat unorthodox for clinical trials.

Table 32. Methods for embryo transfer – ultrasound guidance

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Coroleu et al., 2000[241]	Reference	Clinical	180						
		Ultrasound	182	**1.48**	**1.15**	**1.90**	**1.62**	**1.23**	**2.13**
De Camargo Martins et al., 2004[242]	Reference	Clinical	50						
		Ultrasound	50	1.40	0.82	2.39	-	-	-
		All patients judged to be "easy" by mock transfer							
Li et al., 2005[243]	Reference	Clinical	152						
		Ultrasound	178	**1.48**	**1.06**	**2.07**	-	-	-
Matorras et al., 2002[244]	Reference	Clinical	260						
		Ultrasound	255	**1.45**	**1.04**	**2.02**	**1.57**	**1.08**	**2.29**
				Multiple pregnancy rate 1.10 (0.63, 1.92)					
Corolau et al., 2006[245]	Reference	Standard catheter	95						
		Echogenic catheter	98	1.32	0.97	1.78	-	-	-
				*Twin rate among pregnancies significant higher with echogenic catheter **4.17 (1.31, 13.24)***					
Coroleu et al., 2002[246]	Reference	Clinical	91						
		Ultrasound	93	**1.74**	**1.06**	**2.87**	-	-	-
				Multiple pregnancy 0.56 (0.21, 2.91); miscarriage 0.98 (0.33, 2.91)					
Tang et al., 2001[247]	Reference	Clinical	400						
		Ultrasound	400	1.16	0.90	1.48	1.24	0.95	1.62
				Multiple pregnancy 1.34 (0.82, 2.18)					
Kosmas et al., 2007[240]	Reference	Clinical	150						
		Ultrasound	150	1.00	0.77	1.30	1.24	0.95	1.62
				Multiple pregnancy 1.34 (0.82, 2.18)					

2. Other systematic reviews. We did not identify any other non-Cochrane reviews.

3. Cochrane reviews. The relevant Cochrane review, updated November 2006, concluded that ultrasound guidance significantly improved both pregnancy (OR 1.49; 95 percent CI 1.29-1.72) and live birth rates (OR 1.40; 1.18-1.66).[248] Multiple pregnancy rates were increased, but not significantly (OR 1.26; 0.91-1.75) and ectopic rates non-significantly decreased (OR 0.64; 0.25-1.61).

4. Conclusions. Pre-transfer irrigation does not improve pregnancy or live birth rate, and, based on an intention-to-treat analysis of the one study identified, significantly reduces both

rates. There is no evidence that type of provider changes outcomes. Although pre-treatment with antibiotics significantly lowers measurable bacterial contamination, this does not translate into improved pregnancy or live birth rates. Hyaluronic acid containing media may result in higher pregnancy rates compared to other media.

Ultrasound-guided embryo transfer consistently results in substantial improvements (40 percent relative increase) in pregnancy and live birth rates compared to various "clinical touch" methods. The consistency of this finding and the size of the effect are striking considering that the majority of interventions covered in this review do not show significant differences.

G. Methods for luteal support. Aspiration of follicular cells during oocyte retrieval and suppression of GnRH can inhibit luteinization, which is necessary for progesterone production. The use of exogenous progesterone significantly increases pregnancy rates compared to placebo or no treatment.[249] This section reviews studies published since 2000 that evaluate different progesterone-based regimens; varying routes of administration and timings of these regimens; alternatives to progesterone; and adjunctive treatments.

1. Included studies. Nine studies evaluated different formulations of progesterone (Table 33). In two studies, one with 205 subjects[250] and another with 734,[251] intramuscular progesterone resulted in higher pregnancy and live birth rates, with lower miscarriage rates in the larger study (RR 0.33; 95 percent CI 0.20,0.55), compared to vaginal progesterone. One study did not detect a significant difference between vaginal and oral progesterone.[252] The remaining studies compared various formulations for vaginal administration; none detected a significant difference in pregnancy rates.

Table 33. Methods for luteal support – progesterone formulations

Study	Interventions		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Vaginal vs. intramuscular									
Propst et al., 2001[250]	Reference	Progesterone gel	108						
		IM progesterone	99	1.62	0.94	2.81	**2.05**	**1.13**	**3.73**
Unfer et al., 2004[251]	Reference	Vaginal progesterone	373						
		Intramuscular 17-hydroxyprogesterone	361	**1.59**	**1.27**	**2.00**	**1.50**	**1.17**	**1.92**
				Miscarriage rate IM compared to vaginal 0.33 (0.2, 0.55)					
Vaginal vs. oral									
Chakravarty et al., 2005[252]	Reference	Vaginal micronized progesterone	351						
		Oral dygesterone	79	1.06	0.68	1.23	-	-	-
Vaginal formulations									
Kleinstein and Luteal Phase Study Group, 2005[253]	Reference	Vaginal progesterone gel	212						
		Vaginal progesterone in oil	218	1.14	0.81	1.60	-	-	-

Study	Interventions		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Geber et al., 2007[254]	Reference	Micronized progesterone capsules	122						
		Micronized progesterone gel	122	1.23	0.90	1.67	1.24	0.87	1.77
Ludwig et al., 2002[255]	Reference	Micronized progesterone capsules	53						
		Micronized progesterone gel	73	1.52	0.78	2.96	1.45	0.71	2.98
Tay and Lenton, 2005[256]	Reference	Progesterone vaginal capsules	55						
		Progesterone rectal	35	0.99	0.53	1.85	-	-	-
		Progesterone gel	36	1.03	0.56	1.89	-	-	
		hCG	35	0.99	0.53	1.85	-	-	-
Zegers-Hochschild et al., 2000[257]	Reference	IM progesterone	262						
		Vaginal ring	243	1.00	0.79	1.26	-	-	-
Ng et al., 2003[258]	Reference	Progesterone suppository	30						
		Progesterone gel	30	0.71	0.22	2.25	-	-	-
				Patient preference for gel					

Four studies evaluated hCG (Table 34). Compared to a standard GnRH agonist long protocol with no supplementation, hCG substantially increased pregnancy rates. This increase was not significant, probably due to the small sample size.[259] In three studies comparing hCG to progesterone, there were no significant differences in pregnancy or live birth rates.[256,260-262]

Table 34. Methods for luteal support – hCG

Study	Interventions		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
hCG vs. placebo									
Beckers et al., 2000[259]	Reference	Long protocol, no support	20						
		Short protocol, no support	20	7.06	0.33	151	-	-	-
		Long, protocol, hCG	20	10.0	0.49	203	-	-	-
hCG vs. progesterone									
Ludwig et al., 2001[260]	Reference	Progesterone only	191						
		hCG only	77	1.01	0.69	1.47	0.80	0.43	1.50
		Progesterone + hCG	145	0.79	0.47	1.33	1.01	0.63	1.60
Vimpeli et al., 2001[261]	Reference	Vaginal progesterone	45						
		hCG	44	0.87	0.35	2.15	-	-	-

Study	Interventions		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Martinez et al., 2000[262]	Reference	Progesterone	168						
		hCG	147	0.78	0.49	1.25	-	-	-
Tay and Lenton, 2005[256]	Reference:	Progesterone vaginal capsules	55						
		Progesterone rectal	35	0.99	0.53	1.85	-	-	-
		Progesterone gel	36	1.03	0.56	1.89	-	-	-
		hCG	35	0.99	0.53	1.85	-	-	-

Four studies evaluated different regimens for the timing of beginning or ending progesterone supplementation (Table 35). None found a significant difference.

Table 35. Methods for luteal support – timing of beginning or ending progesterone supplementation

Study	Interventions		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Nyboe Andersen et al., 2002[263]	Reference	Cessation of progesterone with + hCG	150						
		Continue progesterone for 3 weeks after hCG	153	1.02	0.95	1.11	1.04	0.94	1.17
Baruffi et al., 2003[264]	Reference	400 mg vaginal progesterone day of transfer	52						
		400 mg vaginal progesterone day of retrieval	51	0.95	0.51	1.76	-	-	-
Mochtar et al., 2006[265]	Reference	Progesterone beginning day of embryo transfer	127						
		Day of ovum retrieval	127	0.95	0.66	1.37	1.03	0.64	1.70
		Day of hCG for ovulation trigger	130	0.79	0.53	1.16	0.98	0.66	1.67
Williams et al., 2001[266]	Reference	Progesterone day 3 after oocyte retrieval	59						
		Progesterone day 6 after oocyte retrieval	67	0.73	0.52	1.03	-	-	-

Finally, we reviewed studies of adjuncts to progesterone (Table 36). The addition of hCG on days 1, 4, and 7 after transfer significantly increased pregnancy rates (RR 2.31; 95 percent CI 1.06-5.03) in a subsequent cycle in poor responders.[267] The addition of estrogens significantly increased pregnancy and live birth rates in GnRH agonist suppression protocols in two of three studies.[268,269] Finally, a single administration of GnRH agonist added to progesterone and

estrogen support increased pregnancy rates in patients using either a GnRH agonist or antagonist suppression protocol; the increase was significant in the antagonist group (RR 1.41; 95 percent CI 1.04-1.91).

Table 36. Methods for luteal support – adjuncts to progesterone

Study	Interventions		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Progesterone + hCG									
Fujimoto et al., 2002[267]	Reference	IM progesterone	51						
		IM progesterone + hCG days 1, 4, 7 after transfer	63	**2.31**	**1.06**	**5.03**	-	-	-
		Patients who did not conceive during 1st cycle, low luteal E2							
Ludwig et al., 2001[260]	Reference	Progesterone only	191						
		hCG only	77	1.01	0.69	1.47	0.80	0.43	1.50
		Progesterone + hCG	145	0.79	0.47	1.33	1.01	0.63	1.60
Progesterone + estrogen									
Unfer et al., 2004[268]	Reference	Progesterone + placebo	98						
		Progesterone + phytoestrogens	115	**1.93**	**1.34**	**2.77**	**1.91**	**1.23**	**2.96**
Lukaszuk et al., 2005[269]	Reference	P only	50						
		P + 2 mg E2	47	1.42	0.89	2.26	-	-	-
		P + 6 mg E2	69	**1.61**	**1.06**	**2.45**	-	-	-
				Multiple pregnancies significantly higher with E2 regimens (0% P only, 30.4% 2 mg E2, 25.6% 6 mg E2)					
Tay and Lenton, 2003[270]	Reference	Progesterone only	35						
		Progesterone + E2	28	0.76	0.27	2.15	-	-	-
Fatemi et al., 2006[271]	Reference	600 mg progesterone 1 day after retrieval	100						
		600 mg progesterone + 4 mg E2 valerate	101	-	-	-	1.14	0.73	1.79
		GnRH antagonist + rFSH		*Early pregnancy loss 0.98 (0.43, 2.26)*					
Progesterone + estrogen + GnRH agonist									
Tesarik et al., 2006[272]	Reference	P + E2 + Placebo	300						
		P + E2 +GnRH agonist (triptorelin)	300	1.19	0.98	1.45	-	-	-
				GnRH antagonist suppression: ***1.41 (1.04, 1.91)***					

2. Other systematic reviews. We did not identify any other non-Cochrane reviews.

3. Cochrane reviews. The most recent Cochrane review was most recently updated in May 2004 (Table 37).[249] Quantitative findings were largely similar to the qualitative findings described above. Intramuscular progesterone resulted in higher pregnancy and live birth rates

compared to either oral or vaginal progesterone, although this was significant only for live births in the vaginal versus intramuscular group, likely because of the small number of subjects in the oral progesterone studies. Interestingly, multiple pregnancies were significantly increased with intramuscular compared to oral progesterone, even with the small sample size (OR 7.88; 95 percent CI 1.10-56.2), consistent with some implantation advantage. Significant differences were not detected between the different vaginal progesterone formulations.

hCG was significantly better than placebo in terms of live birth rates (OR 1.94; 95 percent CI 1.25-3.01) and miscarriages (OR 0.27; 0.11-0.61). Rates of multiple gestation (OR 2.77; 0.47-16.5) and moderate/severe OHSS (OR 11.17; 1.45- 86.2) were higher.

The addition of hCG to progesterone did not significantly increase pregnancy or live birth rates. In the two studies included in the meta-analysis, the addition of estrogen did not improve pregnancy or live birth rates; however, all three of the studies published subsequent to the Cochrane review do show improved rates.

Table 37. Cochrane review, methods for luteal support[249]

Interventions		N	Efficacy					
			Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
			Relative Effect	Lower 95% CI	Upper 95% CI	Relative Effect	Lower 95% CI	Upper 95% CI
PROGESTERONE FORMULATIONS								
Oral vs. IM progesterone								
Reference	Oral	44						
	IM	39	2.28	0.90	5.82	2.57	0.99	6.70
	2 studies, 1 post-2000							
Vaginal vs. IM progesterone								
Reference	IM	870						
	Vaginal	872	0.82	0.67	1.01	**0.73**	**0.56**	**0.96**
	10 studies, 7 post-2000					*6 studies, 3 post-2000, n=1044*		
Vaginal vs. oral progesterone								
Reference	Oral	164						
	Vaginal	159	1.51	0.93	2.45	1.32	0.79	2.19
	2 studies, 1 post-2000							
Vaginal gel vs. other vaginal								
Reference	Other vag	154						
	Gel	169	1.10	0.67	1.82	1.14	0.62	2.10
	4 studies, 1 post-2000					*2 studies, 1 post-2000, n = 225*		
hCG								
hCG vs. placebo/no treatment								
Reference	Control	431						
	hCG	433	1.27	0.91	1.78	**1.94**	**1.25**	**3.01**
	7 studies, 1 post-2000					*5 studies, 1 post-2000, n = 645*		
Progesterone vs. hCG								
Reference	hCG	806						
	Progesterone	825	1.07	0.85	1.34	0.94	0.70	1.27
	14 studies, 4 post-2000					*9 studies, 2 post-2000, n = 1038*		
ADJUNCTS TO PROGESTERONE								
Progesterone + hCG vs. progesterone								
Reference	Progesterone	576						
	Progesterone + hCG	575	1.10	0.84	1.43	1.05	0.69	1.60
	8 studies, 4 post-2000					*3 studies, 1 post-2000*		

Interventions	N	Efficacy					
		Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
		Relative Effect	Lower 95% CI	Upper 95% CI	Relative Effect	Lower 95% CI	Upper 95% CI
Progesterone + estrogen vs. progesterone alone							
Progesterone	85						
Prog + Estrogen	78	0.89	0.43	1.84	*0.89*	*0.34*	*2.32*
2 studies, 1 post-2000					*1 study, pre-2000, n = 100*		

4. Conclusions. Some form of luteal support is necessary with IVF, since both progesterone and hCG result in improved pregnancy rates compared to no treatment. Although there is no detectable difference between oral progesterone and the various formulations of vaginal progesterone, both result in lower pregnancy and live birth rates compared to intramuscular progesterone. The addition of estrogen to progesterone may improve outcomes, although additional larger studies are needed to confirm these findings. Finally, adding stimulation with a GnRH agonist to progesterone and estrogen in patients down-regulated with a GnRH antagonist improves live birth rates.

H. Other adjunct treatments. A variety of adjunctive treatments have been proposed to help improve pregnancy and live birth rates, decrease multiple pregnancy rates, or prevent complications related to IVF, in both first-line treatment and in patients who either have a worse prognosis or have failed previous therapy.

1. Included studies. We identified seven studies of medical therapy (Table 38). Two involved vasoactive agents[273,274] and did not detect any significant differences. Five other studies involved the use of aspirin, with or without a corticosteroid, or a non-steroidal anti-inflammatory drug (NSAID). Only one showed a significant effect: in a placebo-controlled trial, administration of the NSAID piroxicam 1 day prior to embryo transfer increased pregnancy rates by almost 70 percent (RR 1.69; 95 percent CI 1.14-2.50).[275]

Table 38. Medical therapy

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Vasoactive agents									
Battaglia et al., 2002[273]	Reference	Placebo	19						
		L-arginine	18	-	-	-	0.53	0.15	1.80
Pinheiro et al., 2003[274]	Reference	No treatment	45						
		Terbuatline 10 mg/day x 15 days at oocyte retrieval	90	1.00	0.57	1.75	-	-	-
		Ritodrine 20 mg/day, same schedule	90	0.77	0.42	1.40	-	-	-
Anti-inflammatory/immune system modulation									
Duvan et al., 2006[276]	Reference	No treatment	40						
		Aspirin 100 mg/day	41	0.77	0.40	1.48	-	-	-
		Prednisolone 10 mg/day	50	1.26	0.74	2.13	-	-	-
		Aspirin + prednisolone	56	0.97	0.55	1.69	-	-	-
Moon et al., 2004[275]	Reference	Placebo 1-2 hr prior to transfer	94						
		Piroxicam 10 mg/day prior to transfer	94	**1.69**	**1.14**	**2.50**	-	-	-
Pakkila et al., 2005[277]	Reference	Placebo from gonadotropins until menses or pregnancy test							
		Aspirin 100 mg/day		-	-	-	0.87	0.57	1.34
Ubaldi et al., 2002[278]	Reference	Aspirin 100 mg/day	156						
		Aspirin + prednisolone 5 mg/BID from day 1 of stimulation for 4 weeks	159	0.98	0.79	1.23	1.07	0.81	1.41
Urman et al., 2000[279]		No treatment	136						
		Aspirin 80 mg/day from start of hMG through negative pregnancy test or +FHR	139	0.91	0.69	1.21	-	-	-

Six studies evaluated non-medical adjuncts (Table 39). Cha and Wirth found a two-fold higher pregnancy rate in subjects randomized to receiving intercessory prayer, where strangers prayed specifically for success (RR 2.07; 95 percent CI 1.34-3.22).[280] We did not identify any similar studies, and this particular one raised multiple methodological questions, including issues regarding informed consent. Three studies of acupuncture all showed improvement in pregnancy

and/or live birth rates.[281-283] The three studies differed in the nature of the intervention, as well as the nature of the control – ranging from no acupuncture to acupuncture with a "sham" needle to active acupuncture of points thought to be unrelated to reproduction – making interpretation of the results difficult. Finally, a large Australian study found no differences in pregnancy rates between couples who were asked to abstain from intercourse around the time of embryo transfer and those who were encouraged to engage in intercourse at this time.[284]

Table 39. "Non-medical" adjuncts

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Complementary/alternative medicine									
Intercessory prayer									
Cha and Wirth, 2001[280]	Reference	No prayer	99						
		Prayer	100	**2.07**	**1.34**	**3.22**	-	-	-
Pre-treatment counseling									
Chan et al., 2006[285]	Reference	No counseling	126						
		Eastern Body-Mind-Spirit counseling	101	1.25	0.61	2.57	-	-	-
Acupuncture									
Smith et al., 2006[281]	Reference	Placebo acupuncture (blunt needles)	108						
		Active acupuncture	110	1.24	0.80	1.90	1.38	0.86	2.23
		Immediately before and after transfer							
Dieterle et al., 2006[282]	Reference	Placebo acupuncture (acupuncture on points not related to fertility)	109						
		Active acupuncture	116	**2.16**	**1.30**	**3.58**	**2.07**	**1.19**	**3.59**
		30 minutes before and 30 minutes after transfer							
Wester-gaard et al., 2006[283]	Reference	No acupuncture	100						
		Acupuncture day of embryo transfer	100	-	-	-	**1.76**	**1.11**	**2.79**
		Acupuncture day of transfer + 2 days later	100	-	-	-	1.26	0.74	2.16
				Day of ET + 2 days later vs. day of ET only 0.71 (0.45, 1.10); miscarriage rate highest (33%) day of ET + 2 days later (15% and 21%)					
Peri-transfer abstinence vs. intercourse									
Tremellen et al., 2000[284]	Reference	Abstinence	236						
		Peri-transfer intercourse	242	1.18	0.8	1.73	-	-	-

Finally, several trials of treatments in patients with a lower probability of a successful pregnancy because of known co-conditions or previous ART failure showed benefit (Table 40). Treatment with nitroglycerin,[286] heparin and aspirin,[287] IV immunoglobulin,[288] or letrozole[289] did

not improve pregnancy rates in women with previous poor ovarian response. However, in patients without previous endometrial imaging, hysteroscopy and treatment of any discovered pathology significantly improved both pregnancy and live birth rates compared to repeat treatment without hysteroscopy (RR for live birth 1.70; 95 percent CI 1.22-2.37).[290]

In women aged 40 or older, the addition of dexamethasone[291] or growth hormone[292] both significantly improved outcomes.

In women with PCOS, the addition of metformin reduced the incidence of OHSS and increased pregnancy and live birth rates.[293,294] Both studies were small (52 or fewer subjects/arm), but the differences were significant in the study by Tang and colleagues (RR for live birth 2.67; 95 percent CI 1.15-6.22; for OHSS, 0.48; 0.23, 0.98).[293]

In women with known endometriosis, pre-treatment with a GnRH agonist for 3-6 months prior to initiating an IVF cycle increased pregnancy rates three-fold, although both studies were too small to detect a significant difference.[295,296] The study by Rickes and colleagues[295] is also notable as one of the few IVF studies where cumulative rates over several cycles were used as the endpoint. Laparoscopic removal of endometriomas detected prior to IVF did not improve pregnancy rates significantly.[297]

In patients with hydrosalpinges detected prior to IVF, laparoscopic occlusion or salpingectomy increased live birth rates five- to six-fold.[298] The lower bound of the 95 percent CIs crossed 1.0 for both surgeries combined, but there were only 15 subjects in the no treatment arm, as opposed to 50 in each of the surgical arms. Ectopic pregnancy rates were not evaluable.

Table 40. Adjuncts in patients with poor prognosis

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Previous poor response/implantation failure									
Ohl et al., 2002[286]	Reference	Placebo	68						
		Nitroglycerin 5 mg patch daily from day before transfer until +hCG or menses	70	0.86	0.48	1.55	-	-	-
		Previous implantation failure							
Rama et al., 2006[290]	Reference	No hysteroscopy	255						
		Hysteroscopy/ treatment of pathology	265	**1.64**	**1.28**	**2.10**	**1.70**	**1.22**	**2.37**
		Previous failure							
Stern et al., 2003[287]	Reference	Placebo heparin + aspirin, day of transfer through hCG	74						
		Heparin 5000 u BID + 100 mg aspirin/day	69	-	-	-	1.03	0.46	2.26
		Women with auto-antibodies , previous failure							

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Stephen-son and Fluker, 2000[288]	Reference	Placebo	26						
		IV immuno-globulin within 72 hr preceding transfer, 4 wk later if +hCG	25	1.26	0.32	5.16	-	-	-
		2 or more previous failures							
Goswami et al., 2004[289]	Reference	rFSH	25						
		rFSH + letrozole	13	0.96	0.29	3.23	-	-	-
		Poor ovarian response							
Age > 40									
Avrech et al., 2004[299]	Reference	hMG only	73						
		hMG + buserelin	146	0.69	0.29	1.63	1.17	0.31	4.38
Tesarik et al., 2005[292]	Reference	Placebo	50						
		Growth hormone 8 IU from day 7 until 1 day post-ovulation	50	**-**	**-**	**-**	**5.50**	**1.28**	**23.6**
Keay et al., 2001[291]	Reference	Placebo	145						
		Dexamethasone 10 mg/day	145	**1.56**	**1.00**	**2.44**	-	-	-
				Overall cancellation rate significantly lower in dexamethasone group 0.48 (95% CI 0.23,0.98)					
PCOS									
Tang et al., 2006[293]	Reference	Placebo	49						
		Metformin 850 mg/day from 1st day of down regulation to egg retrieval	52	2.00	0.95	4.21	**2.67**	**1.15**	**6.22**
		PCOS		*Severe OHSS significantly lower in metformin group 0.19 (0.04, 0.82)*					
Kjotrod et al., 2004[294]	Reference	No treatment	36						
		Metformin 1000 mg BID at least 16 weeks until ovulation trigger	37	1.16	0.71	1.87	1.06	0.54	2.09
		PCOS		*OHSS lower in metformin group, small numbers 0.19 (0.02, 1.59)*					
Endometriosis									
Rickes et al., 2002[295]	Reference	No pre-treatment	55						
		GnRH agonist pre-treatment	55	3.33	0.96	11.54	-	-	-
				Cycles/patient: 1.7; control group started sooner post-surgery					
Surrey et al., 2002[296]	Reference	No pre-treatment	26						
		GnRH agonist pre-treatment	25	-	-	-	2.93	0.84	10.25
				Cycles/patient 1.0; control group started sooner post-surgery					
Demirol et al., 2006[297]	Reference	No surgery	50						
		Laparoscopic removal of	49	0.91	0.54	1.54	-	-	-

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
		endometrioma							
Radiologic findings									
Konto-ravdis et al., 2006[298]	Reference	No surgery	15						
		Laparoscopic salpingectomy	50	-	-	-	5.10	0.74	35.2
		Laparoscopic tubal occlusion	50				**6.90**	**1.01**	**46.9**
		Either surgery	100				6.00	0.89	40.5
		Hydrosalpinges					*Salpingectomy vs. occlusion 0.74 (0.45, 1.21)*		
Qublan et al., 2006[300]	Reference	No aspiration	46						
		Cyst aspiration prior to oocyte retrieval	76	1.21	0.32	4.61	-	-	-

2. Other systematic reviews. We did not identify any other non-Cochrane reviews.

3. Cochrane reviews. There are five relevant Cochrane reviews on adjuncts for IVF (Table 41). Reviews of low-dose aspirin (7 studies with over 1200 subjects)[301] and glucocorticoids (13 studies with over 1700 subjects)[302] did not find significant treatment effects.

The review of growth hormone[303] did not find an overall significant treatment effect (OR 1.18; 95 percent CI 0.41-3.37). However, three studies of growth hormone in poor responders published prior to 2000 with a total of 74 subjects had a significant improvement in live birth rates (OR 4.37; 95 percent CI 1.06-18.3). This is consistent with the study by Tesarik and colleagues,[292] which found a five-fold higher live birth rate with growth hormone in women over 40.

Prolonged pre-IVF down- regulation with a GnRH agonist significantly improved pregnancy and live birth rates (OR 9.19; 95 percent CI 1.08-78.2) in three studies with a total of 165 subjects.[304]

Surgical treatment of hydrosalpinges significantly improved pregnancy and live birth rates based on three pre-2000 studies with a total of 295 subjects (OR for live birth 2.13; 95 percent CI 1.24-3.65).[305] This is consistent with the findings of Kontoravdis and colleagues described above.[298]

Table 41. Cochrane reviews, adjunct therapies for IVF

Interventions		N	Efficacy					
			Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
			Relative Effect	Lower 95% CI	Upper 95% CI	Relative Effect	Lower 95% CI	Upper 95% CI
Aspirin[301]								
Reference	Control	622						
	Aspirin	618	1.09	0.93	1.28	0.94	0.63	1.39
	7 studies, 4 post-2000					*2 studies, 1 post-2000, n = 401*		
Steroids[302]								
Reference	Control	865						
	Glucocorticoids	894	1.15	0.93	1.43	1.21	0.67	2.19
	13 studies, 3 post-2000					*3 studies, all pre-2000, n = 424*		
Growth hormone[303]								
	Placebo	48						
	GH	43	1.18	0.41	3.37	1.17	0.38	3.59
	3 studies, all pre-2000		*Poor responders (3 studies, all pre-2000, n = 74, live birth rate increased **4.37 (1.06, 18.3)***					
Endometriosis[304]								
Reference	Control	77						
	Down-regulation	88	**4.28**	**2.00**	**9.15**	**9.19**	**1.08**	**78.2**
	3 studies, 2 post-2000					*1 study, pre-2000, n = 67*		
Surgery[305]								
Reference	No surgery on tube	134						
	Salpingectomy	161	**1.75**	**1.07**	**2.86**	**2.13**	**1.24**	**3.65**
	3 studies, all pre-2000					*Ectopic 0.42 (0.01, 2.14)*		

4. Conclusions. Based on the available evidence, vasoactive agents such as nitroglycerin, beta-agonists, or l-arginine do not improve pregnancy or live birth rates in either first-time or poor prognosis IVF patients. Low-dose aspirin does also not appear to have any effect. The NSAID piroxicam significantly improved pregnancy and live birth rates in a general IVF population, and further studies of NSAIDs are warranted. Randomized trials of intercessory prayer and acupuncture showed benefit, but there are remaining methodological questions which need to be addressed.

Dexamethasone and growth hormone both improved pregnancy and live births in women over 40 undergoing IVF; the growth hormone findings are consistent with earlier studies showing a benefit in poor responders. Metformin reduced the incidence of OHSS, and showed evidence of improvement in pregnancy and live birth rates, in women with PCOS undergoing IVF. Pre-treatment of women with endometriosis with a GnRH agonist for several months prior to IVF improves pregnancy and live birth rates, as do hysteroscopic removal of endometrial lesions and surgical removal or occlusion of hydrosalpinges.

I. Prevention of ovarian hyperstimulation syndrome.

1. Included studies. We identified two studies of interventions designed specifically as prophylaxis against OHSS (Table 42). Gokmen and colleagues[306] found significant reductions in OHSS, with no difference in pregnancy rates, with the use of both hydroxyethyl starch and albumin. In contrast, in a much larger study, Bellver and colleagues[307] found no differences, although the width of the confidence intervals cannot rule out benefit. This may represent differences in patient populations: the rate of OHSS in the no-treatment arm in the Gokmen study was 19.2 percent (16/83) compared to 6.9 percent (21/307) in the Bellver study. There are no other obvious sources for the differences – neither study used placebo or unblended assessment of the endpoints.

Table 42. Interventions to prevent OHSS

Study	Intervention		N	Efficacy					
				OHSS			Clinical/Ongoing pregnancy		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Albumin									
Gokmen et al., 2001[306]	Reference	No treatment	83						
		Prophylactic hydroxyethyl starch	85	**0.29**	**0.11**	**0.75**	1.17	0.54	2.56
		Prophylactic IV albumin	82	**0.25**	**0.09**	**0.72**	1.10	0.49	2.45
Bellver et al., 2003[307]	Reference	No treatment	307						
		Albumin	298	1.10	0.62	1.96	0.78	0.64	0.95

2. Other systematic reviews. We did not identify any other non-Cochrane reviews.

3. Cochrane reviews. There are three relevant Cochrane reviews. The first reviews the use of intravenous albumin[308] and was most recently updated in December 2001. In five studies with a total of 378 subjects, the pooled OR for prevention of OHSS was significantly lower with albumin (OR 0.28; 95 percent CI 0.11-0.73), with no difference in pregnancy rates (OR 1.09; 0.65-1.83). The calculated number-needed-to-treat (NNT) to prevent one case of moderate to severe OHSS based on these estimates was 18. This may explain the difference between the previous studies and that of Bellver and colleagues: although the overall study was much larger, the rate was much smaller. The observed number of cases in the control group, 21, was close to the NNT, meaning that only one or two fewer cases would be expected to be observed in the albumin arm, a difference that would be very unlikely to be detectable.

Two other reviews addressed embryo freezing[309] and coasting (withholding gonadotropins in patients judged to be at risk).[310] There was insufficient evidence to draw any conclusions (two studies of embryo freezing with 26 and 125 subjects that did not show differences, and one study of coasting with a sample size of 30).

4. Conclusions. In one large study published subsequent to the last Cochrane update, IV albumin was not effective in reducing the incidence of moderate to severe OHSS in patients at risk, in contrast to the pooled analysis in the Cochrane review. This difference may be due to the low event rate in the larger study, which resulted in an absolute number of events too small to detect the estimated effect of albumin. Another study with a larger absolute number of subjects would be needed to resolve the issue. Given that many of the interventions discussed above, such as GnRH antagonists, may reduce the risk of OHSS, this may be difficult to accomplish.

V. The Embryo

This section reviews those methods that are applied outside of the female partner's body, from fertilization up to the point of transfer.

A. Fertilization. Although IVF generally results in much higher per-cycle pregnancy rates than interventions that do not involve some type of assisted fertilization, it is possible that other methods might prove equally effective over a longer period of time, providing an alternative for some couples. In addition, although intracytoplasmic sperm injection (ICSI) is now considered the standard of care for couples with male factor infertility, especially severe male factor,[311]

whether or not ICSI improves outcomes compared to traditional IVF in other couples is not clear. Finally, it is possible that some technical aspects of the fertilization process might affect clinical outcomes.

1. Included studies. Studies meeting inclusion criteria are shown in Table 43. In a study comparing treatment in strategies in couples who had not conceived with non-IVF infertility treatment, Hughes and colleagues randomized 139 couples to a cycle of IVF within 6 weeks, or a 90-day "watchful waiting" period.[7] Couples undergoing IVF were significantly more likely to conceive (RR 7.31; 95 percent CI 2.38-23.3) and to have a live birth (RR 20.8; 2.88-151.3). The cumulative 90-day pregnancy rate in the untreated couples was 4.3 percent, which is consistent with the pre-treatment pregnancy rate observed in other large trials.[6]

Goverde and colleagues[312] randomized 178 couples with at least 3 years of infertility (1 year if male factor was a primary cause) to IUI alone, IUI with a mild stimulation protocol, or IVF for up to 6 cycles. Cumulative live births compared to IUI alone were not different with mild stimulation (RR 1.25; 95 percent CI 0.81-1.93) or IVF (RR 1.30; 0.85-2.00). Multiple rates were higher with stimulation (RR 9.00; 1.17-69.4) and IVF (RR 6.40; 0.80-51.0). Patients receiving IVF required fewer cycles.

Three studies comparing IVF to ICSI in patients with non-male factor infertility,[313] tubal factor,[314] or unexplained infertility[315] did not demonstrate significant differences in outcomes between IVF or ICSI.

Three studies of technical aspects of fertilization did demonstrate significant differences in outcomes. Co-incubation of sperm and oocytes for 20 hours resulted in significantly lower live birth rates compared to 2 hour co-incubation (RR 0.59; 95 percent CI 0.43-0.83.[316] Inclusion of n-hydroxyethylpiperazine-n-ethanesulfonate (HEPES) as a buffer in the media used for ICSI significantly reduced pregnancy rate (RR for non-HEPES media 1.34; 95 percent CI 1.08-1.66).[317] Use of a lens warmer for temperature control during the ICSI procedure itself significantly improved live birth rates compared to a thermostat (RR 2.07; 95 percent CI 1.09-3.93).[318]

Table 43. Methods of fertilization

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Observation vs. IVF/ICSI									
Hughes et al., 2004[7]	Reference	90 days wait	71						
		Immediate IVF/ICSI	68	**7.31**	**2.28**	**23.3**	**20.8**	**2.88**	**151.3**
		Failed previous non-IVF therapy		*Cumulative 90-day pregnancy rate in untreated arm 4.3%*					
IUI vs. IVF									
Goverde et al., 2000[312]	Reference	IUI alone	86						
		IUI with mild stimulation	85	-	-	-	1.25	0.81	1.93
		IVF	87	-	-	-	1.30	0.85	2.00
				Cycles/pt: 4.0 IUI with stimulation: Multiples 9.00 (1.17, 69.4) IVF: Multiples 6.40 (0.80, 51.0)					
IVF vs. ICSI									
Bhatta-charya et al., 2001[313]	Reference	IVF	108						
		ICSI	107	0.79	0.59	1.07	-	-	-
		Non-male factor infertility		*Multiples ICSI vs IVF 1.28 (0.71, 2.29)*					
Poehl et al., 2001[314]	Reference	IVF	45						
		ICSI	44	**-**	**-**	**-**	0.68	0.34	1.35
		Tubal factor							
Foong et al., 2006[315]	Reference	IVF	30						
		ICSI	30	1.00	0.60	1.66	1.07	0.63	1.81
		Unexplained							
Technical aspects of fertilization									
Kattera and Chen, 2003[316]	Reference	2 hours	130						
		20 hours	129	-	-	-	**0.59**	**0.43**	**0.82**
		Co-incubation of sperm and oocytes							
Morgia et al., 2006[317]	Reference	HEPES	351						
		No HEPES	357	**1.34**	**1.08**	**1.66**	-	-	-
		Media for ICSI							
Wang et al., 2002[318]	Reference	Thermostat	40						
		Non-thermostat	52	0.69	0.31	1.54	-	-	-
		Lens warmer	29	**2.07**	**1.09**	**3.93**	-	-	-
		Temperature control during ICSI							

2. Other systematic reviews. We did not identify any other non-Cochrane reviews.

3. Cochrane reviews. The relevant Cochrane reviews[319,320] included one trial each, both of which are described above.

4. Conclusions. IVF is superior to watchful waiting in couples who do not conceive after other treatment, but results in similar cumulative pregnancy rates compared to IUI alone or IUI with stimulation, with fewer multiples; time to pregnancy is faster with IVF. Based on the available evidence, outcomes are, at best, no better with ICSI than with IVF in couples without

male factor infertility. Finally, technical aspects of fertilization can have a significant impact on clinical outcomes, and more randomized studies of these technical aspects should be encouraged.

B. Embryo culture.

1. Included studies. We identified two relevant studies that used random allocation of different culture methods and provided data on pregnancy and/or live birth. Quinn and Cooke[321] compared two different media for fertilization and early embryonic development, each formulated to maintain a constant pH under an atmosphere of either five percent or six percent carbon dioxide, and detected no difference. Although the authors stated that the study was designed to show no difference, the sample size of 60 subjects was not adequate to demonstrate equivalence, since the lower bound of the confidence interval was well below 1.0 (RR 1.31; 95 percent CI 0.78-2.19).

Ben-Yosef and colleagues[322] compared two different culture media in 349 subjects; differences were not significant, although there was a trend towards higher rates with the P1 media (RR for pregnancy 1.52; 95 percent CI 0.94-2.43; RR for live birth 1.47; 0.87-2.46).

2. Other systematic reviews. We did not identify any non-Cochrane systematic reviews.

3. Cochrane reviews. Culture conditions were not covered in any Cochrane reviews.

4. Conclusions. There is insufficient evidence to draw any conclusions about the impact of varying culture conditions on clinical outcomes of assisted reproduction.

C. Storage/freezing techniques. Generally, there are more embryos created in a given cycle than can be replaced. These embryos may be frozen (cryopreserved), then thawed and transferred to allow subsequent transfer in the event of a failed cycle or for continuing inability to conceive after a successful first IVF cycle. This section reviews the evidence on the technical aspects of cryopreservation. Other aspects of the IVF process that may have different outcomes in frozen-thawed embryos are discussed in the appropriate section.

1. Included studies. We identified one randomized trial meeting inclusion criteria. Balaban and colleagues randomized 196 couples to cryopreservation with embryo storage in either conventional storage straws, or high-security straws.[323] Because embryos from multiple couples are stored in the same freezer tank, these high-security straws were designed to reduce the theoretical risk of cross-contamination with viral pathogens; physical properties also differ from conventional straws. Equivalent numbers of embryos were transferred in each group. Pregnancy rates were higher with the high-security straws, although the increase did not quite reach statistical significance (RR 1.38; 95 percent CI 0.95-2.00). Multiples were significantly increased (RR 3.42; 1.32-8.85).

2. Other systematic reviews. We did not identify any relevant non-Cochrane reviews.

3. Cochrane reviews. This topic is not covered by any published Cochrane review.

4. Conclusions. The only available evidence on cryopreservation techniques suggests that use of high-security straws for embryo storage increases pregnancy rates; the significant increase in multiple rates suggest that this may be due to improved implantation.

D. Selection of embryos for transfer. A consistent theme throughout this review is that implantation of the embryo is the critical step in determining the outcome of most of the interventions considered here. Improved implantation is the ultimate goal of much of the active research in reproductive medicine; as will be discussed in the section on longer term outcomes, abnormal implantation, resulting from underlying maternal or embryonic characteristics, treatment-specific factors, or both, may contribute to the observed increased risk of certain adverse pregnancy outcomes in infertility patients. The interventions described below – methods for embryo selection for transfer, methods for preparing the embryo for transfer, and number of

embryos to transfer – are all aimed at maximizing the likelihood of at least one successful implantation, ideally without multiple gestation.

1. Included studies. Included studies are shown in Table 44. We identified two randomized trials of two methods for selecting embryos with the highest likelihood of successful implantation.[324,325] Both studies randomized couples to one of two methods. In one arm, selection was based on day 3 morphology and progression scores, and pronuclear morphology assessed on day 1. In the other arm, a score based on the status of zygote cleavage into two cells was added. In both studies, pregnancy rates were not significantly different between arms.

Two studies assessed the use of preimplantation genetic diagnosis (PGD) – a technique in which one or two embryonic cells are removed and examined for known chromosomal abnormalities – in selecting embryos in women 35 years or older.[326,327] In the first study,[326] both pregnancy and live birth rates were lower with PGD, although not significantly. Fewer embryos were transferred in the PGD group: approximately 25 percent of the biopsied embryos were genetically abnormal. In the second study,[327] pregnancy and live birth rates were significantly lower with PGD; since all subjects had two embryos transferred, this difference could not be attributed to fewer transferred embryos.

Table 44. Selection of embryos for transfer

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Embryo scoring									
Chen and Kattera, 2006[324]	Reference	Day 3 morphology + day 1 morphology	165						
		Above + day 1 cleavage	165	0.87	0.61	1.25	-	-	-
Emiliani et al., 2005[325]	Reference	Score only	90						
		Score + cleavage	94	1.13	0.70	1.82	-	-	-
		Single embryo transfer							
Preimplantation genetic diagnosis (PGD)									
Staessen et al., 2004[326]	Reference	Control	190						
		PGD	199	0.71	0.46	1.10	0.72	0.43	1.21
		≥ 37 years		*Multiples 1.43 (0.41, 4.96); number of embryos transferred significantly lower with PGD)*					
Masten-broek, et al., 2007[327]	Reference	Control	206						
		PGD	202	**0.68**	**0.52**	**0.88**	**0.68**	**0.50**	**0.92**
		35-41 years		*All undergoing double embryo transfer*					

2. Other systematic reviews. We did not identify any other non-Cochrane reviews.

3. Cochrane reviews. The relevant review[328] included only studies of PGD. In addition to the paper by Staessen and colleagues described above,[326] a published abstract with an additional 39 subjects was included. Summary odds ratios showed significant reductions in pregnancy rates with PGD (OR 0.56; 95 percent CI 0.32-0.96), with a non-significant reduction in live birth rate (OR 0.64; 0.37-1.09).

4. Conclusions. Although methods for evaluating embryo quality are an active area of research, and various methods are used clinically, we identified only two studies that compared the outcome of two different scoring methods in a randomized trial; neither showed a significant difference in pregnancy rates. Preimplantation genetic diagnosis reduces pregnancy rates when used in women of "advanced maternal age" (a criterion which varies somewhat, but generally includes women aged 35 years or older).

E. Preparation for transfer. Assisted hatching is a procedure that either removes or thins a portion of the outer coat of the embryo, the zona pellucida, based on the hypothesis that unfavorable chemical and physical changes to the zona during embryo culture are a barrier to successful implantation.[329] A variety of methods are used, including laser, mechanical, or chemical disruption.

1. Included studies. Included studies are shown in Table 45, separated by patient population. In four studies in couples with at least one previous failed IVF attempt, assisted hatching generally improved pregnancy and live birth rates, although differences were significant in only one study each for all patients,[330] a subgroup with two or more previous failures,[331] and older women.[332] Multiples were increased, significantly in one study.[330]

Assisted hatching significantly increased,[333] decreased,[334] or had no effect[335,336] on pregnancy rates prior to transfer of frozen-thawed embryos; there is no obvious clinical or methodological explanation for the wide disparity in results.

None of the trials performed for advanced maternal age or other prognostic factors,[334,337-340] or in good prognosis patients[341-343] showed any significant benefit; point estimates for the relative risk were less than 1.0 for all but one study.[343]

Table 45. Assisted hatching

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Previous failure									
Ma et al., 2006[344]	Reference	Control	83						
		Acid assisted hatching	85	1.57	0.95	2.61	1.30	0.72	2.37
		Previous failure, oligospermia		*Multiples 1.5 (0.64, 1.47)*					
Petersen et al., 2005[331]	Reference	Control	75						
		¼ laser hatching	75	1.62	0.87	2.98	1.31	0.68	2.50
		At least 1 previous failure		*2 or more previous failures: pregnancy 3.33 (0.99, 11.2); live birth 3.00 (0.88, 10.2)*					
Rufas-Sapir, et al., 2004[332]	Reference	Control	103						
		Mechanical hatching	104	0.78	0.48	1.27	-	-	-
		≥ 3 previous failures		*Assisted hatching worse for women < 35 (15% vs. 35%), better for women > 40 (30% vs. 22%)*					
Jelinkova et al., 2003[330]	Reference	Control	129						
		Acidic assisted hatching	128	**1.49**	**1.08**	**2.04**	-	-	-
		≥ 2 previous failures		*Multiples **3.02 (1.24, 7.37)***					

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Frozen-thawed embryos									
Nagy et al., 2005[333]	Reference	No lysed cell removal (LCR)	44						
		LCR + laser assisted hatching	44	**2.40**	**1.31**	**4.41**	-	-	-
		Frozen-thawed embryos							
Sifer et al., 2006[335]	Reference	Control	64						
		Pronase assisted hatching	61	0.96	0.46	2.01	-	-	-
		1st frozen-thawed cycle							
Ng et al., 2005[336]	Reference	Control	80						
		Laser zona thinning	80	0.83	0.38	1.82	-	-	-
		Frozen-thawed embryos		*Multiples 3.60 (0.92, 14.1)*					
Primi et al., 2004[334]	Reference	No hatching + placebo	74						
		Hatching + placebo	84	**0.27**	**0.09**	**0.80**	0.33	0.09	1.20
		Hatching + steroid + doxycycline	89	0.70	0.34	1.48	0.83	0.33	2.11
		Frozen-thawed embryos; laser							
Maternal age/poor prognosis									
Petersen et al., 2002[337]	Reference	Control	50						
		Laser zona thinning	50	0.73	0.32	1.65	1.00	0.31	3.24
		≥ 38 years							
Frydman ett al., 2006[260]	Reference	Control	54						
		Laser zona thinning	49	0.89	0.54	1.48	0.76	0.39	1.47
		≥ 37 years							
Makrakis et al., 2006[339]	Reference	Laser	158						
		Mechanical	158	0.77	0.52	1.14	0.84	0.55	1.28
		≥ 39 years							
Primi et al., 2004[334]	Reference	No hatching + placebo	21						
		Hatching + placebo	22	0.57	0.16	2.10	-	-	-
		Hatching + steroid + doxycycline	23	0.91	0.31	2.71	-	-	-
		1st fresh transfer, poor prognosis; laser							
Nadir et al., 2005[340]	Reference	Control	30						
		Laser assisted hatching	60	0.71	0.39	1.28	-	-	-
		Endometriosis							

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Good prognosis									
Sagoskin et al., 2007[341]	Reference	Control	81						
		Laser assisted hatching	118	0.98	0.76	1.28	1.02	0.75	1.39
		Good prognosis							
Baruffi et al., 2000[342]	Reference	Control	51						
		Laser assisted hatching	52	0.83	0.50	1.37	-	-	-
		1st ICSI cycle							
Isik et al., 2000[343]	Reference	Zona intact blastocyst transfer	22						
		Zona free blastocyst transfer (chemical)	24	1.38	0.79	2.39	1.68	0.75	3.77
		> 5 cleavage-stage embryos							

2. Other systematic reviews. We did not identify any non-Cochrane reviews.

3. Cochrane reviews. The relevant Cochrane review,[345] updated in June 2005, includes 24 studies with over 2800 subjects, most predating 2000, and found a statistically significant improvements in pregnancy rates with assisted hatching (OR 1.29; 95 percent CI 1.10-1.52). Only six studies with 516 subjects reported live birth rates; the pooled OR was 1.19 (0.81-1.73).

Multiple pregnancy rate was significantly increased (OR 1.54; 95 percent CI 1.06-2.24). In subgroup analyses, benefit was primarily seen in patients with a poor prognosis or previous implantation failure.

4. Conclusions. Assisted hatching consistently improves pregnancy rates in couples with previous IVF failures; this difference was statistically significant in the largest trial and in pooled meta-analysis, both of which also showed a significant increase in multiple pregnancies. There is insufficient evidence to reach a conclusion about efficacy in other patient populations.

F. Timing of transfer. In natural cycles, fertilization occurs in the fallopian tube. After fertilization, the embryo progresses from a one-cell zygote (fertilization through the first 24 hours) and then, in a process referred to as cleavage, undergoes cell division, reaching eight cells by day 3; over the next several days, division continues and a small cavity, the blastocoel, forms, and differentiation of the cells into those destined to form the placenta and the fetus begins. By day 5, the blastocyst state, the embryo is approximately 80 to 100 cells and has reached the uterine cavity. Implantation generally occurs around day 7.[1]

In IVF, the same embryonic process occurs, but in a culture medium rather than in the mother's reproductive tract, and the embryo is replaced into the uterine cavity. There are trade-offs involved in determining the optimal time for transfer. Earlier transfer shortens the exposure time of the embryo to any adverse effects of the culture process and shortens the overall procedure time for both patients and clinics. Because the interactions between the maternal reproductive tract and the embryo are likely to be site-specific, transfer into the uterus at a stage when the embryo would normally be in the uterus rather than the fallopian tube may be more "physiologic," and methods for evaluating the potential of the embryo for successful implantation are generally more reproducible at later stages.[346,347]

1. Included studies. Included studies are summarized in Table 46. Two studies compared day 1 transfer of zygotes to day 3 transfer and found either no significant difference[348] or significantly lower pregnancy and live birth rates with zygote transfer.[349]

In four studies comparing transfer on day 2 versus day 3, there was no advantage to day 2 transfer[350-352] except in one large study of patients with a poor ovarian response (5 or fewer oocytes retrieved after stimulation).[353] In this study with 472 subjects, day 2 transfer significantly improved both pregnancy and live birth rates (RR for live birth 1.70; 95 percent CI 1.07-2.72).

Ten studies compared day 3 transfer with blastocyst (day 5) transfer. Seven of the 10 [354-360] showed improved pregnancy and/or live birth rates with blastocyst transfer, with significant improvements in two.[355,358] The 2006 study of Papanikolaou and colleagues[355] is of particular interest, since randomization occurred at the time of entry into the trial (avoiding potential biases introduced by randomization at day 3), involved only single embryo transfer in both arms, and demonstrated a large enough difference that the study was stopped at the planned interim analysis. There were no observed differences in other studies in multiple gestation rates, although day 5 transfer did result in a lower number of embryos available for subsequent cryopreservation.[354]

Studies that showed no benefit may have been due to different numbers of transferred embryos[361] or a more limited choice of embryos.[354,362]

Table 46. Timing of transfer

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Day 3 vs. day 1 (zygote)									
Dale et al., 2002[348]	Reference	Day 3	202						
		Day 1	205	0.95	0.74	1.22	-	-	-
		1st cycle		*Multiples **0.60 (0.40, 0.89)***					
Jaroudi et al., 2004[349]	Reference	Day 3	151						
		Day 1	151	**0.62**	**0.43**	**0.89**	**0.64**	**0.42**	**0.99**
				Multiples (twins) 0.56 (0.19, 1.62)					
Day 3 vs. day 2									
Bahceci et al., 2006[353]	Reference	Day 3	235						
		Day 2	237	**1.73**	**1.17**	**2.56**	**1.70**	**1.07**	**2.72**
		Poor ovarian response		*Multiple pregnancy 0.73 (0.3, 1.76)*					
Laverge et al., 2001[350]	Reference	Day 3	372						
		Day 2	374	-	-	-	1.01	0.86	1.18
				Multiples 0.99 (0.69, 1.41)					
Pantos et al., 2004[351]	Reference	Day 3	81						
		Day 2	81	0.97	0.70	1.35	0.94	0.66	1.35
		Day 6	81	**0.77**	**0.54**	**1.11**	**0.57**	**0.36**	**0.90**
				Day 2 multiples 1.10 (0.49, 2.45) *Day 3 multiples 1.20 (0.55, 2.62)*					
Baruffi et al., 2003[352]	Reference	Day 3	53						
		Day 2	53	1.05	0.67	1.63	-	-	-
		ICSI		*Multiples not reported*					

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Day 3 vs. day 5 (blastocyst)									
Kolibi-anakis et al., 2004[354]	Reference	Day 3	234						
		Day 5	226	-	-	-	1.04	0.80	1.35
		Randomized at time of initial evaluation		*Multiples 1.33 (0.74, 2.4)*					
Papa-nikolaou et al., 2006[355]	Reference	Day 3	175						
		Day 5	176	**1.41**	**1.00**	**1.98**	**1.47**	**1.03**	**2.09**
		1st or 2nd cycle; randomized at initial visit		*Single embryo transfer*					
Montag et al., 2006[362]	Reference	Day 3	90						
		Day 4	95	**0.60**	**0.38**	**0.96**	-	-	-
		Day 5	88	**0.40**	**0.23**	**0.71**	-	-	-
		3 embryos cultured/cycle							
Bungum et al., 2003[361]	Reference	Day 3	57						
		Day 5	61	0.83	0.61	1.13	-	-	-
		2 embryos day 3, 1 embryo day 5		*No difference in twinning*					
Karaki et al., 2002[356]	Reference	Day 3	82						
		Day 5	80	1.12	0.68	1.86	-	-	-
				Multiples 0.82 (0.42, 1.62); ≥ triplets 0.26 (0.03, 2.24)					
Levitas et al., 2004[357]	Reference	Day 3	31						
		Day 5	23	1.68	0.51	5.59	-	-	-
		≥ 3 previous failed attempts							
Papa-nikolaou et al., 2005[358]	Reference	Day 3	84						
		Day 5	80	**1.63**	**1.12**	**2.37**	**1.73**	**1.14**	**2.63**
Hreinsson et al., 2004[359]	Reference	Day 2-3	80						
		Day 5-6	64	1.10	0.69	1.76	0.98	0.58	1.65
				Twins 0.57 (0.11, 2.81)					
Hsieh et al., 2000[360]	Reference	Day 5	201						
		Day 2	158	1.12	0.86	1.45	1.09	0.80	1.49
Pantos et al., 2004[351]	Reference	Day 3	81						
		Day 2	81	0.97	0.70	1.35	0.94	0.66	1.35
		Day 6	81	0.77	0.54	1.11	**0.57**	**0.36**	**0.90**
				Day 2 multiples 1.10 (0.49, 2.45); Day 3 multiples 1.20 (0.55, 2.62)					

2. Other systematic reviews. We did not identify any non-Cochrane systematic reviews.

3. Cochrane reviews. There are two relevant Cochrane reviews (Table 47). The first,[346] updated in July 2003, found significant improvement in pooled estimates for pregnancy (OR 1.26; 95 percent CI 1.06-1.51), but not live birth (OR 1.07; 0.84-1.37) for day 3 compared to day 2 transfer. The benefit appeared limited to patients undergoing ICSI.

The second review[347] found a significantly higher pooled live birth rate for blastocyst transfer versus day 3 transfer of 1.35 (95 percent CI 1.05-1.74). Fewer embryos were frozen, with a greater number of cycles with no embryos transferred at all. In subgroup analysis, results were

best in patients with a good prognosis, with high numbers of embryos available for transfer, and in trials where randomization occurred on day 3 rather than prior to cycle initiation.

Table 47. Cochrane reviews, timing of transfer

Interventions		N	Efficacy					
			Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
			Relative Effect	Lower 95% CI	Upper 95% CI	Relative Effect	Lower 95% CI	Upper 95% CI
Day 2 vs. day 3[346]								
Reference	Day 2	1008						
	Day 3	1019	**1.26**	**1.06**	**1.51**	1.07	0.84	1.37
	10 studies, 3 post-2000					*2 studies, 1 post-2000, n = 1200*		
Day 3 vs. day 5 (blastocyst)[347]								
Reference	Day 2/3	1297						
	Day 5/6	1260	-	-	-	**1.35**	**1.05**	**1.74**
	17 studies, 15 post-2000					*9 studies, all post-2000*		

4. Conclusions. The available evidence suggests that zygote transfer is, at best, no better than day 3 transfer and may result in worse pregnancy and live birth rates. Transfer on day 2 may produce better outcomes compared to day 3 in women with poor ovarian response, based on one large trial; pooled meta-analysis results suggest better pregnancy rates, but not necessarily live birth rates, in cycles where ICSI is used. Finally, blastocyst transfer results in better live birth rates than day 3 transfer, especially in patients with a good prognosis. The disadvantage of delaying transfer is a reduction in the number of embryos available for transfer and for cryopreservation.

These results suggest that there continue to be trade-offs between having greater overall numbers of embryos available for transfer versus transfer of fewer, but presumably "better" on average, embryos.

G. Number of embryos transferred. Finally, as a response to increased multiple rates, many European countries have placed regulatory limits on the number of embryos per transfer. The effect of reducing the number of transferred embryos has been tested in a number of clinical trials.

1. Included studies. Included studies are summarized in Table 48. Not surprisingly, transfer of a single embryo consistently resulted in lower pregnancy rates in a given cycle compared to transfer of two embryos,[363-366] with a consistently significant reduction in multiples (almost all twins).

One of these studies[364] compared transfer of two embryos after a traditional GnRH agonist long protocol to transfer of a single embryo after a GnRH antagonist in 404 subjects. The primary outcome was term live births; the study was designed as an equivalence trial, and term live birth met pre-specified equivalence criteria, although overall live birth rate was somewhat lower with single embryo transfer (RR 0.87; 95 percent CI 0.67-1.13). Multiples (RR 0.04; 0.01-0.27) and OHSS (RR 0.47; 0.19-1.27) were lower in the GnRH antagonist/single embryo transfer arm.

Three studies evaluated strategies that involved more than one cycle. Lukassen and colleagues[367] compared one cycle of double embryo transfer to two cycles of single embryo transfer. There was not a significant difference in pregnancy or live birth rates, but multiples

were significantly reduced with single embryo transfer. The study was underpowered to determine equivalence. Heijnen and colleagues[364] compared transfer of three embryos per cycle over a maximum of three cycles to transfer of two embryos per cycle over a maximum of four cycles in women 38 or older. Pregnancy and live births were higher, and multiples lower with the strategy of two embryos over four cycles, but this study of only 45 subjects was underpowered.

A third, much larger study compared double embryo transfer to single embryo transfer with cryopreservation and transfer of the thawed frozen embryo in a second cycle if necessary.[365] The study was designed as an equivalence study and did not meet the pre-specified lower bound difference of a 10 percent absolute difference; however, the lower bound was no worse than an 11.6 percent difference. Again, multiples were significantly reduced with single embryo transfer.

Table 48. Number of embryos transferred

Study	Intervention		N	Efficacy					
				Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
				Rel Eff	Lower 95% CI	Upper 95% CI	Rel Eff	Lower 95% CI	Upper 95% CI
Gardner et al., 2004[363]	Reference	2 blastocysts	25						
		1 blastocyst	23	0.80	0.54	1.19	-	-	-
				*Multiples **0.01 (0.00, 0.95)***					
Lukassen et al., 2005[367]	Reference	1 IVF cycle, 2 embryos transferred	54						
		2 cycles, 1 embryo transferred per cycle	53	1.18	0.81	1.71	1.14	0.70	1.84
		1st cycle or previous successful IVF		*Multiples **0.06 (0.00, 0.95)***					
Heijnen et al., 2007[364]	Reference	GnRH long protocol + 2 embryos	199						
		GnRH antagonist + single embryo	205	0.91	0.75	1.11	0.87	0.67	1.13
		1st cycle or previous successful IVF; age < 38		*Term live births equivalent (primary outcome); multiples **0.04 (0.01, 0.27)**; time to pregnancy faster with long protocol; OHSS 0.47 (0.19, 1.27)*					
Heijnen et al., 2006[368]	Reference	3 embryo transfers over max 3 cycles	22						
		2 embryo transfers over max 4 cycles	23	1.57	0.98	2.50	1.20	0.58	2.46
		1st cycle or previous successful IVF; age ≥ 38		*Multiples 0.12 (0.01, 1.98)*					
Thurin et al., 2004[365]	Reference	Double embryo transfer	330						
		Single embryo transfer, followed by fresh frozen	331	0.56	0.25	1.26	0.91	0.78	1.06
		1st or 2nd IVF cycle		*Multiples **0.02 (0.001, 0.13)***					
Van Montfoort et al., 2006[366]	Reference	Double	154						
		Single	154	**0.53**	**0.37**	**0.76**	-	-	-
		1st IVF cycle, good prognosis		*Multiples **0.04 (0.01, 0.6)***					

2. Other systematic reviews. We did not identify any non-Cochrane systematic reviews.

3. Cochrane reviews. Results of the most recent review[369] are consistent with the findings discussed above (Table 49). Pooled live birth rate for double versus single transfer was 1.94 (1.47-2.55), with pooled odds of multiple gestation 23.55 (8.00-69.2).

Table 49. Cochrane reviews, number of embryos transferred[369]

Interventions		N	Efficacy					
			Clinical Pregnancy			Ongoing Pregnancy/Live Birth		
			Relative Effect	Lower 95% CI	Upper 95% CI	Relative Effect	Lower 95% CI	Upper 95% CI
Single vs. double embryo transfer								
Reference	Single	456						
	Double	453	**2.16**	**1.65**	**2.82**	**1.94**	**1.47**	**2.55**
	4 studies, 3 post-2000					*Multiple pregnancy **23.55 (8.00, 69.29)***		
Single fresh + single frozen vs. double								
Reference	Single fresh + single frozen	330						
	Double	331	1.21	0.89	1.64	1.19	0.87	1.62
	1 study, post-2000					*Multiple pregnancy **62.8 (8.52, 463.6)***		
2 vs. 4 embryos								
Reference	4 embryos	28						
	2 embryos	28	0.75	0.26	2.16	0.35	0.11	1.05
	1 study, pre-2000					*Multiples 0.44 (0.10, 1.97)*		

4. Conclusions. Although double embryo transfer results in higher pregnancy and live birth rates compared to single embryo transfer, multiple rates – almost all twins – are consistently higher. Strategies involving alternative methods for pituitary down-regulation, or involving multiple cycles with fewer embryo transfers per cycle, appear to result in similar live birth rates with fewer multiples.

Longer Term Outcomes (Question 4)

I. Research Question

What are the adverse outcomes of ovulatory drug-induced pregnancies and of pregnancies achieved with in vitro fertilization (IVF)? Is there evidence to link these adverse outcomes with the treatments and not the underlying maternal health or gestational age problems? For the mother, outcomes include preeclampsia, cesarean delivery, gestational diabetes, abruption, placenta previa, and breast and ovarian cancer. For the infant, outcomes include birth defects, prematurity, low birth weight, and long-term outcomes as available.

II. Approach

The relative lack of data on fetal and neonatal outcomes in pregnancies after infertility treatment, especially IVF/ICSI, has been identified as a major research priority.[370] Although the association between multiple pregnancies resulting from infertility treatments and preterm delivery and short-term neonatal morbidity and mortality has been recognized as an issue for

some time,[25] there is increasing evidence that even singleton pregnancies resulting from infertility treatments may be at increased risk for many adverse outcomes.[371]

In this section, we review the literature addressing maternal, fetal, and child outcomes during and after pregnancy (as well as any paternal outcomes reported). Fetal/neonatal outcomes include spontaneous abortion, ectopic pregnancy, abnormal test results in maternal screening for Down's syndrome and other aneuploidies, preterm delivery, low birth weight, and other outcomes. Maternal outcomes during pregnancy include preeclampsia, gestational diabetes, placental abnormalities, and psychological outcomes. Post-delivery outcomes for children include birth to 1 year (congenital anomalies, other physical outcomes), and 1 year and beyond (physical and neurodevelopmental outcomes). Maternal longer term outcomes include cancer and psychological outcomes.

We did not include cesarean section as an outcome. Although cesarean section rates are consistently elevated in women who conceive after infertility treatment,[372] it is unclear how much of this risk is due to differences in obstetric conditions for which cesarean section is indicated, variations in practice between sites, and variations in the threshold for cesarean section among obstetricians and couples.

As noted in the sections above, data on pregnancy outcomes are lacking from most trials of infertility treatments. Given that most studies are underpowered to detect differences in pregnancy rates, it is not surprising that even those studies that do provide data are underpowered to detect outcomes that occur in only a fraction of pregnancies. The only option for examining these outcomes is observational data, either cohort or case-control studies. With the exception of cancer outcomes, the majority of studies were variations of cohort studies – outcomes of women who underwent infertility treatment were compared to outcomes of women who did not. Most of non-cancer studies labeled "case-control" were actually cohort studies with some sampling of women who were not exposed to infertility treatment.

Although we identified several very large population-based studies that provided valuable data on associations, it is important to emphasize that all of the caveats that apply to the interpretation of reported favorable treatment outcomes based on observational studies (including the potential for various types of bias and substantial confounding because of factors related to the selection of a given treatment in a given patient) should also be considered when interpreting the results of observational studies of adverse outcomes after treatment.

III. Search Results

The flow of articles on this topic through the literature search and screening process is depicted in Figure 5.

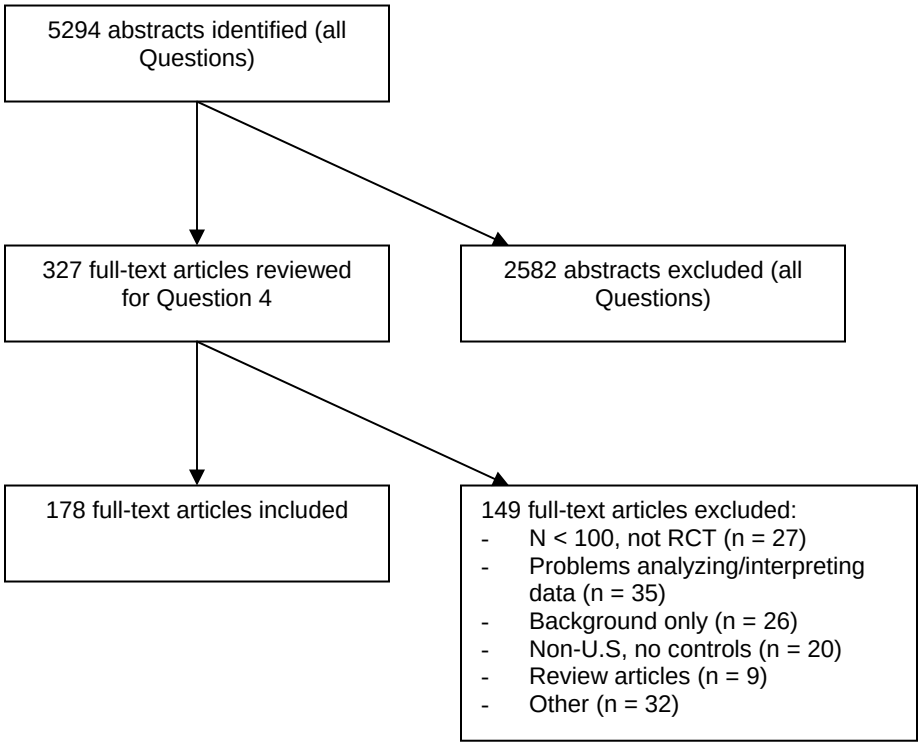

Figure 5. Literature flow diagram – Question 4

IV. Fetal/Neonatal Outcomes

As noted above, the relative lack of data on fetal and neonatal outcomes in pregnancies after infertility treatment, especially IVF/ICSI, has been identified as a major research priority.[370] Although the association between multiple pregnancies resulting from infertility treatments and preterm delivery and short-term neonatal morbidity and mortality has been recognized as an issue for some time,[25] there is increasing evidence that even singleton pregnancies resulting from infertility treatments are at increased risk for many adverse outcomes. This section reviews outcomes occurring from implantation through delivery.

A. Spontaneous abortion. Spontaneous abortion is common, occurring in 25 to 30 percent of all spontaneous conceptions.[373] Maternal age is a particularly strong risk factor for both spontaneous abortion and infertility. In this section, we define spontaneous abortion or pregnancy loss as the loss of the entire pregnancy. Although loss of one or more fetuses in a multiple gestation with an ongoing pregnancy with at least one fetus is not uncommon, we focus here on loss of the entire pregnancy.

1. Included studies. In a prospective cohort of 3259 subjects attempting pregnancy, the spontaneous abortion rate was significantly higher in women who took longer than 12 months to conceive (RR 1.82; 95 percent CI 1.44-2.29).[374] In a study based on the SART registry, spontaneous abortion rates were similar to those in the National Survey of Family Growth.[375]

Age was consistently a major risk for spontaneous abortion across all categories of assisted reproduction techniques.[375-377]

One strikingly consistent finding is that, once one or more fetal heart rates are identified, loss rates are significantly lower for twins than for singletons, especially in women under the age of 35.[375,378-381] This suggests that, in the setting of multiple embryo transfer, factors related to implantation and placentation in either the mother, the embryo, or both, which lead to initiation of a multiple gestation also contribute to the ongoing viability of the pregnancy.

We identified several studies that compared loss rates with IVF versus ICSI. Most studies reported either increased[382-384] or no difference[375] in risk with ICSI; only one showed a significant decrease in loss rates with ICSI.[379] This may reflect differences in the distribution of risk factors due to differences in uses of ICSI, as suggested by studies that found a significant difference only for ICSI performed for male factor infertility (0.73; 95 percent CI 0.53-1.00), and another smaller study which found a higher incidence of abnormal karyotypes with ICSI compared to IVF in the products of conception examined after losses.[385]

2. Other systematic reviews. We did not identify any other published reviews on this topic.

3. Conclusions. Spontaneous abortion does not appear to be more common after assisted reproduction after adjusting for known risks; observed differences between different methods appear to be related to differences in the patient population to which the methods are applied.

B. Ectopic pregnancy. Ectopic pregnancy is more common in pregnancies involving assisted reproduction than in spontaneous conceptions. Even heterotopic pregnancies (simultaneous intra- and extrauterine pregnancies) – which are so rare in spontaneous conceptions that the presence of an intrauterine pregnancy is used to rule out an ectopic pregnancy – appear to be more common after IVF/ICSI.[386-388] As with the majority of adverse outcomes discussed in this section, it is unclear how much of this risk is associated with the underlying condition, the treatments used, or both. Damage to the fallopian tubes from previous infection or endometriosis is clearly a risk factor for both infertility and ectopic pregnancy, while superovulation and multiple embryo transfer increase the probability of heterotopic pregnancy simply by increasing the number of potential embryos that can implant. Abnormal implantation may be related to the underlying infertility, alterations in the normal process of implantation secondary to the treatments used, or both.

1. Included studies. Three relatively small studies examined differences in ectopic rates based on aspects of the procedure itself. Check and colleagues[389] compared rates after fresh versus frozen embryo transfer in 2520 women; they did not detect a significant difference (RR 0.78 for frozen compared to fresh; 95 percent CI 0.45-1.34). Rates were also not significantly increased for fresh versus frozen blastocyst transfer in a smaller series of 744 blastocyst transfers.[390] Jun and Milki[391] reported a significantly higher incidence of ectopic pregnancies after assisted hatching in 623 pregnancies (RR 2.48; 1.05-5.82). However, none of these studies adjusted for potential confounders.

Two studies from the SART registry provided relevant data on ectopic pregnancies in the United States. In a review of risk factors for ectopic pregnancy in over 94,000 pregnancies in the registry,[387] risks were decreased with donor egg or surrogate pregnancies, consistent with maternal factors contributing to increased risk. In fresh, non-donor IVF/ICSI, risk was increased with histories of tubal disease, endometriosis, or other female cause of infertility after adjustment for other risk factors. Risks with fresh versus frozen transfer, IVF versus ICSI, or with assisted hatching, were not different after adjustment. Interestingly, risks were significantly decreased if one or two embryos with good quality scores were transferred, but not with three or more, suggesting that at least some of the contribution to increased ectopic rates is attributable simply to increasing the mathematical probability of implantation. In another registry study comparing

outcomes of women with intrauterine pregnancies alone with heterotopic pregnancies, spontaneous abortion of the intrauterine gestation in heterotopic pregnancies was significantly more likely (RR 2.05; 95 percent CI 1.67-2.51), with the subsequent probability of livebirth significantly reduced (RR 0.70; 0.62-0.79). Risks for low birth weight and preterm delivery were also increased, but not significantly.

2. Other systematic reviews. We did not identify any other systematic reviews on this topic.

3. Conclusions. Although ectopic pregnancy is more common after assisted reproduction than after spontaneous conception, and variations are observed between different methods of ART, most of the difference in risk appears to be related to factors related to the mother and/or embryo rather than specific procedures. There is good evidence discussed earlier that removal of hydrosalpinges prior to undergoing ART reduces the ectopic risk.

C. Maternal serum screening for chromosomal abnormalities. Discussion of options for screening for fetal chromosomal abnormalities, including Down's syndrome, is recommended for all pregnant women.[392] Currently, both first and second trimester screening tests are available; the optimal choice of either or both is based on the availability of the specific tests, the availability of first-trimester chromosomal evaluation using chorionic villus sampling (CVS), and patient preferences. Studies of second trimester serum tests suggested that the false positive rate of testing was higher in women who were pregnant after assisted reproduction; this was clinically relevant not only because of the risk of fetal loss after CVS or amniocentesis for definitive diagnosis, but there was some evidence that women with false positive results were more likely to experience later adverse pregnancy outcomes.[393,394]

1. Included studies. Table 50 shows included studies with estimates of the relative risk (with 95 percent CIs) for false positive results.

Two studies that explicitly reported results for nuchal translucency found increased risks of false positives,[395,396] although this was not observed in a larger, prospective trial.[397] Risks for first trimester serum screening were not significantly increased in three studies, including one with over 38,000 subjects;[397-399] however, second trimester false positive screening results were consistently elevated in four studies,[394,397,400,401] including studies with over 21,000[401] and 38,000 subjects.[397] Of note, in the largest study, the FASTER trial, increased risks were seen with both IVF/ICSI and ovulation stimulation treatments.[397] A particular strength of this study was the validation of exposure. The combination of elevated risk with nuchal translucency and elevated second trimester serum tests led to an overall increased false positive rate with combined screening in the two largest, most recent studies.[396,402]

Two studies provided evidence that some of this observed increase in false positive risk is due to confounding by maternal age;[401,402] adjustment for maternal age resulted in substantial reductions in the risk estimate.

Three studies that explicitly compared results between IVF and spontaneous twins found either a reduced[403] or similar risks for false positive results with nuchal translucency,[404] or similar results for second trimester alpha-fetoprotein.[405]

Table 50. Maternal screening for fetal chromosomal abnormalities

Study	Exposure		N	Measure of Association		
				RR/OR	Lower 95% CI	Upper 95% CI
Abnormal nuchal translucency						
Hui et al., 2005[395]	Reference	Spontaneous	16773			
		ART	301	**2.00**	**1.42**	**2.81**
		Cohort, singletons				
First trimester serum screening						
Lambert-Messer-lian et al., 2006[397]	Reference	Spontaneous	37070			
		Any infertility treatment	962			
		Cohort, FASTER trial		95 % CI of observed screen positive rates included expected rate based on known maternal factors (gestational age, maternal race, diabetes, weight)		
Wojde-mann et al., 2001[398]	Reference	Spontaneous	3029			
		IVF	47	0.87	0.22	3.41
		Ovulation induction	63	0.97	0.32	2.97
		Cohort, screen positive results; 1st trimester				
Orlandi et al., 2002[399]	Reference	Spontaneous	363			
		ART	66	1.75	0.78	3.93
Second trimester serum screening						
Rice et al., 2005[400]	Reference	Spontaneous	596			
		IVF	88	1.25	0.76	2.07
		Cohort				
Muller et al., 2003[401]	Reference	Spontaneous	21014			
		ART	1515	**1.44**	**1.25**	**1.66**
		Cohort		Risks 1.01-1.15, with CIs crossing 1.0 when stratified by maternal age		
Lambert-Messerlia n et al., 2006[397]	Reference	Spontaneous	37070			
		Any infertility treatment	962			
		Cohort, FASTER trial		Observed screen positive rate significantly higher for all groups except embryo donors (but total n for this subgroup only 115) after adjusted for gestational age, maternal race, diabetes, weight		
1st and 2nd trimester combined						
Tul and Novak-Antolic, 2006[402]	Reference	Spontaneous	914			
		IVF	130	**3.01**	**1.57**	**5.78**
		ICSI	54	**4.23**	**1.94**	**9.24**
		Cohort, any positive result		Adjusted for maternal age: IVF: 1.67 (0.79, 3.54); ICSI: **2.78 (1.1, 7.0)**		
Maymon and Shulman, 2002[394]	Reference	Spontaneous	285			
		IVF	71	1.00	0.11	8.84
		Cohort, singletons, 1998-1999; 1st and 2nd trimester		Risk increased for 2nd trimester screening, but CIs cross 1.0		
Maymon and Shulman, 2004[396]	Reference	Spontaneous	1781			
		IVF	99	1.64	0.73	3.68
		Cohort, singletons, 2000-2002; 1st and 2nd trimester		Risk increased for both, significant only for nuchal translucency and PAPP-A		

2. Other systematic reviews. We did not identify any published systematic reviews on this topic.

3. Conclusions. The best available evidence suggests that false positive results for maternal testing for chromosomal abnormalities after ART are more likely for second trimester serum screening, resulting in an increased false positive rate with combined screening strategies. The evidence for first trimester screening is more equivocal, with the largest prospective study showing no difference for nuchal translucency. Some of this increased risk appears to be due to differences in the distribution of maternal age. These results are biologically plausible, especially for second trimester serum screening, where most tests are based on measurement of placental proteins. Abnormal implantation in these patients, or placental abnormalities resulting from spontaneous or purposeful fetal reduction in the setting of multiple pregnancies, may lead to subsequent abnormal levels of these markers. Further research is needed to determine whether adjustment of thresholds for referral for invasive testing in patients pregnant after infertility treatment is needed. In addition, because false positive test results in a general population have been associated in some studies with an increased risk for later pregnancy complications which are also increased in infertility patients, additional research into the potential clinical utility of these results is also needed.

D. Preterm delivery – singletons. This section examines the evidence concerning preterm delivery in singletons.

1. Included studies. Identified studies meeting our inclusion criteria are shown in Table 51. Consistently, women pregnant after IVF/ICSI had a 70 to 150 percent increase in the likelihood of delivery prior to 37 weeks. However, we did not identify any data to help estimate what proportion of these births were early deliveries due to maternal or fetal complications which are more common in these patients, such as preeclampsia (see below), versus preterm delivery secondary to spontaneous preterm labor without an identifying underlying cause. Of note, the one study we identified that was restricted to patients pregnant after superovulation found a similar risk increase.

Table 51. Preterm delivery in singletons

Study	Exposure		N	Measure of Association		
				RR/OR	Lower 95% CI	Upper 95% CI
IVF/ICSI vs. spontaneous						
Koudstaal et al., 2000[406]	Reference	Spontaneous	307			
		IVF	307	**2.56**	**1.52**	**4.30**
		Cohort, matched controls				
Perri et al. 2001[407]	Reference	Spontaneous	2546			
		IVF	95	**2.75**	**1.80**	**4.21**
		Cohort		Preterm birth < 37 wk. Risk estimate increased to **(4.75, 95% CI 2.16, 10.45)** with only matched controls.		
Poikkeus et al., 2006[408]	Reference	Spontaneous	304			
		IVF/ICSI	324	**2.19**	**1.02**	**4.70**
				Preterm birth < 37 wk		
Klemetti et al., 2002[409]	Reference	Spontaneous	111,516			
		IVF	1893	**1.79**	**1.52**	**2.11**
				Preterm birth < 37 wk. Controlled for county, smoking, maternal age, parity, and gravidity.		
Wang et al., 2002[410]	Reference	Spontaneous	660			
		IUI (minimal stimulation)	567	1.24	0.79	1.97
		IVF/GIFT	569	**2.33**	**1.55**	**3.52**

Study	Exposure		N	Measure of Association		
				RR/OR	Lower 95% CI	Upper 95% CI
Single embryo transfer						
De Neubourg et al., 2006[411]	Reference	Spontaneous	59,535			
		Single embryo transfer	251	**1.62**	**1.11**	**2.35**
		Cohort		Preterm birth < 32 wk: 1.01 (0.25, 4.04)		
De Sutter et al., 2006[412]	Reference	Single embryo transfer	404			
		Double embryo transfer	431	**1.69**	**1.05**	**2.70**
		Cohort, singletons only		Preterm birth < 37 wk		
Poikkeus et al., 2007[413]	Reference	Spontaneous	15037			
		Single embryo transfer	269	**2.77**	**2.00**	**3.85**
		Double embryo transfer with single ongoing pregnancy	230	**2.55**	**1.76**	**3.69**
		Cohort		Preterm birth < 37 weeks; risk remained unchanged after adjustment for maternal age, parity, and socioeconomic status		
IVF vs. ICSI						
Rajesh et al., 2006[414]	Reference	IVF only	53			
		IVF + ICSI	103	3.09	0.95	10.0
		Cohort		Preterm birth < 37 wk		
Bonduelle et al., 2002[415]	Reference	IVF	1393			
		ICSI	1300	0.96	0.77	1.21
		Not entirely contemporaneous – IVF 1983-1999, ICSI 1991-1999		Preterm birth < 37 wk		
Superovulation vs. spontaneous						
Ombelet et al., 2006[416]	Reference	Spontaneous	12,021			
		Ovulation induction	12,021	**1.82**	**1.64**	**2.03**
		Cohort, matched controls		Preterm birth < 37 wk		

2. Other systematic reviews. Four systematic reviews consistently found an increased risk of preterm birth among singleton infants following IVF, with odds ratios for birth prior to 37 weeks of 1.98 (1.89-2.08);[417] 1.95 (1.73-2.20);[418] 2.04 (1.80-2.37; with risk for delivery prior to 32 weeks OR 3.22; 95 percent CI 2.03-5.08);[372] and 1.93 (1.36-2.20; with risk for delivery before 33 weeks OR 2.99; 95 percent CI 1.54-5.80).[419] Given that there was considerable overlap in the included studies, the consistency of the risk estimate is not surprising.

3. Conclusions. Preterm delivery is approximately twice as likely in women pregnant after infertility treatment compared to spontaneous pregnancies. The evidence is most consistent for IVF/ICSI, but the risk was similar in a large study of women pregnant after ovulation induction alone. The proportion of these deliveries that are due to early delivery indicated by maternal or fetal complications versus idiopathic fetal delivery is unclear. To date, strategies to prevent idiopathic preterm birth have proven ineffective, although there is recent evidence that progesterone may be effective in some high-risk patients (those with a history of preterm birth or a cervix less than 15 mm on ultrasound).[420] If a significant proportion of these preterm deliveries are idiopathic, a trial of progesterone in women pregnant after ART should be considered; given

the use of progesterone for luteal support, this trial would involve testing whether the continuation of progesterone into the second and third trimesters reduced the incidence of preterm delivery.

E. Preterm delivery – multiples. All multiple gestations are at increased risk for preterm delivery compared to singleton pregnancies, with the average age of delivery decreasing with each additional fetus.[421] However, from both a clinical and scientific viewpoint, the question of whether infertility treatment increases the risk for preterm delivery in multiple gestations compared to spontaneous multiples is of great interest.

1. Included studies. Included studies are summarized in Table 52. Although ART twins are more likely to deliver prior to 37 weeks than spontaneous twins, this increased risk is much smaller than that observed for ART singletons compared to spontaneous singletons. The point estimates for increased risk are consistently much smaller than observed with singletons. Even in a study that included higher order multiples, the point estimate for preterm birth risk was substantially lower for IVF multiples, most of which were twins, compared to IVF singletons.[409] In a cohort of twins resulting from selective reduction of higher order multiple gestation, risk of preterm delivery was significantly increased compared to twin gestations resulting from ART that did not start as higher order multiples.[422]

Because twins from spontaneous conceptions deliver earlier as well, some of this difference may simply reflect a larger proportion of spontaneous pregnancies delivered before 37 weeks; however, those studies that also reported preterm birth using earlier thresholds[423-425] had similar findings.

Table 52. Preterm delivery in twins

Study	Exposure		N	Measure of Association		
				RR/OR	Lower 95% CI	Upper 95% CI
IVF/ICSI vs. spontaneous twins						
Choi et al., 2006[423]	Di-chorionic twins	Spontaneous	156			
		IVF	193	1.35	0.95	1.90
	Mono-chorionic twins	Spontaneous	154			
		IVF	34	1.22	0.68	2.21
		Cohort		Preterm birth < 34 wk		
Huang et al., 2006[424]	Reference	Spontaneous	50			
		IUI	63	0.91	0.57	1.46
		IVF/ICSI	81	1.08	0.71	1.65
		Cohort		Preterm < 37 wk. Similar for birth < 32 wk; unclear if IUI in paper includes superovulation		
Klemetti et al., 2002[409]	Reference	Spontaneous	1396			
		IVF	515	**1.43**	**1.13**	**1.80**
		Includes higher order multiples		Preterm birth < 37 wk		
Koudstaal et al., 2000[426]	Reference	Spontaneous	96			
		IVF	96	1.46	0.83	2.58
		Cohort		Preterm birth < 37 wk		
Manoura et al., 2004[427]	Reference	Spontaneous	148			
		IVF	73	**1.23**	**1.02**	**1.47**
		Cohort		Preterm birth < 37 wk		
Nassar et al., 2003[428]	Reference	Spontaneous	112			
		IVF	56	**3.03**	**1.54**	**5.95**
		Cohort		Preterm birth < 37 wk		

Study	Exposure		N	Measure of Association		
				RR/OR	Lower 95% CI	Upper 95% CI
Pinborg et al., 2004[429]	Reference	Spontaneous	10239			
		IVF	3393	1.04	0.99	1.09
		Cohort		Preterm birth < 37 wk		
Pinborg et al., 2004[430]	Reference	Spontaneous	1496			
		IVF	538	**1.22**	**1.01**	**1.47**
		Cohort		Preterm birth < 37 wk		
Putterman et al., 2003[425]	Reference	Spontaneous	101			
		Ovulation induction	34	0.97	0.71	1.34
		IVF	60	0.88	0.66	1.17
		Cohort		Preterm birth < 37 wk. Similar results for birth < 32 wk.		
Saygan-Karamursel et al., 2006[431]	Reference	Spontaneous	348			
		ICSI	274	**1.20**	**1.08**	**1.32**
		Cohort		Preterm birth < 37 wk		
Ver-straelen et al., 2005[432]	Reference	Spontaneous	2915			
		Superovulation	710	**1.20**	**1.11**	**1.30**
		IVF/ICSI	743	0.96	0.90	1.03
		Cohort		Preterm birth < 37 wk		
Zuppa et al., 2001[433]	Reference	Spontaneous	228			
		ART	32	**1.43**	**1.13**	**1.80**
		Cohort				
Ovulation induction vs. spontaneous						
Ombelet et al., 2006[416]	Reference	Spontaneous	3108			
		Superovulation	3108	1.04	0.99	1.09
				Preterm birth < 37 wk		
ART twins reduced from higher order multiples vs. ART twins that were not reduced						
Cheang et al., 2007[422]	Reference	Non-reduced ART twins	389			
		Reduced ART twins	353	**1.24**	**1.03**	**1.50**
		Cohort		Risk for delivery prior to 28 weeks 2.52 (1.05, 6.05)		

2. Other systematic reviews. Two systematic reviews reported similar findings. The first, which also included a review of outcomes of singleton pregnancies, found that the relative risk for preterm birth in ART twins compared to spontaneous twins was substantially lower than the relative risk for preterm birth in ART singletons compared to spontaneous singletons, with summary relative risks of 1.07 (95 percent CI 1.02-1.13) for delivery prior to 37 weeks, and 0.95 (0.78-1.15) for delivery prior to 32 weeks.[372] The second study found an increased risk for delivery for ART twins compared to spontaneous twins between 32 and 36 weeks in studies matched for maternal age (OR 1.48; 95 percent CI 1.05-2.10), and increased risk of delivery prior to 37 weeks when parity was also matched;[419] however, these relative risk estimates were still lower than the relative risks observed for singletons. These findings are not necessarily contradictory, given differences in study inclusion criteria, analytic methods, and the potential impact of different definitions of preterm birth. The most striking finding is the within-study finding of Helmerhorst and colleagues that the summary risk, using identical methods and study selection criteria, is so much lower for twins than for singletons.[372]

3. Conclusions. Twins resulting from either ART or spontaneous conceptions are more likely to deliver prior to 37 weeks than singleton ART or spontaneous conceptions, and both twins and singletons resulting from ART are more likely to deliver prior to term than twins and

singletons born after spontaneous conception. However, the evidence is fairly consistent that the relative *increase* in preterm delivery risk associated with ART is substantially higher for singletons than for twins. This may be due to a higher proportion of spontaneous twins being born below a given gestational age threshold. It is also consistent with the hypothesis that, given multiple embryo transfer, twin pregnancies are more likely in the setting of maternal and/or embryonic features which confer a better chance of establishing a successful pregnancy. However, from a clinical and public health perspective, the fact that twins overall are more likely to deliver prior to term compared to singletons means that, even with a smaller increase in relative risk, the absolute number (or attributable risk) of preterm twins associated with ART will be substantial.

F. Low birth weight – singletons. Given that weight at birth increases with increasing gestational age, one would expect low birth weight (defined as less than 2500 g) or very low birth weight (less than 1500 g) to be more common in a group more likely to have preterm delivery. The more interesting question is whether, for a given gestational age, infants born after infertility treatment are smaller than infants born after spontaneous conception.

1. Included studies. In general, all of the studies cited above that reported an increased risk of preterm delivery also reported increased risks of low birth weight and very low birth weight. However, only a few provided data on gestational age-specific relative weights, most often expressed as the proportion below the 10th percentile ("small for gestational age," or SGA), adjusted for the appropriate population. A Finnish study[434] did not detect a difference in SGA in 118 singleton pregnancies after IVF in women with unexplained infertility compared to either an age- and parity-matched group of women with spontaneous pregnancies or women with other diagnoses. However, in a Dutch study of 307 ART pregnancies and 307 controls matched for known risk factors for preterm birth and low birth weight, the risk of SGA was considerably increased (RR 2.08; 95 percent CI 1.21-3.70).[406] A Danish population-based study found a similarly elevated risk (RR 1.38; 1.22-1.56).[435] Similarly, data from the SART registry in the United States found that the standardized risk ratio for term low birth weight among ART infants was significantly elevated (RR 2.6; 2.4-2.7), and substantially higher than the risk observed with preterm infants (RR 1.4; 1.3-1.5).[436]

Two other studies provide evidence suggesting a role for implantation and placentation in this increased risk. A large (more than 60,000 subjects) population-based Danish study[437] found similarly increased risks for SGA in singleton pregnancies both in women treated for infertility (RR 1.40; 1.23-1.60) and in women spontaneously conceiving after more than 12 months of attempting pregnancy (RR 1.24; 1.10-1.40), consistent with an underlying maternal and/or embryonic cause. Risks were also elevated for ART singletons that originally started with more than one gestation ("vanishing twins") compared to ART pregnancies that started as singletons (RR 1.48; 1.03-2.11).[438]

2. Other systematic reviews. The three relevant systematic reviews all found significantly increased risks of low birth weight and very low birth weight among singletons born after assisted reproduction. Where SGA was reported, all three reviews also reported consistently elevated risks for SGA: 1.59 (95 percent CI 1.20-2.11);[419] 1.60 (1.25-2.04);[418] and 1.40 (1.15-1.71).[372]

3. Conclusions. In addition to the expected increased risk of low and very low birth weight associated with an increased rate of preterm birth, singleton infants born after infertility after in vitro fertilization are more likely to be in the lowest percentiles of birth weight for a given gestational age than infants born after spontaneous conception. Since intrauterine growth is

strongly dependent on placental function, this observation is consistent with an increase in abnormalities of implantation/placentation in IVF pregnancies. Again, the extent to which this is a function of treatments, maternal/embryonic factors, or both is unclear from the available evidence, although studies demonstrating increased risks in subfertile women who spontaneously conceive, and in singleton "survivors" after loss of a twin suggest a strong contribution from maternal/embryonic factors.

G. Low birth weight–multiples. At any given gestational age, birth weight will decrease as the number of fetuses increase, and thus twins are more likely to be classified as low or very low birth weight. Again, the main clinical and scientific question of interest is whether gestational age-specific weights for multiples born after infertility treatment are less than those for multiples born after spontaneous conception.

1. Included studies. As was seen in the review of preterm birth, the reported relative risk of low or very low birth weight in multiples born after infertility treatment (mostly twins) compared to spontaneous multiples was lower, with confidence intervals including unity, at least partly because the preterm birth risk difference was lower. Three of the included studies[426,434,435] did not detect a difference in the rates of SGA among assisted reproduction and spontaneous twins, while one[439] demonstrated a significantly lower risk for IVF twins compared to spontaneous twins (RR 0.78; 95 percent CI 0.64-0.94), and similar risks for twins after ovulation induction compared to spontaneous twins (RR 0.99; 0.83-1.19).

2. Other systematic reviews. The relative risks of low birth weight and SGA were not significantly different between IVF and spontaneous twins in the two relevant systematic reviews.[372,419] No data were available for higher order multiple gestations; given the small numbers of spontaneous higher order multiples, estimates of risk would likely be quite imprecise.

3. Conclusions. The available evidence suggests that there is not an increased risk for low and very low birth weight among ART twins compared to spontaneous twins, in contrast to the observed relationship between ART and spontaneous singletons. Likewise, the relative distribution of gestational age-specific weights also appears to be similar.

V. Maternal Outcomes during Pregnancy

Implantation of the embryo appears to be one of the most critical steps in establishing a normal pregnancy in both natural and assisted reproduction. Early pregnancy loss occurs in 25 to 30 percent of conceptions,[373] and although chromosomal abnormalities are the most common single etiology,[440] relatively small variations in the complex process may affect the likelihood of a successful pregnancy.[441] Implantation is the biggest remaining barrier to improving pregnancy rates in assisted reproduction.[442,443]

Implantation appears to play a key role in the etiology of many complications of pregnancy, including preeclampsia, abnormalities of fetal growth, and placental abnormalities such as placenta previa and abruption.[444,445] Given the association between assisted reproduction and disorders of fetal growth noted above, an increased risk of maternal complications associated with implantation is biologically plausible.

A. Preeclampsia. Preeclampsia, a disorder manifested by hypertension and proteinuria, which can lead to significant maternal and fetal morbidity and mortality, commonly occurs in women with several characteristics that are frequently seen in women who become pregnant

after infertility treatment, including first pregnancies, maternal age greater than 35, multiple gestation, and obesity.[446]

1. Included studies. Identified studies meeting inclusion criteria are summarized in Table 53. As seen there, the risk of preeclampsia was consistently elevated in women after assisted reproduction with IVF and ICSI. Of interest, although there was a non-significant trend for increasing risk with increasing BMI in one cohort,[447] and a decrease in the point estimate of the risk after adjustment for pre-pregnancy BMI in another,[439] obesity alone cannot explain the risk. The group at theoretically highest risk would be women with PCOS, since obesity is a common feature of the syndrome, yet ovulation or superovulation with clomiphene or gonadotropins, the two treatments most likely to be used in PCOS, had smaller risk estimates than IVF, with confidence intervals that crossed 1.0, in two studies that included patients who had received both types of treatments.[448,449] In all the studies involving singleton pregnancies, risks remained significantly elevated after adjustment for potential confounders such as maternal age and parity. In two of the three studies of multiple gestations,[430,431,448] risks also remained significantly elevated after adjustment

There were no data to allow any assessment about the degree to which the association between infertility treatment, particularly IVF/ICSI, is related to the treatment (abnormal implantation leading to a greater likelihood of preeclampsia) or the underlying condition (factors associated with abnormal implantation that contribute to both infertility and preeclampsia). One line of evidence that would support the underlying condition hypothesis would be data showing an increased risk among women with unexplained infertility compared to women with other causes, especially women with normal ovarian and endometrial function, such as those with tubal infertility.

Table 53. Preeclampsia in pregnancies after infertility treatment

Study	Exposure		N	Measure of Association		
				RR/OR	Lower 95% CI	Upper 95% CI
IVF						
Dokras et al., 2006[447]	Study Type	Cohort; n = 1293, fresh IVF cycles		Trend for increased risk for preeclampsia with increasing BMI, but insufficient power except when comparing BMI < 25 to BMI ≥ 40		
Erez et al., 2006[450]		Controls	2336			
		Cases	292	**2.35**	**1.68**	**3.29**
	Study type	Case-control		OR adjusted for chronic HTN, diabetes, primiparity, twin discordance, and maternal age, 1.08 (0.74, 1.39)		
Ochsen-kuhn, et al., 2003[451]	Reference	Spontaneous*				
		IVF/GIFT*		**3.65**	**1.02**	**13.0**
	Study type	Cohort (includes GIFT); n = 400 *Singletons				
Tabs et al., 2004[452]	Reference	Spontaneous				
		IVF		**5.16**	**1.67**	**15.9**
	Study type	Cohort; n = 39,256; singletons		Eclampsia risk 12.3 (1.68, 90.9); not adjusted for maternal age or parity		
ICSI						
Saygan-Kara-mursel et al., 2006[431]		Spontaneous				
		ICSI		**2.79**	**1.35**	**5.80**
	Study type	Cohort, n = 622; twins		Adjusted for maternal age 2.14 (0.91, 5.02)		

Study	Exposure		N	Measure of Association		
				RR/OR	Lower 95% CI	Upper 95% CI
Ovulation induction/superovulation and IVF/ICSI						
Lynch et al., 2002[448]	Reference	Spontaneous				
		Clomiphene		1.79	0.97	3.30
		Gonadotropins		2.25	0.99	5.10
		IVF/ICSI		**4.66**	**2.59**	**8.37**
	Study type	Cohort; n = 528; all multiple gestations		Only IVF/ICSI significantly associated after adjustment for maternal age (OR 2.8; 1.7-7.0)		
	Reference	Spontaneous				
		Ovulation induction		1.37	0.52	3.59
		IVF		**1.96**	**1.34**	**2.86**
	Study type	Cohort; n = 36,062; singletons				
Any ART						
Pinborg et al., 2004[430]		Cohort: n = 1436; twins		OR adjusted for maternal age and parity: 1.0 (0.5, 1.7) (crude RR not reported)		
Kozinszky et al., 2003[453]	Reference	Spontaneous				
		ART		**1.67**	**1.09**	**2.54**
		Cohort; n = 777; singletons		Matched for age and parity		
Any infertility treatment						
Hernan-dez-Diaz et al., 2007[454]	Reference	Spontaneous				
		Any infertility		**1.77**	**1.37**	**2.30**
	Study type	Cohort, n = 5151		Risk decreased after adjustment for prepregnany BMI, parity, multiple gestation (1.30; 1.00, 1.90). Both history of infertility and diagnosis of gestational hypertension based on subject self-report.		

2. Other systematic reviews. In the meta-analysis of Jackson and colleagues,[418] the risk for preeclampsia among singleton pregnancies after IVF was significantly elevated (OR 1.55; 95 percent CI 1.23-1.95).

3. Conclusions. The risk of preeclampsia is consistently elevated in women undergoing infertility compared to women with spontaneous pregnancies, even after adjustment for common risk factors. Several studies suggest that the risk is higher for women undergoing IVF/ICSI compared to women treated with ovulation induction or superovulation. The extent to which this association is due to the underlying etiology of infertility versus the treatment is unclear.

B. Other complications/outcomes. Other complications/outcomes reported included gestational diabetes, placental abnormalities, and psychological outcomes.

1. Included studies. Gestational diabetes is also associated with risk factors common in infertility patients; in particular, as discussed above, anovulation is often associated with insulin resistance prior to pregnancy. The studies we identified (Table 54) did not provide consistent evidence for an increased risk.

Table 54. Gestational diabetes in pregnancies after infertility treatment

Study	Exposure		N	Measure of Association		
				RR/OR	Lower 95% CI	Upper 95% CI
IVF						
Dokras, et al., 2006[447]	Study type	Cohort; n = 1293, fresh IVF cycles		Trend for increased risk for gestational diabetes with increasing BMI, but insufficient power except when comparing BMI < 25 to BMI ≥ 40		
Pinborg et al., 2004[430]	Study type	Cohort		OR adjusted for maternal age and parity: 1.9 (0.9,4.0) (crude RR not reported)		
ICSI						
Saygan-Kara-mursel et al., 2006[431]	Reference	Spontaneous				
	Study type	Cohort, n = 622; twins		Adjusted for maternal age: 3.22 (1.17, 8.85)		
Gonadotropins						
Vollen-hoven, et al., 2000[455]	Reference	Spontaneous				
		PCOS with Gonadotropins		1.29	0.62	2.70
	Study type	Cohort; n = 120				
Ovulation induction and IVF/ICSI						
Shevell et al., 2005[449]	Reference	Spontaneous				
		Ovulation induction		1.69	0.82	3.47
		IVF		0.80	0.48	1.32
	Study type	Cohort; n = 36,062; singletons				

However, there was very strong and consistent evidence of an association between assisted reproduction and placental abnormalities such as placenta previa or placental abruption in two large cohort studies (Table 55).

Table 55. Placental abnormalities in pregnancies after infertility treatment

Study	Exposure		N	Measure of Association		
				RR/OR	Lower 95% CI	Upper 95% CI
IVF or ICSI						
Romund-stad, et al., 2006[456]	Reference	Spontaneous singletons				
		ART singletons		**7.24**	**5.86**	**8.94**
		Spontaneous twins				
		ART twins		**3.82**	**2.02**	**7.21**
	Study type	Cohort; n = 502,840		Placenta previa – Adjusted for maternal age, parity, previous C-section, duration between births, year of birth: singletons **5.5 (4.4, 7.0)**; twins **2.9 (1.5, 5.8)**. Risk also increased in women with both spontaneous and ART conceptions.		
Ovulation induction and IVF						
Shevell et al., 2005[449]	Reference	Spontaneous				
		Ovulation induction		1.36	0.19	9.65
		IVF		**3.61**	**2.03**	**6.41**
	Study type	Cohort; n = 36,062		Placental abruption – ovulation 2.34 (0.59, 9.31), IVF **3.09 (1.74, 5.49)**		

Finally, we identified three Scandinavian studies that addressed psychological outcomes using standardized, validated instruments during pregnancy. In a cohort of 112 nulliparous

women and 82 male partners assessed during the first trimester, women in the IVF group reported significantly more muscular tension and irritability, while men in the IVF group reported more somatic and psychic anxiety, detachment, indirect aggression, and guilt.[457] In another study of 216 subjects, overall scores on a standardized marital function scale were high in both IVF and spontaneous conception parents, with IVF parents being consistently higher on 6 of 10 subscales; scores declined at 12 months postpartum for the control group but remained high in the IVF group.[458] A Finnish cohort using validated pregnancy-specific scales found no difference in pregnancy-related anxiety (RR for severe anxiety 1.23; 95 percent CI 0.83-1.86) or fear of childbirth (severe fear RR 1.08; 95 percent CI 0.72-1.63) when comparing nulliparous women after spontaneous or assisted conception.[459]

2. Other systematic reviews. Gestational diabetes was significantly increased in the review of Jackson and colleagues (OR 2.00; 95 percent CI 1.36, 2.99).[418] Risks were also substantially higher for preeclampsia (OR 1.55; 1.23-1.95) and placenta previa (OR 2.87; 1.54-5.37).

3. Conclusions. The risk of pregnancy complications associated with implantation – preeclampsia, placenta previa, and placental abruption – is consistently elevated in the studies we identified. This increased risk is biologically plausible, but it is unclear if this association is because of the underlying etiology or the treatment itself. Further insight into this question could be gained through properly designed and adequately powered studies that compare the incidence of these conditions between infertile women with tubal infertility only versus women with other conditions, especially unexplained infertility. Data on the risk of gestational diabetes are less consistent. Finally, the limited available data suggest that psychological outcomes during pregnancy for couples undergoing assisted reproduction are similar, or better than, couples after spontaneous pregnancy. Further studies of this question in other settings, and including fathers, are warranted.

VI. Infant Outcomes from Birth to 1 Year

A. Congenital anomalies. This section considers reports of congenital anomalies in ART-conceived children from birth to age 1 year.

1. Included studies. Table 56 summarizes studies meeting our inclusion criteria. In general, there is an increased risk of major malformations among infants born after IVF or ICSI which is also seen in those studies that included women receiving other types of infertility treatment. In those studies with sufficient size and data to allow controlling for potential confounders, risks decrease; in the largest population-based study, years of involuntary childlessness was a significant confounder.[460] There is insufficient evidence to determine whether there is a clear relationship with specific abnormalities, including disorders of imprinting.

Table 56. Congenital anomalies, birth to 1 year, in children conceived through assisted reproduction

Study	Exposure		N	Measure of Association		
				RR/OR	Lower 95% CI	Upper 95% CI
All malformations						
Anthony et al., 2002[461]	All mal-formations	Spontaneous	314,605			
		ART	4224	**1.20**	**1.01**	**1.43**
				1.03 (0.6-1.23) after adjustment for maternal age, race, parity		
	Major	Spontaneous	314,605			
		ART	4224	1.23	0.84	1.79
	Minor	Spontaneous	314,605			
		ART	4224	1.17	0.89	1.53
		Cohort (registry linkage)				
Belva et al., 2007[462]	Major	Spontaneous				
		ICSI		**2.94**	**1.10**	**7.88**
	Minor	Spontaneous				
		ICSI		1.42	0.89	2.25
		Cohort		60% response rate, self-report		
Bonduelle et al., 2002[415]	Major	IVF	2955			
		ICSI	2840	0.89	0.68	1.17
Bonduelle et al., 2004[463]	Reference	Spontaneous	266			
		ICSI	300	**2.30**	**1.00**	**5.32**
Bonduelle et al., 2005[464]	Reference	Spontaneous	538			
		IVF	437	**2.85**	**1.46**	**5.59**
		ICSI	540	1.88	0.90	3.95
Zhu et al., 2006[465]	Any ICD-10 malformation	Spontaneous, ≤ 12 months	50,870			
		Spontaneous, > 12 months	5764	**1.20**	**1.07**	**1.35**
		Infertility treatment	4588	**1.39**	**1.23**	**1.57**
				Adjusted for maternal age at conception, pre-pregnancy BMI, smoking, alcohol intake, coffee consumption, and occupational status. OR increased with time to pregnancy. Genital malformations only subgroup significantly elevated.		
Zadori et al., 2003[466]	Singleton	Spontaneous	188			
		IVF	188	4.07	0.45	36.72
	Twin	Spontaneous	174			
		IVF	174	0.49	0.04	5.56
				Controls matched for maternal age, parity, gravidity		
El Hage et al., 2006[467]		Spontaneous	2168			
		IVF	780	**2.30**	**1.26**	**4.19**
				Matching or adjustment not reported; IVF/ICSI patients significantly older		
Hansen et al., 2002[468]	All	Spontaneous	4000			
		IVF	837	**2.25**	**1.69**	**2.98**
		ICSi	301	**2.16**	**1.40**	**3.32**
	Singleton	Spontaneous	3906			
		IVF	527	**2.39**	**1.72**	**3.33**
		ICSI	186	**2.44**	**1.47**	**4.07**
				OR remained approximately 2 after adjusting for maternal age, parity, infant sex, and correlation between siblings		

Study	Exposure		N	Measure of Association		
				RR/OR	Lower 95% CI	Upper 95% CI
Kallen et al., 2005[460]	Reference	Spontaneous	2 million			
		IVF/ICSI	16,280	**1.27**	**1.18**	**1.36**
				ORs decrease, CIs include 1 after adjusting for year of birth, maternal age, parity, years of involuntary childlessness, maternal smoking		
Katalinic et al., 2004[469]	Reference	Spontaneous	8016			
		ICSI	3372	**1.45**	**1.26**	**1.67**
Klemetti et al., 2005[470]	Reference	Spontaneous	26,489			
		Non-IVF Rx	2930	**1.24**	**1.03**	**1.49**
		IVF	3926	**1.52**	**1.25**	**1.84**
Koivurova et al., 2002[471]	Reference	Spontaneous				
		IVF		1.53	0.83	2.81
Ludwig and Katalinic, 2002[472]	Reference	Spontaneous	30,940			
		ICSI	3372	**1.25**	**1.11**	**1.40**
Merlob et al., 2005[473]	Reference	Spontaneous	51,576			
		ART	1632	**1.73**	**1.48**	**2.03**
Olson et al., 2005[474]		Spontaneous	8442			
		IUI	343	1.13	0.70	1.82
		IVF	1462	**1.41**	**1.12**	**1.76**
Kuwata et al., 2004[475]		Spontaneous	94			
		Ovulation induction	113	2.3	0.7	7.3
		GIFT	83	**3.7**	**1.2**	**11.8**
		IVF	74	**3.5**	**1.1**	**11.5**
		ICSI	42	**6.7**	**2.1**	**21.9**
Buckett et al., 2007[476]		Spontaneous	350			
		In vitro maturation	55	1.27	0.51	3.18
		IVF	217	1.10	0.61	1.98
		ICSI	160	1.49	0.83	2.68
Specific anomalies						
Wu et al., 2006[477]	Neural tube	Controls	1608			
		Cases	18	Unadjusted ORs: 4.50 (1.45, 13.93) History of infertility treatment: 9.29 (2.95, 29.26) Clomiphene: 9.85 (2.72,35.71) Small number of cases prevents multivariate adjustment		
		Case-control				
Whiteman et al., 2000[478]	Neural tube	Unexposed	694			
		Treated for subfertilty	694	0.93	0.45	1.95
		Case-control (29 cases)				
Kallen and Robert-Gnansia, 2005[479]	Cranio-synostosis	No infertility treatment	706,450			
	Case-cohort	Any infertility treatment	22,770	1.13	0.66	1.93
		Case-control		Only significant exposure 1st trimester exposure to anti-convulsants		
Reefhuis et al., 2003[480]	Cranio-synostosis	Controls	833			
		Cases	41	**2.70**	**1.28**	**5.69**
		Case-control		Risk for clomiphene, IUI similar		

Study	Exposure		N	Measure of Association		
				RR/OR	Lower 95% CI	Upper 95% CI
Genetic abnormalities						
Aboulghar et al., 2001[481]	Reference	Spontaneous	430			
		ICSI	430	**30.03**	**1.80**	**501.13**
		Abnormal karyotype				
Lidegaard et al., 2005[482]	Imprinting disorders	Spontaneous	442,349			
		ICSI	6052	0.68	0.04	10.96

2. Other systematic reviews. We identified one relevant systematic review.[483] Summary odds ratios for IVF/ICSI combined were significantly elevated (OR 1.29; 95% CI 1.01, 1.67), but risks associated with either IVF or ICSI were not.

3. Conclusions. Risks for major congenital anomalies are increased after infertility treatment, but much of this risk appears to be related to maternal and/or paternal characteristics, including a history of subfertility or infertility. Given the relative rarity of specific birth defects, identifying an association between a specific exposure and subsequent risk is difficult.

B. Physical. This section considers adverse physical outcomes in ART-conceived children from birth to age 1 year.

1. Included studies. Ericson and colleagues conducted a population-based study in Sweden involving 9056 children born after IVF and over 1.4 million children born after spontaneous conception or other infertility treatment using linked data from ART and hospitalization registries.[484] After adjustment for maternal age, smoking, and parity, children born after IVF had an increased risk of hospitalization for any cause (OR 1.84; 95% CI 1.76-1.92). Risks were increased for term infants (OR 1.34; 1.27-1.41), singletons (OR 1.40; 1.32-1.48) and twins (OR 1.17; 1.07-1.27). The risk estimate decreased and became non-significant for term infants when compared to term infants born after other non-ART infertility treatment or spontaneous time to conception greater than 12 months. Hospitalization rates were highest in the first year, but stayed persistently elevated through age 6; rates were also increased with increasing time to conception. For specific diagnoses, adjusted risks were significantly increased for cerebral palsy, epilepsy, any neurologic diagnosis, tumors (although risk for invasive cancer was not increased), asthma, infection, and congenital malformations.

In an Israeli study of 8161 very low birth weight infants (1396 born after IVF, 6765 born after spontaneous conception), there were no significant differences in risk of any adverse outcome after adjustment for maternal age, gestational age, birth weight, SGA, ethnicity, antenatal steroid therapy, maternal hypertension, delivery mode, and resuscitation for singletons (n = 5975, 4.8 percent from IVF pregnancies), twins (n = 1694, 40.4 percent from IVF pregnancies) or triplets (n = 492, 90.0 percent from IVF pregnancies).[485] However, point estimates for almost every outcome were elevated, and confidence intervals were quite wide. Given the relatively small numbers, especially of spontaneous multiples, it is possible that adjustment for potential confounders, while appropriate, decreased the study's power to detect clinically relevant differences

2. Other systematic reviews. Risks for admission to the neonatal intensive care unit (NICU) and perinatal mortality for IVF singletons were elevated in all of the relevant systematic reviews,[372,418,419] although it is unclear to what extent this was due to the observed differences in preterm birth and low birth weight. Conversely, differences were not observed between IVF and spontaneous twins.[372,486]

3. Conclusions. In the neonatal period, although there is evidence of an increased risk for adverse outcomes, especially among singletons, it is unclear to what extent this is due to the observed increased preterm delivery rate. Large-scale studies that control for gestational age and birth weight are needed. In later infancy, there is a significantly increased hospitalization rate among children born after IVF/ICSI compared to the general population, but rates are similar when compared to children born to couples with a history of treated and untreated subfertility.

VII. Childhood Outcomes at 1 Year and Beyond

A. Physical. This section considers the evidence on adverse physical outcomes in ART-conceived children at age 1 year and beyond. We focused our review on large, preferably population-based, studies.

1. Included studies. As noted above, Swedish hospitalization rates through age 6 were significantly increased in IVF/ICSI children compared to the general population, although rates for children born at term were not increased when compared to similar children whose parents had experienced longer time to conception.[484] In a similar study in Denmark, IVF/ICSI twins has similar hospitalization/surgery rates compared to spontaneous twins, but significantly higher than IVF/ICSI singletons (term and preterm).[487] Increased risks for surgery by age 5 were also observed in a Belgian study among both IVF and ICSI children.[464]

Three large population-based studies found no evidence of an increase in childhood cancer rates in children conceived through assisted reproduction, including in Denmark (standardized incidence ratio [SIR] 1.14; 95% CI 0.8-1.5),[488] the Netherlands (SIR 0.99; 0.35-2.8),[489] and Australia (SIR 1.39; 0.40-4.77).[490] A case-control study did find an association between acute myelogenous leukemia (AML) in children with Down syndrome and a history of "ever trying more than 12 months to achieve pregnancy" (OR 2.22; 95 percent CI 1.44- 4.33).[491] However, this risk was not significantly increased for the index pregnancy (OR for trying more than 12 months for the index pregnancy compared to unplanned or conceived in less than 12 months 1.26; 95 percent CI 0.49-3.24).

2. Systematic reviews. We did not identify any other published systematic reviews of long-term outcomes in this age group.

3. Conclusions. Children born after assisted reproduction have an increased risk of hospitalization and surgery compared to general population controls. At least some of this risk is likely related to the underlying condition causing infertility, rather than to the treatment itself. It is also unclear to what extent these hospitalizations are secondary to conditions related to perinatal events, such as preterm delivery, versus an increased risk of conditions with later onset. Although no differences are observed between twins after treatment compared to other twins, twins born after infertility treatment are more likely to require additional hospitalization than singletons with the same history. Finally, there does not appear to be an increased risk of childhood cancers in children of women who received infertility treatments.

B. Neurological and developmental outcomes. The outcomes considered in this section can be divided into two broad categories: (a) those where there is an obvious physical and/or mental component to the outcome, such as cerebral palsy or epilepsy; and (b) more subtle abnormalities in intellectual and emotional development.

1. Included studies. A Danish study of over 83,000 children reported risks for epilepsy were increased in children of women with untreated subfertility (OR 1.38; 95% CI 1.00-1.89), women

treated with ovulation induction (OR 1.83; 1.09-3.06), and women treated with IVF/ICSI (OR 1.73; 1.06-2.71).[492]

Data on the relative incidence of cerebral palsy suggests that any increased risk of cerebral palsy in children born after fertility treatment is related to the increased risk of preterm birth described above. In a large Swedish study with over 14,000 subjects,[493] IVF was associated with an increased risk of cerebral palsy (RR 1.34; 0.95-1.89) and treatment at a childhood disability center (RR 1.70; 1.30-2.21). However, when stratified by plurality, the increased risk for cerebral palsy was seen only with IVF singletons compared to spontaneous singletons (RR 2.74; 1.29-5.86), but not with IVF twins compared to spontaneous twins (RR 1.07; 0.57-2.00). This is strikingly similar to the results described above for preterm birth and SGA. Another Swedish study found an increased risk for cerebral palsy among IVF singletons, especially if the pregnancy had started as a higher order gestation;[494] risk for cerebral palsy in IVF singletons was also confounded by SGA and prematurity.[435] A Danish population-based study[495] found no difference in the incidence of neurological sequelae, including cerebral palsy, or need for special services, when comparing IVF singletons, IVF twins, or spontaneous twins; presumably, the risk for all three groups was higher than for spontaneous singletons. The results of these studies suggest that any increased risk of cerebral palsy associated with ART may be related to the increased risk of premature delivery and SGA.

In general, the available evidence on development in children born after infertility treatment is reassuring, although the majority of the studies have been relatively small, and several are limited by differential accrual and/or dropout. All of the studies identified in our search focused on children born after IVF and/or ICSI showed either no differences in scores on any standardized neurodevelopment or learning scale,[496,497] or small differences that were explained by differences in other predictors such as paternal education level.[498,499] A population-based case-control study in Denmark found a lower risk of autism after infertility treatment (OR 0.37; -95 percent CI 0.14-0.98);[500] however, the diagnosis of autism in this case was based on hospital or clinic ratings.

2. Other systematic reviews. We did not identify any other systematic reviews relevant to this topic.

3. Conclusions. The available evidence suggests that there is not an increase in the risk of adverse neurodevelopmental outcomes in children born after infertility treatment that is not associated with the underlying condition of infertility or the well-established increased risk resulting from prematurity and SGA. The findings of the Scandinavian cerebral palsy studies, which show increased risks of cerebral palsy between IVF singletons compared with spontaneous singletons, but not IVF and spontaneous twins (or IVF singletons) are strikingly similar to the literature on prematurity and SGA among IVF singletons and twins described above. The available evidence on learning and other developmental outcomes is reassuring, but larger studies across a wider population are needed.

VIII. Maternal Outcomes: Long-Term

A. Breast cancer. Long-term exposure to estrogen and/or progestins, manifested through such markers as early menarche, late menopause, nulliparity, and late onset of first pregnancy, has long been associated with an increased risk of breast cancer. Because these factors are also associated with infertility (especially anovulation[501]), and because many infertility treatments may lead to transient increases in estrogen and/or progesterone, infertility treatment could

plausibly increase the risk of breast cancer.[502] Because breast cancer is the most common cancer in women,[503] even a relatively small increase in relative risk could translate into a large increase in the absolute risk.

1. Included studies. Included studies are summarized in Table 57. Consistently, use of clomiphene or gonadotropins was not significantly associated with an increased risk of breast cancer, especially when compared to other infertile controls and adjusted for other potential confounders such as age at followup and family history.

Cancers diagnosed within a short time of the onset of treatment are unlikely to be caused by the treatment itself. The intensive schedule of medical contacts associated with medical treatment could lead to earlier detection; alternatively, treatment could increase the rate of growth enough to make a subclinical cancer present earlier (these explanations are not mutually exclusive). The included studies did not provide conclusive evidence for this effect. An Israeli study[504] found that the standardized incidence ratio decreased when cases diagnosed within the first year after the beginning of treatment were excluded, consistent with both earlier detection and treatment-based acceleration of pre-existing tumors. On the other hand, a large U.S. cohort study[505] found similar elevations in the standardized incidence ratio (SIR) and the standardized mortality ratio (SMR), suggesting similar stage distributions in infertile patients, which is inconsistent with earlier detection.

The same U.S. cohort study[505] found some evidence of an increased risk 20 years after exposure, but these risks did not reach statistical significance (clomiphene OR 1.39; 95 percent CI 0.9-2.1; gonadotropins OR 1.54; 0.84-3.2). If this association is real, the number of cases should increase as the cohort of women who received treatment ages, since the incidence of breast cancer increases with age, allowing a more precise estimate of the risk.

The observed association of progesterone and breast cancer seen in a large Danish study[506] should be interpreted with caution, since the actual number of reported exposures was much smaller than the number of women likely to have been exposed, given the ubiquity of progesterone for luteal support in ART.

Table 57. Infertility treatments and breast cancer

Study	Exposure		N	Measure of Association		
				RR/OR	Lower 95% CI	Upper 95% CI
Exposure to clomiphene and/or gonadotropins						
Brinton et al., 2004[505]	Reference	Population (standardized incidence ratio)				
		No exposure to clomiphene		**1.28**	**1.1**	**1.5**
		Clomiphene		**1.29**	**1.1**	**1.6**
		No exposure to gonadotropins		**1.28**	**1.1**	**1.4**
		Gonadotropins		1.40	0.9	2.0
	Study Type	Cohort ; n = 8431		Adjusted within-group risks (adjusted for age at followup, calendar year, site, and family history): clomiphene 1.02 (0.8, 1.3); gonadotropins 1.07 (0.7, 1.6). Risk estimates higher 20 years after exposure (clomiphene 1.39 (0.9, 2.1), gonadotropins 1.54 (0.8, 3.2).		
Brinton et al., 2004[505]	Reference	Population (standardized incidence ratio)				
		All subjects		**1.29**	**1.1**	**1.4**
		Population (standardized mortality ratio)		-	-	-
		All subjects		**1.58**	**1.1**	**2.2**
	Study Type	Cohort ; n = 8431		Same study as above; similar findings for mortality suggests no detection bias in patients with infertility		
Burkman et al., 2003[507]	Reference	Controls	4682			
		Cases	4575	0.9	0.8	1.2
	Study type	Case-control		Risk increased in women treated with hMG ≥ 6 months/cycles (ORs for all subgroups >2.0, 95% CIs do not include 1.0)		
Terry et al., 2006[508]	Reference	No infertility				
		Ovulatory infertility, no induction		1.37	0.94	1.99
		Ovulatory infertility, induction		**0.60**	**0.42**	**0.85**
		Other infertility		0.67	0.35	1.25
	Study type	Cohort; n = 116,741		Adjusted hazard ratios		
Jensen et al., 2007[506]	Reference	Infertility, no treatment				
		Gonadotropins		1.20	0.82	1.78
		Clomiphene		1.08	0.85	1.39
		hCG		0.94	0.73	1.21
		GnRH		1.28	0.75	2.19
		Progesterone		**3.36**	**1.60**	**7.07**
	Study type	Cohort, n = 54,362				
At least 1 cycle IVF						
Dor et al., 2002[509]	Reference	Population (standardized incidence ratio)				
		IVF		0.69	0.46	1.66
	Study Type	Cohort; n = 5026				

Study	Exposure		N	Measure of Association		
				RR/OR	Lower 95% CI	Upper 95% CI
Kristiansson et al., 2007[510]	Reference	1st births				
		No IVF				
		IVF		0.74	0.40	1.26
	Study Type	Cohort, n = 647,704		Women identified as having 1st birth from 1988-2001		
Venn et al., 2001[511]	Reference	No IVF				
		IVF		1.18	0.55	2.52
	Study type	Cohort: n = 29,700; outcome: breast cancer death				
Any infertility treatment						
Gauthier et al., 2004[512]		Unexposed	85948			
		Any treatment	6602	0.95	0.82	1.11
		Treated with drugs/IVF		0.94	0.78	1.12
	Study Type	Cohort ; n = 92,550				
Lerner-Geva et al., 2003[504]	Reference	Population (SIR)				
		Any treatment		1.02	0.33	2.39
	Study type	Cohort: n = 1082; any treatment for infertility 1984-1992		SIR decreased when cancers detected within 1st year of infertility treatment excluded – detection bias		
Lerner-Geva et al., 2007[513]	Reference	Population (SIR)				
		Any treatment		1.14	0.95	1.40
	Reference	Untreated infertility				
		Treated infertility		1.11	0.79	1.56
	Study type	Cohort: n = 5788; any treatment for infertility 1984-1992		SIR decreased when cancers detected within 1st year of infertility treatment excluded – detection bias		

2. Other systematic reviews. We did not identify any other systematic reviews.

3. Conclusions. In general, infertility treatments involving ovarian stimulation do not appear to be associated with an increased risk of breast cancer, although non-significantly elevated risks were seen 20 years after exposure in one study, suggesting that continued monitoring is warranted.

B. Ovarian cancer. Several case-control studies published in the 1990s reported a significant increase in the risk of ovarian cancer in women receiving ovulation stimulating drugs; the association was biologically plausible, since increased ovulation (early menarche, late menopause, nulliparity, no breast feeding, no use of oral contraceptives) has consistently been associated with an increased risk of breast cancer.[502] Although ovarian cancer is not as common as breast cancer, the morality rate is much higher.[503]

1. Included studies. Included studies are summarized in Table 58. As with breast cancer, the association appears to be with infertility itself rather than with any particular treatment. For example, a large U.S. study found almost identical risks across all categories of clomiphene or gonadotropin use in a cohort of infertile patients.[514] Of note, the risks were both higher (suggesting a stronger association) and had wider confidence intervals (reflecting the relative rarity of ovarian cancer compared to breast cancer) when compared to risks for breast cancer in the same study. As with breast cancer, there were non-significant increases with increasing duration since exposure; in addition, women who were nulliparous at the time of followup also had an increased risk (OR 1.75; 95 percent CI 0.5-5.7). In another publication from the same study,[515] the risk was significantly elevated with primary infertility (OR 2.73; 1.8-4.0), but not secondary infertility (OR 1.44; 0.9-2.2). When stratified by infertility etiology, risks were

significantly increased for endometriosis, tubal factor, and anovulation, but not for male, cervical, or uterine factor; because ovarian cancer arises from the surface of the ovary, it is biologically plausible that conditions which may result in abnormal stimulation of the ovary (such as PCOS) or inflammatory reactions of the ovarian surface (such as endometriosis or pelvic inflammation) would be associated with ovarian cancer, while infertility causes not associated with abnormalities of the ovary would not.

An Israeli cohort study[504] found an increased SIR in women who received any treatment for infertility (SIR 5.0; 95 percent CI 1.02-14.6), but the SIR decreased when tumors detected within the first year of treatment were excluded, consistent with increased detection as part of the infertility evaluation, more rapid growth of prevalent tumors as the result of treatment, or both.

Table 58. Infertility treatments and ovarian cancer

Study	Exposure		N	Measure of Association		
				RR/OR	Lower 95% CI	Upper 95% CI
Exposure to clomiphene and/or gonadotropins						
Brinton et al., 2004[514]	Reference	Population (SIR)				
		No exposure to clomiphene		**2.09**	**1.4**	**3.0**
		Clomiphene		**1.79**	**1.0**	**3.0**
		No exposure to gonadotropins		**1.95**	**1.4**	**2.7**
		Gonadotropins		2.26	0.7	5.3
	Study Type	Cohort ; n = 8429		Adjusted within-group risks non-significantly higher in women with > 12 cycles clomiphene (OR 1.54, 95% CI 0.5, 5.1) or > 9 cycles gonadotropins (OR 1.21, 95% CI 0.4, 3.9); or more than 15 years since exposure (clomiphene OR 1.48, 95% CI 0.7, 3.2; gonadotropin OR 2.46, 95% CI 0.7, 8.3). Risk also increased in women who were still nulliparous at followup (OR 1.75, 95% CI 0.5, 5.7). No other adjusted ORs above 1.2.		
Brinton et al., 2004[515]	Reference	Population (SIR)				
		Primary infertility		**2.73**	**1.8**	**4.0**
		Secondary infertility		1.44	0.9	2.2
	Study Type	Cohort ; n = 8429		Risks significantly increased for endometriosis, tubal factor, anovulation; not significant for male, cervical, uterine. Highest risk with endometriosis.		
Parazzini et al., 2001[516]	Reference	Controls	2411			
		Cases	1031	1.35	0.71	2.57
	Study type	Case-control				
Rossing et al., 2004[517]	Nulliparous	Controls	311			
		Cases	140	0.88	0.32	2.42
	Parous	Controls	948			
		Cases	613	0.85	0.45	1.59
	Study type	Case-control		Risk increased for nulliparous infertile women (1.59;1.01-2.50) but not for parous women with history of infertility (0.91; 0.69-1.19).		
At least 1 cycle IVF						
Dor et al., 2002[509]	Reference	Population (SIR)				
		IVF		0.57	0.01	3.2
	Study Type	Cohort; n = 5026				

Study	Exposure		N	Measure of Association		
				RR/OR	Lower 95% CI	Upper 95% CI
Any infertility treatment						
Lerner-Geva et al., 2003[504]	Reference	Population (SIR)				
		Any treatment		**5.0**	**1.02**	**14.6**
	Study type	Cohort: n = 1082; any treatment for infertility 1984-1992		SIR decreased when cancers detected within 1st year of infertility treatment excluded – detection bias		
Cusido et al., 2007[518]	Reference	Controls				
		Any history of infertility		0.45	0.18	1.10
	Study type	Case-control (controls benign ovarian surgery)		Borderline tumors only		
Tworoger et al., 2007[519]	Reference	No infertility				
		Female infertility		**1.36**	**1.07**	**1.75**
		Male infertility		1.23	0.68	2.25
	Study type	Cohort, n=121,700		Adjusted for age, BMI, parity, history of tubal ligation, smoking history, age at menarche, age at menopause, duration of postmenopausal hormone use, and duration of oral contraceptive use		

2. Other systematic reviews. We identified two systematic reviews. The first[520] pooled data from eight case-control studies with 5207 cases and 7705 controls, adjusting for age, race, family history of ovarian cancer, duration of oral contraception use, tubal ligation, gravidity, education, and site. Time to pregnancy was significantly associated with risk (greater than 5 years compared to less than 1 year: OR 2.67; 95 percent CI 1.91-3.74). Fertility drug use was not associated with ovarian cancer among nulliparous, subfertile women (any use OR 1.60; 95 percent CI 0.90-2.87; greater than 12 months use OR 1.54; 0.45-5.27). An association with borderline tumors, but not invasive cancers, was found for fertility drug use in nulligravid women (OR 2.43; 95 percent CI 1.01-5.88). Certain causes of infertility were associated with ovarian cancer risk: endometriosis (OR 1.73; 1.10-2.71) and unexplained infertility (OR 1.19; 1.00-1.40).

The second review used published data from seven case-control studies and four cohort studies.[521] Among case-control studies, cancer risk was increased when cases were compared to general population or hospital-based controls (OR 1.52; 95 percent CI 1.18-1.97), but not with infertile controls (OR 0.99; 0.67-1.45). An association was not observed in the cohort studies comparing treated and untreated subjects with infertility (adjusted hazard ratio 0.67; 95 percent CI 0.32-1.41).

3. Conclusions. Ovarian cancers are even more strongly associated with an infertility diagnosis than breast cancer; however, use of ovulation-stimulating drugs does not appear to increase the risk above baseline levels in this patient population. As with breast cancer, increasing risk with increased duration with treatment cannot be ruled out with confidence.

C. Other cancers. As with breast cancer, many of the risk factors associated with endometrial cancer are associated with infertility, especially anovulation.[501] Data on associations with other cancers might provide insight into issues related to study design and interpretation.

1. Included studies. Identified studies are summarized in Table 59. We identified one case-control study examining the risk of endometrial cancer and use of fertility drugs,[522] which found no association. One major limitation of this study is that exposure status was by self-report only, with no verification.

Two cohort studies examined the association with a variety of cancers. A Swedish study found no association, either globally (OR 1.00; 95 percent CI 0.71-1.36) or for individual cancers, although the risk of carcinoma in situ of the cervix was significantly lower in IVF patients when the date of conception, rather than the date of first treatment, was used as the start of followup.[510] One explanation for this is that women undergoing infertility treatment are screened more intensively than similarly aged women, given that the screening interval in the Swedish program is 3 years in reproductive aged women;[523] treatment of lesions detected during the infertility evaluation would lead to a decreased prevalence by conception, with subsequent decreased detection through screening. This provides supportive evidence that contact with the medical system during infertility evaluation and treatment may lead to increased detection of prevalent cancers. Similarly, an Israeli study[504] found non-significantly increased SIRs for both cervix (SIR 4.6; 95 percent CI 0.93-13.5) and other non-reproductive cancers (SIR 2.05; 0.98-3.78), with a decrease in SIR when cancers detected within the first year after beginning treatment were excluded. This is consistent with an increased detection of prevalent cancers in this patient population, either through increased detection, acceleration of tumor growth, or both.

Table 59. Infertility treatments and other cancers

Study	Exposure		N	Measure of Association		
				RR/OR	Lower 95% CI	Upper 95% CI
Endometrial cancer						
Ben-shushan et al., 2001[522]		No fertility drugs	128			
		Any fertility drug	255	1.43	0.53	3.81
	Study Type	Case-control		Exposure by self-report only		
Any cancer						
Kristians-son et al., 2007[510]	Reference	No IVF				
		IVF		1.00	0.71	1.36
	Study type	Cohort; n = 647,704 (1st births)		CIS of cervix significantly lower in IVF when date of conception used as start of followup – ?detected/treated prior to IVF referral		
Lerner-Geva et al., 2003[504]	Reference	Population (SIR)				
		Cervix		4.6	0.93	13.5
		Other		2.05	0.98	3.78
	Study type	Cohort: n = 1082; any treatment for infertility 1984-1992		SIR decreased when cancers detected within 1st year of infertility treatment excluded—detection bias		
Venn et al., 2001[511]	Reference	No IVF				
		IVF		0.72	0.46	1.13
	Study type	Cohort: n = 29,700; outcome: cancer death				

2. Other systematic reviews. We did not identify any other systematic reviews on this topic.

3. Conclusions. There is no available evidence suggesting an increased risk of other cancers with either infertility or infertility treatment. Available data on the incidence of preinvasive and invasive cervical cancer is consistent with increased detection as part of the infertility evaluation.

D. Other long-term outcomes. The inability to spontaneously conceive within a "normal" time frame, the nature of evaluation and treatment, and the risk of pregnancy or neonatal complications are all associated with significant emotional impact.[18,524] This section discusses the available evidence on long-term psychological outcomes in parents.

1. Included studies. The majority of studies compared mean or median scores on validated quantitative scales. We summarize results for individual studies.

Post-partum. Fisher and colleagues[525] found no significant difference in postpartum depression using the Edinburgh Postnatal Depression Scale between spontaneous, ovulation induction, or IVF mothers, but within the cohort of 745, there were only 12 ovulation induction pregnancies and 45 IVF pregnancies, limiting the study's power.

ART versus spontaneous conception: singletons. Three studies evaluated marital and parenting skills over time. McMahon and Gibson[526] followed a cohort of 133 IVF and spontaneous singleton pregnancies through 12 months post-delivery, using both self-reported and observer-based scales. At 30 weeks, IVF mothers had lower self-esteem, greater external locus of control, and much higher anxiety about defects in baby and injury during birth, while fathers had lower self-esteem, higher trait anxiety, and lower marital satisfaction. At 4 months post-delivery, IVF infants had more fussing, but there were no significant differences in maternal behaviors (despite self-reported lower feelings of competence among IVF mothers). Finally, at 12 months, there were no differences in any self-reported items for mothers, but IVF fathers reported lower self-esteem and less caring from spouses. IVF mothers reported more difficult infants, but no differences in observed behaviors

In a Finnish cohort of 748 singleton pregnancies,[527] overall parenting scores at 2 months post-delivery were higher for ART mothers, and increased significantly from 2 to 12 months, while parenting scores did not improve in the spontaneous conception group. Obstetric risk factors and problems and difficult child characteristics were negatively associated with parenting scores in the spontaneous group but not in the ART group. A second paper from this study found similar patterns for marital adjustment – overall marital functioning measured using standard scales was substantially better at 2 months post-partum for ART couples.[528]

Effect of multiple gestation. In an ART-only cohort, Ellison and colleagues[529] compared singletons to twins to triplets among 249 ART conceptions. The prevalence of difficulty meeting material needs, lower quality of life, and social stigma were significantly increased in parents of multiples, with an evident dose-response: prevalences were higher in triplets than twins. Depression and lower marital satisfaction were also increased, but not significantly.

In a UK study,[530] mothers of multiples were more likely to report significant parenting stress and depression, and less likely to be employed at 12 months than mothers of IVF or spontaneous singletons. Another study from the UK[531] also found a significantly increased risk for post-partum depression (defined as a score greater than 12 on the Edinburgh Postnatal Depression Scale; RR 3.43; 95 percent CI 1.01-11.6).

Tully and colleagues[532] found no differences in any scale of parental or child behavior at 5 years between spontaneous twins or twins from ovulation induction or IVF in a cohort of 242 twin pregnancies. In a Japanese cohort study of 990 multiples, Yokoyama and colleagues[533] found depressive symptoms more common in infertility groups in univariate analysis; in multivariate analysis, the only significant predictors of depressive symptoms were at least one disabled child and no method for alleviating stress. The univariate association between infertility and depressive symptoms was likely due to a higher incidence of higher order multiples, because higher order multiples will deliver earlier on average (resulting in a greater risk of disability), and, for a given gestational age at delivery, larger numbers of children increase the likelihood that at least one of them will be disabled.

2. Other systematic reviews. We identified one systematic review on this topic.[534] The review identified 27 relevant articles that included control groups and used validated

instruments. At baseline, there were no substantial emotional differences in women undergoing IVF compared to controls; those that were present resolved with pregnancy. A subgroup of women had persistent emotional difficulties after unsuccessful IVF.

3. Conclusions. Based on the available literature, there are no differences in psychological outcomes, including parenting skills, when comparing singleton pregnancies resulting from ART to spontaneous conceptions. If anything, mothers of infants resulting from ART have better outcomes, although there is some evidence that fathers may do worse on some scales. Multiple gestations significantly increase stress and depressive symptoms, especially for mothers of infants with chronic disabilities; to the extent that women undergoing ART are more likely to experience multiples, especially preterm multiples, they are more likely to experience these symptoms. Clearly further research is needed. One caveat is that all of these studies were performed outside the United States – the extent to which differences in socioeconomic factors between couples undergoing ART in the United States and in other countries might affect these outcomes is unclear.

Chapter 4. Discussion

This review has several limitations.

No literature search strategy has 100 percent sensitivity. We used standard electronic searching strategies, using appropriate key words, supplemented by hand searches of key articles and systematic reviews; we also asked peer reviewers of the draft report to suggest any relevant articles which may have been missed. At every stage of the review process, the presumption was towards inclusion if there was any doubt. However, it is entirely possible that some relevant articles may not have been identified in our search, and that the results of these articles would have changed our conclusions. In addition, studies may have been published subsequent to the cut-off date of our search (January 2008) that would affect our conclusions.

We limited our search to English-language articles. This may have led to omission of studies that would otherwise have met our inclusion criteria, especially for studies related to complementary and alternative medicine adjuncts, or observational studies of less common outcomes or different ethnic groups. Exclusion of abstracts may have led to the omission of important results, especially negative findings or more recent findings which have not yet appeared in press.

We did not include published abstracts. The primary effect of this exclusion is that very recently presented studies which have not yet been published but which may be relevant to this report have not been included.

We limited studies comparing the short-term results of different interventions to randomized trials. Although the randomized trial is considered the reference standard for evaluating treatment efficacy, it is possible that an observational study with sufficient sample size and enough detail on potential confounders to allow adequate statistical methods would have provided useful additional information. However, recent experience comparing the results of observational studies and randomized trials suggests that even when observational studies use state-of-the-art methodology, their results may not be confirmed by randomized trials. We also excluded studies that explicitly stated that they used a method of "quasi-randomization" (for example, allocating treatment based on alternate days of the week), since these study designs have been shown to be more likely to have biased results or exaggerated results,[36] especially in the context of small trials.[535]

We limited studies comparing longer term outcomes to observational studies with at least 100 subjects and with a reasonable comparison group. Again, this may have led to the omission of potentially useful case series, or small case-control studies with particularly strong associations.

We did not perform meta-analyses for several reasons. First, based on the volume of literature to review and the rapid changes in clinical practice in this field, we limited our review to articles published in 2000 or later – comprehensive meta-analyses would have required more extensive searches. Second, both the Cochrane Menstrual Disorders and Subfertility Group, as well as independent researchers, have been quite active in producing formal meta-analyses, and, especially for more recent updates, there is no reason to believe we would have reached substantively different results. Third, given the diversity of patient populations and clinical protocols, there was substantial clinical heterogeneity among the included studies. In this setting, we believe a qualitative description of findings and methodological issues, along with specific recommendations for future research, is at least as helpful as a quantitative estimate of

relative effect. Finally, the pooled results of multiple small trials do not always agree with the results of larger individual studies;[536,537] the existence of a well-done meta-analysis does not necessarily obviate the need for an appropriately designed and sized trial, particularly if the goal is to establish equivalence.

Chapter 5. Future Research

Study Design and Data Collection

Many, if not most, of the issues regarding study design discussed in this report have been consistently identified by other authors as barriers to drawing inferences about the safest and most effective interventions in reproductive medicine.[36,538,539] These include the use of surrogate endpoints, failure to report key endpoints such as live birth, analysis based on non-independent measures such as cycles or embryos rather than the patient or couple, inadequate sample size, failure to follow "standard-of-care" in treatment allocation, and the use of inappropriate statistical measures. Studies of longer term outcomes face a particular challenge in identifying the appropriate control group.

Potential ways that some of these deficiencies can be addressed include:

- **More multi-center trials.** Given the large sample sizes needed to demonstrate improvement in live birth rates, let alone differences in less common outcomes, it is highly unlikely that any one center could efficiently complete an adequately powered study for most questions. Any individual center with a high enough volume to recruit sufficient subjects in a reasonable time may well be too busy to have the necessary research infrastructure. Given the relative patient volume in academic compared to private centers, this may require identifying new ways to better incorporate large private centers into clinical trials, particularly non-industry trials.

- **Consensus on a clinically meaningful minimal difference for all important outcomes.** Study planning and peer review of grants and manuscripts would be much simpler if there were a consistent, generally accepted target. This threshold is somewhat arbitrary, and should include input from patients and the general public. Given that sample sizes of greater than 300 per arm are necessary to show a difference of 10 percent, given current IVF success rates, any difference smaller than 10 percent, even if judged important by patients or clinicians, is likely to require larger studies than are currently fundable.

- **Development and use of standards for collecting data and/or reporting results to facilitate meta-analysis.** For a variety of reasons, including academic pressure to publish, logistical issues in setting up and conducting multi-center trials, and the time required to conduct large scale trials,[539] the smaller clinical trial conducted in an individual center is unlikely to be completely replaced by a mega-network for doing multicenter trials. In addition, even for large trials, sample size may be inadequate for less common outcomes, suggesting that there will be an ongoing need for meta-analysis. Development and use of a standard data set, using common definitions for outcomes and collection of data on key variables known to affect outcome, would facilitate these pooled analyses. Ideally, this would include options for long-term followup of both mother and baby.

- **More trials using cumulative outcomes over several cycles.** Ultimately, the probability that a couple will have a successful outcome over a full course of treatment,

which may include multiple cycles, is more important than the individual cycle probability. Trials should, to the degree possible, reflect the clinical strategy. Depending on the estimated effect difference, a cumulative study might require fewer subjects, but more total overall cycles. There may well be trade-offs between the costs of several cycles in a subject versus the costs of recruitment.

Barriers to High-Quality Research

We found that only approximately 20 percent of the included studies were performed in the United States. While this is roughly equivalent to the proportion of ART cycles performed in the United States compared to other countries,[540] it is not necessarily consistent with a goal of U.S. scientific leadership. There are several factors which contribute to this disparity:

- **Available data.** Many European countries, in particular, have well-established national registries for a variety of outcomes that allow linkage, selection of appropriate controls, and large numbers. Although the U.S. ART registry is comprehensive, the main limitation is that there is no patient identifier, meaning that (a) the unit of analysis must be the cycle, rather than the patient, and (b) there is no way to link ART data to patient outcomes that might appear in other databases/registries, such as cancer or death registries.

- **Incentives for evidence.** As mentioned in the Introduction, the United States does not have either government or third-party payers generating pressure for evidence, compared to countries with single-payer or other systems that provide reimbursement for infertility services. This may be short-sighted: in a setting where a patient must pay for infertility but an insurance company pays for obstetric, neonatal, and, potentially, long-term health needs, the patient has every incentive to maximize the chances of pregnancy over the fewest cycles, since the greater long-term costs associated with multiple pregnancies are borne by outside payers (this discussion obviously considers only costs, not patient preferences for different outcomes). It is inherently difficult in most clinical settings to adequately counsel patients about balancing quantitative risks and benefits; this task is made even more difficult when the evidence base is inadequate. In addition, both practitioners and patients may not have sufficient familiarity with the methodological issues involved in interpreting outcome statistics to use this information to make truly informed decisions. For example, although the American Society for Reproductive Medicine (ASRM)/SART registry provides clinic-specific per-cycle data, these data are not adjusted for individual patient characteristics that may affect the likelihood of a successful outcome.

- **Regulatory pressure for clinical trials.** There is no FDA requirement for approval of new procedures, or variations on old procedures. Criteria for approval of medical devices rarely, if ever, include randomized trial data on efficacy of interventions using these devices. Only drugs used for specific indications require documentation of effectiveness in a randomized trial; not surprisingly, of the topics reviewed above, randomized trials

were most common for newer pharmaceutical agents such as GnRH antagonists and recombinant hormones.

- **Legislative barriers.** The 1996 Dickey-Wicker Amendment to the 1996 Department of Health and Human Services appropriations bill states that no federal funds may be used for the following: "the creation of a human embryo or embryos for research purposes, or research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero." "Human embryo" is defined broadly as "any organism, not protected as a human-subject under 45 C.F.R. 46 . . . that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells." This standard is applied both to embryos intended for termination or discarding, and those intended to be carried to term. Since almost any clinical trial of assisted reproduction would carry some risk to some embryos, this has had the practical effect of inhibiting federally funded research. Recent controversies over the potential use of embryos for stem-cell research have added further pressures that inhibit research protocols.

Many of these barriers are the consequence of long-standing issues (e.g., paying for health care, abortion) that are unlikely to be resolved in the near future. However, a major step towards improving both the quality of data available for research and the immediate outcomes data available for patients would be mechanisms for ensuring that data in the ART registry are able to be analyzed at the individual patient level, and that validated risk adjustment methods are used for reporting clinic-specific results.

Areas for Prioritizing Research

I. Clinical Research

This review found that there is insufficient evidence to draw conclusions about the relative safety and efficacy of the majority of interventions used in ART.

First, high-quality, adequately powered studies of interventions currently in use should be the highest priority.

The few studies we identified regarding technical aspects of ART (for example, studies comparing the method for thermal regulation during ICSI[318]) suggested that, in some cases, the techniques and equipment used for individual aspects of the process can have a measurable impact on clinical outcomes. As new technologies are introduced, every effort should be made to test their clinical impact (or lack thereof) using appropriate study designs.

Studies of procedures performed on men, and on health outcomes in men after ART, even if no procedure is performed, should be a high priority. The few studies of psychological outcomes in men we did identify suggested that fathers may have more problems after ART compared to mothers.

Finally, as discussed in the section on preterm birth, the increased risk of preterm birth in ART singletons is equivalent to the increased risk observed in women with a history of prior preterm birth. Given this large relative and absolute risk, the effectiveness of progesterone for preventing preterm delivery in women with a history of preterm birth,[420] and the evidence for the

need for progesterone supplementation after ART, an appropriately designed and powered trial of continuing progesterone throughout pregnancy in singleton pregnancies after ART should be considered.

II. Epidemiologic Research

Larger, longer term studies of outcomes in both mother and infant are needed. Ideally, these should be prospective, with adequate characterization of the exposure – in particular, identifying ways in which exposures differ from current practice to allow better estimation of the risk for current patients. Particular emphasis should be put on the long-term followup of participants in clinical trials.

One area we would highlight in particular is the association between infertility and infertility treatment, difficulty with implantation, and subsequent risk of adverse outcomes of pregnancy related to placentation. Insights derived from basic and translational research, particularly research that crosses disciplines, could prove invaluable both for infertility patients and obstetric patients. In addition, there is growing evidence of a link between adverse pregnancy outcomes and an increased risk of maternal cardiovascular morbidity and mortality in later life.[541,542] If the link between infertility and adverse pregnancy outcomes is primarily due to the infertility rather than the treatment, then certain types of infertility besides PCOS (where the link is thought to be related to the accompanying insulin resistance) may also represent a risk factor for subsequent cardiovascular morbidity and mortality.

III. Health Services Research

Finally, there are several promising avenues for health services research.

There are almost no data using utilities or other standard measures for patient preferences or decisionmaking in infertility. Studies finding that many couples consider a multiple gestation to be a favorable outcome, especially when compared to the prospect of either no pregnancy or prolonged treatment,[543-547] suggest that further research into decisionmaking is needed. Such research would also help interpret the results of studies of the impact of insurance coverage changes, which to date show variable results.[30,31] If cost-effectiveness analysis is ultimately going to be a tool for helping policymakers, then methods have to be developed that allow translation of outcomes of infertility treatment, which involve three (or more) individuals, into a common denominator such as quality-adjusted life years. The relative lack of a third-party intermediary between patient and clinician suggests that further studies of infertility practice as a market may provide insight into the potential impact of “market-based” reforms in other areas of health care.

Chapter 6. Conclusions

Ovulation Induction without Assisted Conception (Question 2)

I. General Issues

Despite screening 181 full-text articles for eligibility, we are limited in our ability to draw conclusions about most of the topics discussed under Question 2. Several methodologic issues were consistently seen in our review.

First, there were relatively few randomized trials compared to the overall volume of literature. Although this is obviously a problem not limited to studies of ovulation induction, or reproductive medicine in general, there are several unique barriers to conducting appropriately designed studies in this field; these barriers are discussed in detail in the "Future Research" chapter, above.

Second, the majority of the studies do not provide data on live birth rates or other obstetric outcomes. Although there is ongoing debate about the most appropriate primary outcome for studies in infertility,[539] live birth per couple is widely considered both methodologically and clinically appropriate and important. Although surrogate outcomes such as ovulation and pregnancy may require smaller sample sizes or shorter duration trials, the intuitively appealing link between surrogates and the ultimate outcome of live birth is not always borne out when ultimately tested.[548] For example, increased ovulation rates with metformin compared to clomiphene have been observed in some randomized trials, but as discussed in the Results chapter, do not translate into increased live birth rates.

Second, the size of individual studies was almost universally too small to detect clinically important differences in pregnancy and live birth rates. Given that live birth is a dichotomous outcome, large sample sizes will be necessary; the largest study, the PPCOS study, enrolled over 200 women per arm to establish a 15 percent absolute difference in live birth rates. There does not appear to be consensus on what should be the minimal clinically important difference; given that there are frequently tradeoffs between live birth rate and the risk of multiple gestation or other complications, this difference may vary with different treatments in different patient populations. Again, this should be a high priority for future research, one which should ideally involve clinicians, policymakers, and patients, using rigorous methods for estimating preferences for different outcomes. One of the few studies to use standard methods for quantifying patient preferences found that women were willing to take on an increased risk of short-term complications and multiples in order to increase their absolute live birth rate by 5 percent,[549] a difference which would require very large (> 1000 subjects) trials to determine.

A corollary of the sample size issue is that studies which do have sufficient power to detect differences in live birth rates are highly unlikely to have the power to detect clinically important differences in less common outcomes such as multiple gestation, pregnancy complications, and short-term complications of treatment such as OHSS. As others have pointed out,[36] the lack of a statistically significant difference in an outcome is not the same as demonstration of equivalence, especially given that the confidence intervals for these less common outcomes is almost always quite wide. Studies specifically designed and powered to detect differences in other important

clinical outcomes, or greater consensus on study design issues to reduce heterogeneity and improve the precision and reliability of meta-analytic methods, are needed.

One strength of the literature on ovulation induction and superovulation is that the majority of trials, especially more recent trials,[550] involve randomization to a treatment arm and continued treatment on that arm for a specified period of time. This is important from both a statistical[36] and clinical viewpoint, since most treatments are continued for several cycles. One goal of protocol design in clinical trials is to reflect clinical practice as much as possible. Study designs that randomize couples to a single treatment cycle of a treatment strategy generally do not reflect typical practice and may miss differences in cumulative rates of outcomes that are not detectable after a single cycle.

II. Ovulation Induction in Anovulatory Women

Based on our review, there are several aspects of interventions for ovulation induction in women with PCOS for which there is either strong evidence, promising evidence from single studies worth confirming with additional trials, or evidence of short-term benefit needing confirmation of long-term safety.

Clomiphene is an effective first-line therapy for women with PCOS. Metformin is, at best, no more effective, and, based on a large multi-center trial, less effective than clomiphene alone. Potential explanations for the disparity between the findings of the two randomized trials published to date, such as genetic variability in responses to the different agents, are worth further investigation. The effect of both drugs on spontaneous abortion rates should be investigated in properly designed trials.

Although a statistically significant effect is not observed in individual studies, meta-analyses do demonstrate a significant increase in pregnancy rates in clomiphene-resistant women treated with metformin. Whether these results translate into improved live birth rates should be confirmed in larger studies, although the lower overall birth rate in this population will require large studies.

Pre-treatment with oral contraceptives, co-treatment with n-acetyl-cysteine, and co-treatment with dexamethasone all resulted in large and statistically significant increases in pregnancy rates in combination with clomiphene in clomiphene-resistant anovulatory women, along with increased multiple gestation rates. These findings warrant further investigation, particularly if multiple gestations can be avoided.

Use of laparoscopic cautery, followed by ovulation induction if necessary, results in similar pregnancy and live birth rates, with significantly lower multiple gestation rates, compared to immediate gonadotropin use in clomiphene-resistant women. The addition of metformin may result in further improvements in pregnancy and live birth rates. There are no data on the long-term sequelae of laparoscopic ovarian cautery, and long-term followup studies to assess the risk of pelvic adhesions, premature ovarian failure, or early menopause are warranted.

III. Superovulation in Ovulatory Women

The available literature does not allow any conclusions about the relative efficacy of different estrogen inhibitors, although 5 mg of letrozole appears to be superior to 2.5 mg. Pooled data shows significantly higher pregnancy rates with gonadotropins compared to estrogen inhibitors,

but data are too limited to draw conclusions about live birth rates. There is a trend towards higher rates of multiple pregnancy and OHSS with gonadotropins compared to estrogen inhibitors, but the number of events, even in pooled studies, prevents definite conclusions.

There do not appear to be substantial differences in pregnancy rates between different gonadotropin preparations. Higher doses increase the risk of multiples and OHSS without significant improvement in pregnancy rates. The addition of GnRH antagonists to superovulation protocols may increase both pregnancy rates and twin gestation rates. Further studies adequately powered for the outcome of live birth per couple are needed.

Hysteroscopic resection of endometrial polyps noted on ultrasound prior to IUI increases pregnancy rates.

Assisted Conception: IVF and ICSI (Question 3)

I. General Issues

There are several consistent issues with the majority of studies reviewed for Question 3, many of which are shared with trials of ovulation induction and superovulation and most of which have been identified by other authors,[36,538,550] including variation in definition of endpoints, especially related to pregnancy, lack of concealment of treatment allocation, and lack of blinding where it is feasible. Three issues deserve particular attention.

Sample size is a recurrent problem. Very few of the studies reviewed for this Question had a priori sample sizes for pregnancy or live birth – most used surrogate markers, such as number of oocytes retrieved in a given cycle. Given a baseline live birth rate per cycle of IVF in the United States of 34 percent,[10] an alpha of 0.05, and a power of 80 percent, approximately 1100 subjects would be needed per arm to demonstrate a 5 percent absolute improvement in live birth rates, 320 to show a difference of 10 percent, and 135 to show a difference of 15 percent. Only two of the 237 articles included under Question 3 had more than 300 subjects per arm. On the other hand, failure to detect a significant difference is not the same as demonstrating equivalence or non-inferiority – equivalence studies generally are designed so that the lower 95 percent bound of the new intervention is within some pre-specified level, and, as a rule, require more subjects than superiority studies. For example, if the point estimates for live birth rates of two different arms in a study were 34 percent and 39 percent, a sample size of 1200 subjects per arm would be required to conclude that the second intervention was no more than 5 percent worse than the first; 390 subjects per arm would be required to conclude that there was no more than a 10 percent difference. Very few of the studies we identified had adequate power to declare equivalence or non-inferiority. Even one of the largest studies, a trial of double embryo transfer versus single embryo transfer followed by frozen-thawed transfer with 330 subjects per arm,[365] which was explicitly designed and powered as an equivalence study, was unable to demonstrate that the lower bound of the difference between the two interventions was not more than 10 percent.

A second, related issue is the inferences frequently drawn by study authors about relative safety. If almost none of the studies had the power to detect an absolute difference of 10 percent (or, at a baseline of 34 percent, a relative risk of 1.29) for a live birth outcome, the power to detect differences in outcomes that are a fraction of live births, such as multiple pregnancies or

complications such as OHSS, is even lower. For the most part, it is almost impossible to estimate relative safety based on single trials.

Another issue relates to the duration of the intervention. The vast majority of the studies reviewed randomized subjects to only a single cycle of the interventions being investigated. Although this facilitates translating results most frequently reported on a per-cycle basis to a per-subject basis, it may not reflect the clinical scenario likely to be most relevant. If an intervention would be used clinically in subsequent cycles if a pregnancy does not result, then, ideally, the intervention should be continued in the same couple for some pre-specified amount of time or number of cycles in trials of that intervention. Alternatively, if embryos are cryopreserved for use in subsequent cycles, the results of those frozen-thawed transfers should be included in the reported cumulative rates. Cumulative results were much more common in studies of ovulation induction compared to IVF.

II. The Female Partner

A. Methods for down-regulation. Despite the issues described immediately above, there is reasonable evidence regarding certain aspects of IVF/ICSI.

We did not identify clear evidence of the superiority of any specific protocol involving GnRH agonists. In the setting of endometrial preparation for frozen-thawed embryo transfer, two relatively large studies had conflicting results regarding the benefit of adding an agonist; further research is needed.

Although only one individual study comparing GnRH agonists to antagonists found a significant difference in pregnancy or live birth rates (in favor of agonists), formal meta-analysis shows a significantly lower pregnancy and live birth rate with the use of antagonists; antagonists do result in significant decreases in gonadotropin requirements, and a significant decrease in the risk of OHSS.

Pretreatment with an oral contraceptive to assist with scheduling GnRH antagonist cycles resulted in decreases in pregnancy rates in all three identified studies; this reduction was statistically significant in one.

B. Methods for ovarian stimulation. Again, most individual studies were underpowered. Pooled results of individual trials suggest that hMG is superior to rFSH in long protocol GnRH agonist regimens, with higher multiple pregnancy rates, and that the addition of rLH to rFSH improves live birth rates in poor responders. Based on differences in the amount of gonadotropin required, there may be economic advantages to some formulations, but formal economic evaluations ultimately will require more precise estimates of effect.

C. Methods to trigger oocyte maturation. Timing of hCG administration for follicular maturation is important for optimizing live birth rates – delays of 48 hours after one ultrasound threshold (at least 3 follicles of at least 17 mm) resulted in significant decreases in live births. The optimal timing and threshold have not been determined. There does not appear to be any difference in pregnancy or live birth rates, or other major outcomes, between rhCG and uhCG, although injection site reactions are more common with uhCG. In cycles using a GnRH antagonist for pituitary down-regulation, use of hCG is superior to use of a GnRH agonist.

D. Methods for oocyte retrieval. Choice of analgesia for oocyte retrieval does not appear to affect pregnancy rates. Variability in outcome measures makes between-study comparisons difficult regarding specific techniques. Techniques involving some form of sedation result in

lower intraoperative pain, but this does not appear to adversely affect overall patient perceptions and satisfaction.

E. Methods for endometrial preparation for frozen-thawed embryo transfer. There is insufficient evidence to determine the optimal method for endometrial preparation for frozen-thawed embryo transfer.

F. Methods for embryo transfer. Pre-transfer irrigation does not improve pregnancy or live birth rate and, based on an intent-to-treat analysis of the one study identified, significantly reduces both rates. There is no evidence that type of provider changes outcomes. Although pre-treatment with antibiotics significantly lowers measurable bacterial contamination, this does not translate into improved pregnancy or live birth rates.

Ultrasound-guided embryo transfer consistently results in substantially improved (40 percent relative increase) pregnancy and live birth rates compared to various "clinical touch" methods. The consistency of this finding and the size of the effect are striking considering that the majority of interventions evaluated in this review do not show significant differences.

G. Methods for luteal support. Some form of luteal support is necessary with IVF, since both progesterone and hCG result in improved pregnancy rates compared to no treatment. Although there is no detectable difference between oral progesterone and the various formulations of vaginal progesterone, both result in lower pregnancy and live birth rates compared to intramuscular progesterone. The addition of estrogen to progesterone may improve outcomes, although additional larger studies are needed to confirm these findings. Finally, adding stimulation with a GnRH agonist to progesterone and estrogen in patients down-regulated with a GnRH antagonist improves live birth rates.

H. Other adjuncts. Based on the available evidence, vasoactive agents such as nitroglycerin, beta-agonists, or l-arginine do not improve pregnancy or live birth rates in either first-time or poor prognosis IVF patients. Low-dose aspirin also does not appear to have any effect. The NSAID piroxicam significantly improved pregnancy and live birth rates in a general IVF population, and further studies of NSAIDs are warranted. Randomized trials of intercessory prayer and acupuncture showed benefit, but there are remaining methodological questions which need to be addressed.

Dexamethasone and growth hormone both improved pregnancy and live births in women over 40 undergoing IVF; the growth hormone findings are consistent with earlier studies showing a benefit in poor responders. Metformin reduced the incidence of OHSS and showed evidence of improvement in pregnancy and live birth rates in women with PCOS undergoing IVF. In women with endometriosis, pre-ART surgical management does not improve outcomes, but pretreatment with a GnRH agonist for several months prior to IVF improves pregnancy and live birth rates. Other surgical interventions shown to improve outcomes are hysteroscopic removal of endometrial lesions and surgical removal or occlusion of hydrosalpinges.

I. Methods for prevention of OHSS. One study published since the most recent Cochrane review found no benefit for intravenous albumin in preventing OHSS, in contrast to previous studies and the Cochrane review. This may be due to the low event rate observed in this study.

III. The Embryo

A. Methods for fertilization. IVF results in much higher birth rates within 90 days than watchful waiting in eligible patients, although cumulative pregnancy rates were similar in one trial comparing IVF to IUI and stimulated IUI. There is no evidence of benefit for ICSI

compared to IVF in patients with non-male factor infertility. Technical aspects of the fertilization procedure, such as media and equipment used, may have significant impact on outcomes.

B. Culture methods. There is insufficient evidence to draw any inferences regarding the effect of culture media on pregnancy or live birth

C. Methods for selection. The addition of a zygote cleavage score to embryo quality scoring based on morphology did not result in improved pregnancy or live birth rates. Preimplantation genetic screening resulted in lower overall pregnancy and live birth rates in women 37 and older.

D. Preparation for transfer. Assisted hatching improves pregnancy and live birth rates in couples with previous IVF failure, but there is insufficient evidence to draw inferences about benefits in other groups.

E. Timing of transfer. The available evidence suggests that zygote transfer is, at best, no better than day 3 transfer and may result in worse pregnancy and live birth rates. Transfer on day 2 may produce better outcomes compared to day 3 in women with poor ovarian response, based on one large trial; pooled meta-analysis results suggest better pregnancy rates, but not necessarily live birth rates, in cycles where ICSI is used. Finally, blastocyst transfer results in better live birth rates than day 3 transfer, especially in patients with a good prognosis. The disadvantage of delaying transfer is a reduction in the number of embryos available for transfer and for cryopreservation, and the increased risk of monozygotic twinning.[551]

F. Number to transfer. Although double embryo transfer results in higher pregnancy and live birth rates compared to single embryo transfer, multiple rates – almost all twins – are consistently higher. Strategies involving alternative methods for pituitary down-regulation, or involving multiple cycles with fewer embryo transfers per cycle, appear to result in similar live birth rates with fewer multiples.

Longer Term Outcomes (Question 4)

I. General Issues

Our review of the current evidence on fetal and maternal outcome raises several important issues which need to be considered in interpreting the existing literature, and in planning future research.

A. Study design. First, although we found several consistent associations that should be considered by patients, clinicians, and policymakers in making decisions about various aspects of infertility, it is important to remember that the overwhelming majority of the literature consists of observational studies. The most common design was a modified cohort study, where all of the women exposed to a particular treatment were compared to a sample, either random or matched for known confounders, and the incidence of the outcomes compared. We also identified several population-based cohort studies, where all infertility patients were compared to all other pregnant women and their infants in a given geographic area. Case-control studies, in which all of the subjects with a given outcome are selected along with a matched or unmatched sample of subjects without the outcome, were much less common, and were, appropriately, primarily used for less common outcomes, such as cancer and specific congenital abnormalities. Although

these study designs are valid and well-established tools for epidemiologic research, it is important to remember the strong potential for unmeasured confounding, especially when examining the association between a clinical treatment and the outcomes of interest. All of the reasons for using caution when interpreting the results of observational studies reporting clinical benefits apply to observational studies of adverse outcomes. Ideally, data from randomized trials would be used, but, given the relative rarity of many important outcomes relative to the number of women treated or number of children, and the consistently small sample size chosen for most randomized trials in this field, pooling of data is likely to be required.

B. Appropriate controls. For many of the outcomes discussed under this Question, any association between a specific treatment and that outcome could be either a true causal association, or an association between the underlying reason for the treatment and the subsequent outcome. In many cases, associations that were significant when infertility patients were compared to the general population weakened quantitatively when other infertility patients, or women with a prolonged time to conception, were used as controls. Although identifying such women may be difficult in many situations, failure to consider the appropriateness of the control group could easily lead to misinterpretation of study results.

C. The "moving target." In a field where there are few barriers to rapid change in practice, it is highly likely that in many cases even the best study of a long-term outcome may have little benefit for current clinical practice. This is certainly true of outcomes likely to occur 10 or more years after treatment, such as cancers, but may well be true of shorter time intervals as well. Changes in indications, in the types of patients considered appropriate or inappropriate for a given treatment, and changes in aspects of the treatment itself that might affect these outcomes can render results irrelevant for current patients. For outcomes such as cancer, information can still be helpful if it helps target preventive efforts; however, for many shorter-term outcomes, particular those related to pregnancy and early childhood, even very strong and consistent associations may be due to factors which are no longer present.

D. Generalizability to the United States. The majority of studies we identified were performed outside the United States. The extent to which differences among infertility patients in factors such as race/ethnicity, socioeconomic status, and education affect observed associations is unclear.

With these caveats, we will summarize the results of the review for this Question.

II. Short-term Fetal Outcomes

A. Spontaneous abortion. Spontaneous abortion, defined as loss of the entire pregnancy (rather than loss of one or more fetuses with survival of at least one fetus), does not appear to be more common after assisted reproduction after adjusting for known risks; observed differences between different methods appear to be related to differences in the patient population to which the methods are applied. Loss of the entire pregnancy is less common for twins than for singletons after multiple embryo transfer; this is the first of many outcomes we reviewed where the relative risk estimate for a given outcome was consistently higher when the comparison was between IVF singletons and spontaneous singletons, rather than IVF twins and spontaneous twins.

B. Ectopic pregnancy. Similarly, although ectopic pregnancy is more common after assisted reproduction than after spontaneous conception, and variations are observed between

different methods of ART, most of the difference in risk appears to be related to factors related to the mother and/or embryo rather than specific procedures.

C. Maternal screening for fetal chromosomal abnormalities. The best available evidence suggests that false positive results for maternal testing for chromosomal abnormalities after assisted reproduction are more likely for second trimester serum screening, resulting in an increased false positive rate with combined screening strategies that incorporate both modalities. Although some of this increased risk appears to be due to differences in the distribution of maternal age, the risk remained elevated in one large study even after adjustment. Further research is needed to determine the clinical implications of this finding.

D. Preterm delivery. Preterm delivery is approximately twice as likely in women pregnant with singleton pregnancies after infertility treatment compared to spontaneous singleton pregnancies. The evidence is most consistent for ART, but the risk was similar in a large study of women pregnant after ovulation induction alone. The proportion of these deliveries that is due to early delivery indicated by maternal or fetal complications versus spontaneous preterm delivery is unclear, as is the potential benefit of preventive strategies such as progesterone in this population. Conversely, in the majority of studies, the risk of preterm birth in IVF twins compared to spontaneous twins is either not elevated, or elevated to a lesser degree compared to the risk seen in ART singletons compared to spontaneous singletons. However, even though the relative risk of preterm delivery is lower for ART twins compared to spontaneous twins, the higher baseline risk for preterm delivery among twins means that the absolute number of preterm twin deliveries in ART pregnancies is large.

E. Low birth weight. Much of the elevated risk of low birth weight is due to the increased risk of preterm birth. However, studies that examined gestational age-specific weights found an increased risk of small-for-gestational age infants among singleton, but not twin, pregnancies after infertility treatment.

III. Maternal Pregnancy Outcomes

Women pregnant after infertility treatment are at increased risk for disorders potentially related to abnormal implantation, including preeclampsia, placenta previa, and placental abruption. The extent to which specific treatments or underlying maternal/embryonic characteristics contribute to this risk is unclear. Gestational diabetes risk may also be increased, although this association is weaker and less consistent. Finally, although data on psychological outcomes during pregnancy are quite limited, the data that are available suggest that women pregnant after infertility treatment have outcomes as good as, and perhaps better than, women pregnant after spontaneous conception.

The consistent association between fetal and maternal outcomes related to implantation is biologically plausible and is a promising area for future research.

IV. Infant Outcomes – Birth to 1 Year

A. Congenital anomalies. Risks for major congenital anomalies are increased after infertility treatment, but much of this risk appears to be related to maternal and/or paternal characteristics, including a history of subfertility or infertility. Given the relative rarity of

specific birth defects or syndromes, identifying an association between a specific exposure and subsequent risk is difficult.

B. Other outcomes. In the neonatal period, although there is evidence of an increased risk for adverse outcomes (including cerebral palsy), especially among singletons, it is unclear to what the extent this is due to the observed increased preterm delivery rate after ART (a major risk factor for many adverse outcomes), or is instead independently associated with infertility and/or infertility treatment. Large-scale studies that control for gestational age and birth weight are needed. In later infancy, there is a significantly increased hospitalization rate among children born after IVF/ICSI compared to the general population, but rates are similar when compared to children born to couples with a history of treated and untreated subfertility.

V. Child Outcomes – Beyond 1 Year

A. Physical outcomes. Children born after assisted reproduction have an increased risk of hospitalization and surgery compared to general population controls. At least some of this risk is likely related to the underlying condition causing infertility, rather than to the treatment itself. Finally, there does not appear to be an increased risk of childhood cancers in children of women who received infertility treatments.

B. Neurodevelopmental outcomes. The available evidence suggests that there is not an increase in the risk of adverse neurodevelopmental outcomes in children born after infertility treatment that is not associated with the underlying condition of infertility or the well-established increased risk of prematurity and SGA. The available evidence on learning and other developmental outcomes is reassuring, but larger studies across a wider population are needed.

VI. Maternal Long-Term Outcomes

A. Cancers. In general, infertility treatments involving ovarian stimulation do not appear to be associated with an increased risk of breast cancer, although non-significantly elevated risks were seen 20 years after exposure in one study, suggesting that continued monitoring is warranted. Ovarian cancers are even more strongly associated with an infertility diagnosis than breast cancer; use of ovulation stimulating drugs does not appear to increase the risk above baseline levels in this patient population. As with breast cancer, increasing risk with increased duration with treatment cannot be ruled out with confidence. There is no available evidence suggesting an increased risk of other cancers with either infertility or infertility treatment. Available data on the incidence of preinvasive and invasive cervical cancer is consistent with increased detection as part of the infertility evaluation.

B. Other outcomes. Based on the available literature, there are no differences in psychological outcomes, including parenting skills, when comparing singleton pregnancies resulting from ART to spontaneous conceptions. If anything, mothers of infants resulting from ART have better outcomes, although there is some evidence that fathers may do worse on some scales. Multiple gestations significantly increase stress and depressive symptoms, especially for mothers of infants with chronic disabilities; to the extent that women undergoing ART are more likely to experience multiples, especially preterm multiples, they are more likely to experience these symptoms. Clearly, further research is needed.

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Acronyms and Abbreviations

ACOG	American College of Obstetrics and Gynecology
AHRQ	Agency for Healthcare Research and Quality
ART	Assisted reproductive technology
ASRM	American Society for Reproductive Medicine
BMI	Body mass index
CC	Clomiphene citrate
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
FDA	U.S. Food and Drug Administration
FSH	Follicle-stimulating hormone
GIFT	Gamete intrafallopian transfer
GnRH	Gonadotropin-releasing hormone
hCG	Human chorionic gonadotropin
HEPES	n-hydroxyethylpiperazine-n-ethanesulfonate
hMG	Human menopausal gonadotropin
HRQOL	Health-related quality of life
ICI	Intracervical insemination
ICSI	Intracytoplasmic sperm injection
IUI	Intrauterine insemination
IVF	In vitro fertilization
LH	Luteinizing hormone
NICU	Neonatal intensive care unit
NIH	National Institutes of Health
NNT	Number-needed-to-treat
NSAID	Non-steroidal anti-inflammatory drug
OCP	Oral contraceptive pill
OHSS	Ovarian hyperstimulation syndrome
OR	Odds ratio
ORWH	Office of Research on Women’s Health
PCOS	Polycystic ovarian syndrome
PGD	Preimplantation genetic diagnosis
PPCOS	Pregnancy in Polycystic Ovary Syndrome study
RCT	Randomized controlled trial
rFSH	Recombinant follicle-stimulating hormone
rhCG	Recombinant human chorionic gonadotropin
rLH	Recombinant luteinizing hormone
RR	Relative risk
SART	Society for Assisted Reproductive Technology
SGA	Small for gestational age
SIR	Standardized incidence ratio
uFSH	Urinary follicle-stimulating hormone
ZIFT	Zygote intrafallopian transfer

Appendix A: Exact Search String

Database: Ovid MEDLINE® (1966 to August Week 2 2005)

Later updated through January Week 4 2008

Search Strategy:

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1 *reproductive techniques/ or *reproductive techniques, assisted/ or *embryo transfer/ or exp *fertilization in vitro/ or *gamete intrafallopian transfer/ or *oocyte donation/ or *zygote intrafallopian transfer/ (17110)
2 *fertility agents/ or *fertility agents, female/ or *clomiphene/ or *menotropins/ or *metformin/ (5216)
3 exp *insemination, artificial/ or exp *ovulation induction/ (7431)
4 Pregnancy Outcome/ (19904)
5 exp Pregnancy Complications/ (225332)
6 pregnancy rate/ or birth rate/ (8686)
7 Ovarian Hyperstimulation Syndrome/ (981)
8 exp Ovarian Neoplasms/ (39423)
9 exp Endometrial Neoplasms/ (7690)
10 exp Breast Neoplasms/ (124437)
11 "Quality of Life"/ (47871)
12 Cesarean Section/ (21813)
13 exp Pregnancy, Multiple/ or Twins/ (19011)
14 exp ABNORMALITIES/ (292667)
15 exp Infant, Newborn, Diseases/ (109923)
16 Fetal Growth Retardation/ (8564)
17 (or/1-3) and (or/4-16) (6491)
18 limit 17 to (humans and english language) (5300)
19 Preimplantation Diagnosis/ (910)
20 18 not 19 (5240)
21 limit 20 to yr="1990 - 2005" (4551)
22 limit 21 to yr="1995 - 2005" (3738)
23 limit 22 to "review articles" (367)
24 22 not 23 (3371)
25 from 24 keep 1-10 (10)
26 prevalence/ or risk factors/ (328058)
27 exp *infertility/ or *anovulation/ (24278)
28 26 and 27 (728)
29 infertility/ep or anovulation/ep (314)
30 28 or 29 (979)
31 embryo research/ or research embryo creation/ or laparoscopy/ or hysterosalpingography/ or hysteroscopy/ or ultrasonography/ (87033)
32 infertility/ or anovulation/ (6919)
33 31 and 32 (249)
34 30 or 33 (1219)

35 limit 34 to (humans and english language) (938)
36 35 not 19 (937)
37 limit 36 to yr="1990 - 2005" (769)
38 limit 37 to yr="1995 - 2005" (548)
39 21 or 37 (5257)
40 22 or 38 (4239)
41 limit 40 to "review articles" (491)
42 40 not 41 (3748)
43 limit 39 to "review articles" (602)
44 39 not 43 (4655)
45 limit 44 to abstracts (3853)
46 limit 42 to abstracts (3155)
47 45 not 46 (698)
48 from 47 keep 1-698 (698)
49 limit 46 to yr="1995 - 1999" (1388)
50 limit 46 to yr="2000 - 2002" (888)
51 limit 46 to yr="2003 - 2005" (879)
52 from 49 keep 1-1388 (1388)
53 from 50 keep 1-888 (888)
54 from 51 keep 1-879 (879)

Appendix B: List of Excluded Studies

All excluded studies listed below were reviewed in their full-text version. Following each reference, in italics, is the reason for exclusion. "Excluded," in this context, means "not included for data abstraction." Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles.

The following list does not include articles that were excluded because they were published before 2000 (n = 906) or those considered only for Questions 1b and 1c.

Aboulghar M, Evers JH, Al-Inany H. Intra-venous albumin for preventing severe ovarian hyperstimulation syndrome [Full Review]. Cochrane Database of Systematic Reviews 2002, Issue 2. Art. No.: CD001302. DOI: 10.1002/14651858.CD001302.
Full Text: Exclude Q3-Review article (Cochrane).

Aboulghar MM, Aboulghar MA, Mansour RT, et al. Pregnancy rate is not improved by delaying embryo transfer from days 2 to 3. Eur J Obstet Gynecol Reprod Biol 2003;107(2):176-9.
Full Text: Exclude Q3-Not RCT.

Abusheikha N, Salha O, Sharma V, et al. Monozygotic twinning and IVF/ICSI treatment: a report of 11 cases and review of literature.[erratum appears in Hum Reprod Update 2000 Nov-Dec;6(6):621 Note: Abusheika N [corrected to Abusheikha N]]. Hum Reprod Update 2000;6(4):396-403.
Full Text: Exclude Q4-N < 100 (not RCT).

Acevedo B, Sanchez M, Gomez JL, et al. Luteinizing hormone supplementation increases pregnancy rates in gonadotropin-releasing hormone antagonist donor cycles. Fertil Steril 2004;82(2):343-7.
Full Text: Exclude Q3-Donor egg.

Agrawal R, Holmes J, Jacobs HS. Follicle-stimulating hormone or human menopausal gonadotropin for ovarian stimulation in in vitro fertilization cycles: a meta-analysis. Fertil Steril 2000;73(2):338-43.
Full Text: Exclude Q3-Review article.

Aktan E, Bozkurt K, Ozer D, et al. Effects of coasting on the outcome of intracytoplasmic sperm injection-embryo transfer cycles. Australian & New Zealand Journal of Obstetrics & Gynaecology 2004;44(4):298-301.
Full Text: Exclude Q3-Not RCT.

Al-Inany H, Aboulghar M. GnRH antagonist in assisted reproduction: a Cochrane review. Hum Reprod 2002;17(4):874-85.
Full Text: Exclude Q3-Review article (Cochrane).

Al-Inany H, Aboulghar M, Mansour R, et al. Meta-analysis of recombinant versus urinary-derived FSH: an update. Hum Reprod 2003;18(2):305-13.
Full Text: Exclude Q3-Review article.

Al-Inany HG, Aboulghar M, Mansour R, et al. Recombinant versus urinary human chorionic gonadotrophin for ovulation induction in assisted conception [Full Review]. Cochrane Database of Systematic Reviews 2005, Issue 2. Art. No.: CD003719. DOI: 10.1002/14651858.CD003719.pub2.
Full Text: Exclude Q3-Review article (Cochrane).

al-Mizyen E, Sabatini L, Lower AM, et al. Does pretreatment with progestogen or oral contraceptive pills in low responders followed by the GnRHa flare protocol improve the outcome of IVF-ET? J Assist Reprod Genet 2000;17(3):140-6.
Full Text: Exclude Q3-Not RCT.

Alborzi S, Motazedian S, Parsanezhad ME, et al. Comparison of the effectiveness of single intrauterine insemination (IUI) versus double IUI per cycle in infertile patients. Fertil Steril 2003;80(3):595-9.
Full Text: Exclude Q2-Relevant data uninterpretable.

Albuquerque LE, Saconato H, Maciel MC. Depot versus daily administration of gonadotrophin releasing hormone agonist protocols for pituitary desensitization in assisted reproduction cycles [Full Review]. Cochrane Database of Systematic Reviews 2005, Issue 1. Art. No.: CD002808. DOI: 10.1002/14651858.CD002808.pub2.
Full Text: Exclude Q3-Review article (Cochrane).

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Appendix C: Data Abstraction Forms (Questions 2-4)

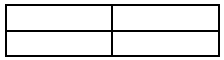
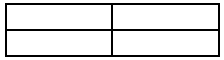
Question 2: Among women of reproductive age, what are the benefits and risks of Clomid® and Pergonal® (or other injectable super-ovulatory drugs), and Glucophage®, and how do they vary in different patient populations?

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
StudyID	**Geographical location:** [city & state (U.S.) or city & country (foreign)]	**Age:** Mean (SD): Median: Range:	**Definition(s) of outcome(s):** Pregnancy:	[For each treatment, report outcomes with 95% CIs (if given) and p-values for differences. Abstract data only when outcomes are reported on a per-patient basis; otherwise EXCLUDE.]	[IF ARTICLE SHOULD BE EXCLUDED, PLEASE EXPLAIN WHY HERE]
	Study dates: [month & year]	**Race/ethnicity (n [%]):**	Live birth: Multiples:	1) [2x2 table for RR – List outcome here and replace "Exp +" and "Exp -" in far left column of 2x2 table with labels for interventions; if placebo included, enter this in bottom row of 2x2 table, under the active intervention.]	[COMMENT ON BIASES, ETC. AFFECTING CLINICAL INTERPRETATION]
	Size of population (no. of patients): [num/denom for screening studies]	**Diagnoses (n [%]):** Unexplained infertility: Endometriosis: Male factor: Tubal factor:	Complications (specify):		**Quality assessment:** [+ if appropriate quality, - if not; add text as needed to describe]
	Number of cycles analyzed:	PCOS: Other (specify):			Randomization method: Blinding: Dropout rate < 20%: Adequacy of randomization concealment:
	Number of cycles per patient: [please calculate]	**Inclusion criteria:**		2) [2x2 table for RR – List outcome here and replace "Exp +" and "Exp -" in far left column of 2x2 table with labels for interventions; if placebo included, enter this in bottom row of 2x2 table, under the active intervention.]	**This article is also relevant to:** [delete as appropriate]
	Study type: RCT [exclude all other study designs]	**Exclusion criteria:**			Question 1b Question 1c Question 3 Question 4
	Interventions: [list]			3) [Free-text outcome]:	
				4) [Free-text outcome]:	

Question 3: Among women of reproductive age, which laboratory, clinical, and other practice approaches result in the highest successful singleton pregnancy (or live-born) rates, and what practices lead to high multiple rates?

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
StudyID	**Geographical location:** [city & state (U.S.) or city & country (foreign)]	**Age:** Mean (SD): Median: Range:	**Definition(s) of outcome(s):**	[For each treatment, report outcomes with 95% CIs (if given) and p-values for differences. Abstract data only when outcomes are reported on a per-patient basis; otherwise EXCLUDE.]	[IF ARTICLE SHOULD BE EXCLUDED, PLEASE EXPLAIN WHY HERE]
	Study dates: [month & year]	**Race/ethnicity (n [%]):**	Pregnancy: Live birth: Multiples:	1) [2x2 table for RR – List outcome here and replace "Exp +" and "Exp -" in far left column of 2x2 table with labels for interventions; if placebo included, enter this in bottom row of 2x2 table, under the active intervention.]	[COMMENT ON BIASES, ETC. AFFECTING CLINICAL INTERPRETATION]
	Size of population (no. of patients): [num/denom for screening studies]	**Diagnoses (n [%]):** Unexplained infertility: Endometriosis: Male factor: Tubal factor:	Complications (specify):		**Quality assessment:** [+ if appropriate quality, - if not; add text to describe]
	Number of cycles analyzed:	PCOS: Other (specify):			Randomization method: Blinding: Dropout rate < 20%: Adequacy of randomization concealment:
	Number of cycles per patient: [please calculate]	**Inclusion criteria:**		2) [2x2 table for RR – List outcome here and replace "Exp +" and "Exp -" in far left column of 2x2 table with labels for interventions; if placebo included, enter this in bottom row of 2x2 table, under the active intervention.]	**This article is also relevant to:** [delete as appropriate]
	Study type: RCT [exclude all other study designs]	**Exclusion criteria:**			Question 1b Question 1c Question 2 Question 4
	Interventions: [list]			3) [Free-text outcome]: 4) [Free-text outcome]:	

Question 4: What are the adverse outcomes of ovulatory drug-induced pregnancies and of pregnancies achieved with IVF? Is there evidence to link these adverse outcomes with the treatments and not the underlying maternal health or gestational age problems?

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
StudyID	**Geographical location:** [city & state (U.S.) or city & country (foreign)] **Study dates:** [month & year] **Size of population (no. of patients):** [num/denom for screening studies] **Number of cycles analyzed:** **Number of cycles per patient:** [please calculate] **Study type:** [delete all that do not apply] RCT Cohort Case-control Other (specify)	**Age:** Mean (SD): Median: Range: **Race/ethnicity (n [%]):** **Diagnoses (n [%]):** Unexplained infertility: Endometriosis: Male factor: Tubal factor: PCOS: Other (specify): **Inclusion criteria:** **Exclusion criteria:**	**Definition(s) of outcome(s):** [Include: - C-section rates for singletons, where reported; - data on fetal reduction, where reported]	[Please calculate ORs (case-control) or RRs (RCT, cohort), as appropriate. If possible and appropriate, stratify results by age.] 1) [2x2 table – List outcome here and replace "Risk +" and "Risk -" in far left column of 2x2 table with labels for risk factors/interventions; if placebo included, enter this in lower row of 2x2 table, under the active intervention.]  2) [2x2 table – List outcome here and replace "Risk +" and "Risk -" in far left column of 2x2 table with labels for risk factors/interventions; if placebo included, enter this in lower row of 2x2 table, under the active intervention.]  3) [Free-text outcome]: 4) [Free-text outcome]:	[IF ARTICLE SHOULD BE EXCLUDED, PLEASE EXPLAIN WHY HERE] [COMMENT ON BIASES, ETC. AFFECTING CLINICAL INTERPRETATION] **Quality assessment:** [+ if appropriate quality, - if not; add text to describe] *For RCT:* Randomization method: Blinding: Dropout rate < 20%: Adequacy of randomization concealment: *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): Large sample size: Adequate description of the cohort: Use of validated method for ascertaining exposure: Use of validated method for ascertaining clinical outcomes: Adequate follow-up period: Completeness of follow-up: Analysis (multivariate adjustments) and reporting of results: *For case-control study:* Valid ascertainment of cases: Unbiased selection of cases: Appropriateness of the control population: Comparability of cases and controls with respect to potential

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
					confounders: Appropriateness of statistical analyses: **This article is also relevant to:** [delete as appropriate] Question 1b Question 1c Question 2 Question 3

Appendix D: Evidence Tables

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Al-Fadhli, Sylvestre, Buckett, et al., 2006 **#50070**	**Geographical location:** Montreal, Canada **Study dates:** Mar 2004-Jan 2005 **Size of population (no. of patients):** 72 **Number of cycles analyzed:** 72 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** Population: Patients undergoing superovulation and IUI Compare 2.5 vs. 5 mg daily dose of letrozole administered from day 3-7 When at least 1 follicle > 18 mm, 10,000 U hCG SC administered and IUI performed 24-48 hours later	**Age:** Mean (SD): 2.5mg: 31.8 ± 0.3 5mg: 31.8 ± 0.7 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 72 (100%) **Inclusion criteria:** - Infertility > 1 year - Age < 40 years - Menstrual cycle 25-35 days - Patent tubes on HSG - Normal semen analysis **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: + urine hCG or serum β-hCG > 10 mIU/ml with intrauterine gestational sac Live birth: NR Multiples: Yes Complications: OHSS	1) Pregnancy: Preg + / Preg - / Total 5mg: 10 / 28 / 38 2.5mg: 2 / 32 / 34 12 / 60 / 72 Rel risk: 4.47 (Lower 95% CI 1.05, Upper 95% CI 19.00) 2) No multiple pregnancies 3) No ovarian hyperstimulation	**Comments:** - No information about blinding - 2.5 mg and 5 mg dose may look different - No information about allocation concealment **Quality assessment:** Randomization method: + Blinding: - (not discussed) Dropout rate < 20%: + Adequacy of randomization concealment: - (not discussed)

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Al-Fozan, Al-Khadouri, Tan, et al. 2004 **#11710**	**Geographical location:** Montreal, Quebec, Canada **Study dates:** Jul 2002-Sep 2003 **Size of population:** 154 **Number of cycles analyzed:** 238 **Number of cycles per patient:** 1.8 **Study type:** RCT **Interventions:** Compared the use of letrozole vs. CC in pts undergoing ovulation induction	**Age:** Mean (SD): Letrozole: 30.7 (0.5) CC: 31.5 (0.5) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 100% **Inclusion criteria:** - Infertility at least 1 yr - Patent tubes by HSG - Normal semen analysis **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Pregnancy rate: Preg + / Preg - / Total Letroz: **13** / **61** / 74 CC: **11** / **69** / 80 24 / 130 / 154 value **Rel risk** 1.28 (0.61 – 2.67) 2) Pregnancy outcome: Letrozole: 11.5% (13 pts) - 11 ongoing pregnancy - 2 ectopic pregnancy Clomid: 8.9% (11 pts) - 7 ongoing pregnancy (one set of twins) - 4 ectopic pregnancy No statistically significant difference between 2 groups.	**Comments:** Did not provide definition of pregnancy **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +
Ali Hassan, El-Gezeiry, Nafaa, et al., 2001 **#3190**	**Geographical location:** Alexandria, Egypt **Study dates:** NR **Size of population:** 97 **Number of cycles analyzed:** 316 **Number of cycles per patient:** 3.26 **Study type:** RCT **Interventions:** Compare ovulation induction protocol using Ketoconazole (CYP17a antagonist) pretreatment	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: NR Endometriosis: NR Male factor: 0 Tubal factor: NR PCOS: 0 **Inclusion criteria:** - PCOS and insulin resistance - Normal semen analysis **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: + hCG Live birth: Yes Multiples: Yes Complications: NR	1) Pregnancy rate (intention-to-treat): Preg + / Preg - Keto + CC: 17 / 32 / 49 CC only: 8 / 40 / 48 25 / 72 / 97 Lower 95% CI / Upper 95 % CI **Rel risk** 2.08 (0.99 – 4.36) 2) Live births: LB + / LB - Keto + CC: 16 / 33 / 49 CC only: 7 / 41 / 48 23 / 74 / 97	**Comments:** - Baseline patient characteristics not described - Unblinded, no placebo - No intention-to-treat analysis in paper - Did continue treatment for multiple cycles—greater number of cycles in ketoconazole group **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	for 85 days prior to CC treatment with CC alone. Population: Insulin resistant PCOS pts				

		Lower 95% CI	Upper 95 % CI
Rel risk	2.24	1.01	4.95

3) Multiple pregnancy:

	Multi +	Multi -	
Keto + CC	8	9	17
CC only	6	2	8
	14	11	25

		Lower 95% CI	Upper 95 % CI
Rel risk	0.63	0.33	1.19

4) Cycles per subject:
Ketoconazole + CC: 3.7
CC only: 2.8
Higher drop-out rate in clomiphene only

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Allegra, Marino, Coffaro, et al., 2007 **#50110**	**Geographical location:** Palermo, Italy **Study dates:** May 2002-Dec 2004 **Size of population (no. of patients):** 104 **Number of cycles analyzed:** 302 **Number of cycles per patient:** 302/104 = 2.9 cycles per patient **Study type:** RCT **Interventions:** Population: Women undergoing controlled ovarian stimulation (COS)/IUI treatment	**Age:** Mean (SD): rFSH + Cetrolex: 33.0 ± 4.0 rFSH only: 32.5 ± 3.6 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 63 (60%) Endometriosis: 4 (4%) Mild male factor: 37 (36%) **Inclusion criteria:** - Unexplained infertility or mild male factor infertility (abnormal semen variables but normal morphology 5% and total number of motile	**Definition(s) of outcome(s):** Pregnancy: β-hCG 2 wk after IUI and TVUS 6-7 weeks gestation to detect fetal cardiac activity Live birth: NR Multiples: Higher order multiples defined by 3 or more gestational sacs at US Complications: Ovarian hyperstimulation (not defined)	1) Pregnancy (intention-to-treat):	**Comments:** - Regimens are different so blinding affected - No placebo for Cetrorelix **Quality assessment:** Randomization method: + Blinding: - (regimens are different and no placebo for Cetrorelix) Dropout rate < 20%: + Adequacy of randomization concealment: +

	Preg +	Preg -	
rFSH + Cetrorelix	28	24	52
rFSH only	16	36	52
	44	60	104

		Lower 95% CI	Upper 95 % CI
Rel risk	1.75	1.08	2.83

2) Twin gestations (intention-to-treat):

	Preg +	Preg -	
rFSH + Cetrorelix	4	48	52
rFSH only	1	51	52
	5	99	104

		Lower 95% CI	Upper 95 % CI
Rel risk	4.00	0.46	34.59

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		spermatozoa after Pellet Swim-up ≥ $5x10^6$/ml) or minimal to mild endometriosis (stage I-II) - Age > 18 but ≤ 38 - BMI between 18-30kg/m^2 - Normal menstrual cycles 24-35 days - Normal basal serum FSH, TSH and prolactin - Normal uterine cavity and bilateral tubal patency by HSG and/or hydolaparoscopy with chromosalpingography and hysteroscopy **Exclusion criteria:** NR		3) No higher order multiples 4) No ovarian hyperstimulation	
	Compare the use of recombinant FSH (rFSH) with GnRH antagonist Cetrorelix vs. rFSH alone rFSH + Cetrorelix: rFSH 75-150 IU per day depending on age (≤ 30 vs. > 30 years) for 5 days. Cetrorelix 0.25 mg per day when follicle ≥ 14 mm only if LH was < 10 mIU/ml, progesterone l< 2ng/ml and E2 > 200 pg/ml. When leading follicle 18 mm, 10,000 IU hCG given and Cetrorelix discontinued. rFSH: same regimen as above 2 inseminations performed 20 and 34 hrs after hCG. All women given natural micronized progesterone 400 mg per day vaginally in 2 divided doses started 2 days after 2nd IUI.				

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Badawy, Baker El Nashar, and El Totongy, 2006 **#50330**	**Geographical location:** Benha, Egypt **Study dates:** Oct 2003-Apr 2005 **Size of population (no. of patients):** 804 **Number of cycles analyzed:** 804 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** Population: women with unexplained infertility Compare CC with N-acetyl-cysteine (NAC) vs. CC alone CC + NAC = CC 50 mg bid and NAC 1200 mg/d po for 5 days starting cycle day 2 CC + sugar placebo = CC same dose as above and sugar with the same volume as NAC	**Age:** Mean (SD): CC+NAC: 27.9 ± 4.2 CC+placebo: 28.1 ± 3.7 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 804 (100%) **Inclusion criteria:** - 1 year of continuous marriage without conception - Patent fallopian tubes by HSG - Normal ovulating cycles by midluteal serum progesterone levels - Normal laparoscopic findings - Normal semen analysis **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: + hCG in the absence of menstruation 2 weeks after hCG administration Live birth: NR Multiples: Yes Complications: Miscarriage, OHSS (no definition provided)	1) Pregnancy: Preg + / Preg - / Total CC+NAC: 90 / 314 / 404 CC+placebo: 108 / 292 / 400 198 / 606 / 804 Rel risk: 0.83 (Lower 95% CI 0.65, Upper 95% CI 1.05) 2) Multiple gestation: Multi + / Multi - / Total CC+NAC: 8 / 396 / 404 CC+placebo: 12 / 388 / 400 20 / 784 / 804 Rel risk: 0.66 (Lower 95% CI 0.27, Upper 95% CI 1.60) 3) No difference in miscarriage rates (CC + NAC 6.7% vs. CC + placebo 7.4%) 4) No cases of OHSS	**Comments:** - Blinding might be affected if patients detect a different taste between NAC and sugar - No information about randomization method but sealed envelopes were used **Quality assessment:** Randomization method: - Blinding: + (radiologist and lab personnel were blinded, patients might not be blinded if taste of sugar and NAC was different) Dropout rate < 20%: + Adequacy of randomization concealment: +
Balasch,	**Geographical location:**	**Age:**	**Definition(s) of**	1) Pregnancy (intention-to-treat):	**Comments:**

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Fabregues, Creus, et al., 2001 **#5560**	Barcelona, Spain **Study dates:** NR **Size of population (no. of patients):** 29 **Number of cycles analyzed:** 26 subjects each 2 cycles 3 subjects just 1 cycle **Number of cycles per patient:** As above **Study type:** RCT **Interventions:** Population: CC-resistant chronic anovulatory infertility treated with 2 different recombinant human FSH regimens Step up regimen: start dose 75 IU and increased by 37.5 IU after 14 days if no ovarian response on US (i.e. no follicle ≥ 10 mm). Additional dose increases after 7 day period if necessary. Increase until ovarian response seen on US then same dose continued until follicle > 17 mm. - hCG 10000 IU to induce ovulation. Hcg held if ≥ 4 follices were > 14 mm. Step down regimen: start dose 300 IU (cycle day 3) f/b 3 days free of	Mean (SD): 31.1±0.6 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** PCOS: 26 (100%) **Inclusion criteria:** - Failed to ovulate with CC or not conceived after at least ovulatory cycles on CC at doses ≤ 200 mg/d for 5 days **Exclusion criteria:** - Abnormal male partner semen parameters - Abnormal HSG or laparoscopy - History of pelvic surgery or PID	**outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: OHSS, definition NR	Data for 1st cycle before crossover Preg + / Preg - / Total Step up: 2 / 13 / 15 Step down: 1 / 13 / 14 3 / 26 / 29 Rel risk: 1.87 (Lower 95% CI 0.19, Upper 95 % CI 18.38) 2) No cases of ovarian hyperstimulation	- Randomization method and allocation concealment were not discussed - No blinding because entirely different regimens for step up and step down **Quality assessment:** Randomization method: - (no discussion regarding method) Blinding: - (no blinding because regimens were different) Dropout rate < 20%: + Adequacy of randomization concealment: - (no discussion regarding concealment)

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	treatment (cycle days 4-6). rhFSH restarted on day 7 with 75 IU until day 9. Then protocol the same as the step up method. Each woman received both treatment approaches with an interval of ≥ 1 month between treatments. Data for 1st cycle before cross-over are presented				
Bayar, Tanriverdi, Barut, et al., 2006 **#60050**	**Geographical location:** Zonguldak, Turkey **Study dates:** Jan 2002-Jan 2003 **Size of population (no. of patients):** 50 (4 in letrozole lost to follow-up) **Number of cycles analyzed:** 119 **Number of cycles per patient:** 2.6 **Study type:** RCT **Interventions:** Letrozole 200 mg/day days 3-7 vs clomiphene 100 mg/day days 3-7; IUI in subjects with borderline male infertility	**Age:** Median (range): Letrozole: 31 (23-39) Clomiphene: 31 (24-39) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR, but limited to unexplained infertility, early stage endometriosis, and mild male infertility **Inclusion criteria:** - Infertility lasting > 1 year - Documentation of ovulation with midluteal serum P levels > 5 ng/mL (conversion factor 3.18 nmol/L), normal hormonal profile (TSH, PRL, T, and DHEAS), and day 3 FSH ≤ 12 IU/L **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: Yes Multiples: NR Complications: NR	1) Clinical pregnancy per randomized patient: Preg + / Preg - / Total Letrozole: **5** / **20** / 25 CC: **8** / **17** / 25 Total: 13 / 37 / 50 Rel risk: Value 0.63; Lower 95% CI 0.24; Upper 95% CI 1.65 2) Live birth per randomized patient: Preg + / Preg - / Total Letrozole: **5** / **20** / 25 CC: **7** / **18** / 25 Total: 12 / 38 / 50 Rel risk: Value 0.71; Lower 95% CI 0.26; Upper 95% CI 1.95	**Comments:** Alternate odd-even numbers; included only because included in Cochrane review **Quality assessment:** Randomization method: - Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -
Bayram, van	**Geographical location:**	**Age:**	**Definition(s) of**	1) Ongoing pregnancy rate – compared patients	**Comments:**

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Wely, Kaaijk, et al. 2004 **#14110**	The Netherlands (multicenter study) **Study dates:** Feb 1998-Oct 2001 **Size of population:** 168 **Number of cycles analyzed:** 647 **Number of cycles per patient:** 3.85 (3.2 for rFSH group, 4.5 for cautery group) **Study type:** RCT **Interventions:** Compared the use of electrocautery strategy or recombinant FSH to induce ovulation in CC-resistance POCS pts At time of laparoscopy, randomized to immediate rFSH vs. electrocautery; if no ovulation after 8 weeks or resumption of anovulation after electrocautery, begun on CC (50 mg up to 150 mg); if no ovulation after 150 mg, rFSH begun 45/83 started CC, 21 of these started FSH after failure of CC, 2 immediate rFSH (protocol violation)	Mean (SD): Electrocautery: 28.5 (3.7) RFSH: 28.7 (4.1) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** PCOS: 100 **Inclusion criteria:** - Chronic ovulation and PCOS by US - CC resistance: persistent anovulation after CC 150 mg **Exclusion criteria:** - Other causes of infertility - Subfertility - Male factor - Age > 40 - Tubal occlusion - Endometriosis stage III or IV	**outcome(s):** Ongoing Pregnancy: A viable pregnancy of at least 12 wk Live birth: Yes Multiples: NR Complications: SEE NOTE BELOW Primary outcome of the study is the ongoing pregnancy rate Secondary outcomes were: Ovulation, miscarriage, ectopic pregnancy, multiple pregnancy, and live birth	who received electrocautery strategy (patients pregnant from electrocautery and the rest who receive CC and FSH as well) vs. rFSH group: Preg + / Preg - / Total Electro: **56** / **17** / 83 rFSH: **57** / **28** / 85 113 / 45 / 158 **Rel risk** Value 1.14, Lower 95% CI 0.94, Upper 95% CI 1.39 2) Live birth rate, electrocautery strategy vs. rFSH: LB + / LB - / Total Electro: **53** / **30** / 83 rFSH: **51** / **34** / 85 104 / 64 / 168 **Rel risk** Value 1.06, Lower 95% CI 0.84, Upper 95% CI 1.35 3) Number of miscarriages: Electrocautery: 7 rFSH: 7 4) Number of multiple births: Electrocautery: 1 rFSH: 9 (RR 0.11; 95% CI 0.01, 0.86) 5) Time to 50% pregnancy rate approximately 8 weeks shorter in rFSH group (not significant)	Somewhat faster time to pregnancy in rFSH group **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +
Baysoy, Serdaroglu, Jamal, et al., 2006	**Geographical location:** Istanbul, Turkey **Study dates:** NR	**Age:** Mean (SD): Letrozole: 27.2 ± 5.5 HMG: 28.1 ± 4.3	**Definition(s) of outcome(s):** Pregnancy: viable fetus by	1) Pregnancy (intention-to-treat): Preg + / Preg - Letrozole: 7 / 33 / 40	**Comments:** - No intention-to-treat analysis - Patients not blinded. Specialist performing US and IUI was blinded.

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#50520	**Size of population (no. of patients):** 80 **Number of cycles analyzed:** NR **Number of cycles per patient:** Not explicitly stated but appears to be 1 cycle per patient **Study type:** RCT **Interventions:** Population: Unexplained infertility for 2 years Compare letrozole to HMG with IUI Letrozole: 5 mg/d from day 3-7 of IUI cycle HMG: 75IU on day 3 if age < 30 years or 150 IU for women > 30 years starting day 3 for 5 days	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 80 (100%) **Inclusion criteria:** - Unexplained infertility: lack of conception after 2 years of unprotected intercourse - Regular menstrual cycles 26-34 days - Normal pelvic US - HSG and/or laparoscopy Showing tubal patency - Normal thyroid and reproductive hormones - Normal semen analysis - At least 1 ovulation induction treatment cycle with IUI **Exclusion criteria:** NR	TVUS Live birth: NR Multiples: Yes Complications: OHSS (no definition provided)	HMG 6 34 40 13 67 80 Rel risk 1.17 (Lower 95% CI 0.43, Upper 95 % CI 3.17) 2) Multiple gestation (intention-to-treat): Multi + / Multi + Letrozole 1 39 40 HMG 1 39 40 2 78 80 Rel risk 1.00 (Lower 95% CI 0.06, Upper 95 % CI 15.44) 3) 1 case of moderate OHSS in the HMG group	- 2 different HMG doses were used depending on age; no information on how many received each of the HMG doses **Quality assessment:** Randomization method: + Blinding: + (specialist was blinded; patients were not blinded) Dropout rate < 20%: - Adequacy of randomization concealment: - (not discussed)
Boostanfar, Jain, Mishell Jr., et al., 2001	**Geographical location:** Los Angeles, LA **Study dates:** Aug 1997-Nov 1999	**Age:** Mean (SD): - TMX:26.6 (4.2) - CC: 26.5 (4.4) Median: NR	**Definition(s) of outcome(s):** Pregnancy: NR (the paper did, however, state the	1) Cumulative pregnancy rate: Out + / Out - / Total TMX **10** **36** 46	**Comments:** - Pregnancy was not a primary outcome - Primary outcome is ovulation

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#5300	**Size of population:** 86 (96 randomized) **Number of cycles analyzed:** 204 **Number of cycles per patient:** 2.37 **Study type:** RCT **Interventions:** Compared Tamoxifen to Clomid Tamoxifen dosage started from 20 mg D5-9. If pts were not ovulated, the dose will increase to 40, and 60 mg. Clomid doses started at 50 mg, up to 150 mg D5-9. Population: Unexplained infertility	Range: NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: NR Endometriosis: NR Male factor: NR Tubal factor: NR PCOS: NR Other (anovulation): 100% **Inclusion criteria:** - Normal SA - Normal pelvic anatomy - Evidence of tubal patency **Exclusion criteria:** - Abnormal SA - Tubal blockage - Age>40 - Evidence of uterine fibroid - FSH>20 - P4 > 3 ng/ml - Hyper- or hypothyroidism - Hyperprolactinemia - Hepatic or renal disease - History of exposure to any ovulation induction medication. - Any contraindication of using these 2 agents	outcome of all pregnancies) Live birth: NR Multiples: NR Complications: NR	CC **6** **34** 40 Total 16 70 86 Value / Lower 95% CI / Upper 95% CI **Rel risk** 1.45 0.58 3.63 2) Cumulative clinical pregnancy: Out + / Out - / Total TMX **9** **37** 46 CC **6** **34** 40 Total 15 71 86 Value / Lower 95% CI / Upper 95% CI **Rel risk** 1.30 0.51 3.35 3) 26 out of 46 patients using TMX ovulated (vs. 30/40 in CC group). 4) Cycles per patient: TMX: 2.46 CC: 2.28	**Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +
Branigan and Estes, 2003 **#16410**	**Geographical location:** Bellingham, WA **Study dates:** NR **Size of population:** 48	**Age:** Mean (SD): 28.2 (3.4) **Race/ethnicity (n [%]):** NR	**Definition(s) of outcome(s):** Pregnancy: + hCG and ultrasound at 7 wk gestation	1) Cumulative pregnancy rate: Preg + / Preg - Study group 13 11 24	**Comment:** - Most pts not on OCP were not ovulated with this protocol - Did use cumulative pregnancy rate over multiple cycles, but CC not continued if no ovulation in first

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Number of cycles analyzed: 89 **Number of cycles per patient:** 1.85 **Study type:** RCT **Interventions:** Grp 1 Desogen for 42d - 50d. After the withdrawal bleeding, CC 100 mg started on 5d - 9d. Grp 2 No treatment for one or two cycles (38d - 56d), followed by 100 mg of CC on 5d - 9d. hCG 10,000 U was given to all pts who have leading follicle ≥ 20 mm.	**Diagnoses (n [%]):** Unexplained infertility: NR Endometriosis: NR Male factor: 0 Tubal factor: 0 PCOS: NR Other (specify): NR **Inclusion criteria:** - Anovulation after CC 150 mg - Age < 36 - Pt tubes - Normal fasting serum glucose and insulin level - Normal prolactin, TSH and FSH - DHEAS≤200u/ml - Normoestrogenic - No contraindication for OC use - Male partner has normal SA **Exclusion criteria:** NR	Live birth: NR Multiples: NR Complications: NR	Control 1 23 24 14 34 48 Rel risk 13.00 (Lower 95% CI 1.84, Upper 95 % CI 91.71)	cycle—more than twice as many cycles in OC group **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: - Adequacy of randomization concealment: -
Branigan and Estes, 2005 **#9110**	**Geographical location:** Bellingham, WA **Study dates:** NR **Size of population (no. of patients):** 71 **Number of cycles analyzed:** NR **Number of cycles per patient:** NR **Study type:** RCT	**Age:** Mean (SD): Group 1: 34.1 ± 1.1 Group 2: 33.4 + 1.3 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: NR Endometriosis: NR Male factor: 0 Tubal factor: 0 PCOS: NR Other (specify): **Inclusion criteria:** 1. Previously documented dominant follicle ≥ 12mm	**Definition(s) of outcome(s):** Pregnancy: serum hCG levels and 7-week gestational ultrasounds Live birth: NR Multiples: Yes Complications: NR	1) Pregnancy (intention to treat): Preg + / Preg - CC+hCG 3 32 35 CC only 0 36 36 3.49 68 71 Rel risk 6.38 (Lower 95% CI 0.32, Upper 95 % CI 126.20) 2) No miscarriages 3) No multiple gestations	**Comments:** - No discussion regarding blinding - CC dose was different for Group 1 (100mg) and Group 2 (150mg) **Quality assessment:** Randomization method: + Blinding: -, not discussed Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Interventions: Population: Previously anovulatory patients on clomiphene citrate (CC) alone Compare whether low-does hCG could be used to complete folliculogenesis and results in successful ovulation and pregnancy Group 1: 100mg CC days 5-9; hCG 10,000 IU IM when lead follicle ≥ 20mm. Group 2: 150mg CC days 5-9	while receiving 100mg CC 2. Age < 40 years 3. Normal uterine cavity and patent tubes by either hysterosapingogram or laparoscopy and hysteroscopy 4. Normal fasting glucose and insulin levels, serum prolactin, TSH, FSH and DHEAS < 200 µg/mL. 5. Normal semen analysis **Exclusion criteria:** NR			
Checa, Prat, Robles, et al., 2006 **#51010**	**Geographical location:** Barcelona, Spain **Study dates:** Apr-Sep 2004 **Size of population (no. of patients):** 67 **Number of cycles analyzed:** 67 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** Population: Infertile patients undergoing controlled ovarian hyperstimulation (COH) and IUI	**Age:** Mean (SD): Cetrorelix: 33 (4.9) 32 (4.1) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Male factor: 12 (18%) Female fertility: - Unexplained infertility: 29 (43%) -Endometriosis: 5 (7%) -Tubal factor: 11 (16%) -Uterine factor: 2 (3%) -Cervical: 8 (12%) -PCOS: 0 Other: - Primary infertility: 60 (90%) - Secondary infertility: 7 (10%)	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: Yes (twins) Complications: NR	1) Pregnancy: Preg + / Preg - rFSH+ Cetrorelix: 7 / 28 (35) rFSH: 4 / 28 (32) 11 / 56 (67) Rel risk: 1.60 (Lower 95% CI 0.52; Upper 95 % CI 4.96) 2) Twin gestation: Multi + / Multi - rFSH+ Cetrorelix: 3 / 32 (35) rFSH: 0.49 / 32 (32) 3.49 / 64 (67) Lower 95% CI / Upper 95 % CI	**Comments:** - Regimens were different which can affect blinding - No allocation concealment **Quality assessment:** Randomization method: + Blinding: - (not discussed and regimens were different) Dropout rate < 20%: + Adequacy of randomization concealment: - (not discussed)

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Rel risk 5.68 0.29 112.12	
	Compare rFSH only to rFSH + Cetrorelix in patient with > 1 and < 4 follicles with diameter ≥ 17 mm rFSH only: rFSH 75-100 IU qd SC starting on day 3. Day 7 and on, dose of rFSH was adjusted based on follicular growth until hCG 250µg sc. IUI 24-48hrs later. rFSH + Cetrorelix: rFSH as above until follicle ≥ 17 mm, then ½ dose of rFSH and Cetrorelix 0.25 mg SC for 2 days	**Inclusion criteria:** - Age 18-39 - Normal menstrual cycle 24-35 days - FSH ≤ 10 IU/L day 1-3 - Normal uterus and fallopian tubes on HSG **Exclusion criteria:** - PCOS - Stage III or IV endometriosis			
Christin-Maitre, Hugues, and Recombinant FSH group, 2003 **#16050**	**Geographical location:** Bondy, France **Study dates:** NR **Size of population (no. of patients):** 83 **Number of cycles analyzed:** 157 **Number of cycles per patient:** 1.9 **Study type:** RCT **Interventions:** Population: CC-resistant PCOS Compare rFSH step-up versus step-down protocol for 3 cycles	**Age:** Mean (SD): 28.8 ± 3.2 Step-up: 28.8 ± 3.0 Step down: 28.7 ± 3.4 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** PCOS: 83 (100%) **Inclusion criteria:** - PCOS diagnosed by WHO type II criteria - CC resistant if failed to ovulate after 3 cycles with CC 100 mg/d for 5 days or failed to conceive after 6 cycles with this treatment - Oligo/amenorrhea or anovulatory cycles for 2 years - TVUS > 8 follicles between 2-8 mm with	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: Yes Complications: Miscarriage (definition NR)	1) Pregnancy (intention-to-treat): Preg + / Preg - Step up 17 / 27 — 44 Step down 12 / 27 — 39 29 / 54 — 83 Rel risk 1.26 (Lower 95% CI 0.69, Upper 95 % CI 2.29) 2) Multiple gestations (intention-to-treat): Multi + / Multi - Step up 2 / 42 — 44 Step down 3 / 36 — 39 5 / 78 — 83 Rel risk 0.59 (Lower 95% CI 0.10, Upper 95 % CI 3.35) 3) Miscarriage rate: 12.5% step-up vs. 16.7%	**Comments:** - Randomization method not described - Numbered sealed envelopes were used - No information about blinding **Quality assessment:** Randomization method: - (no information provided) Blinding: - (no information provided) Dropout rate < 20%: + Adequacy of randomization concealment: +

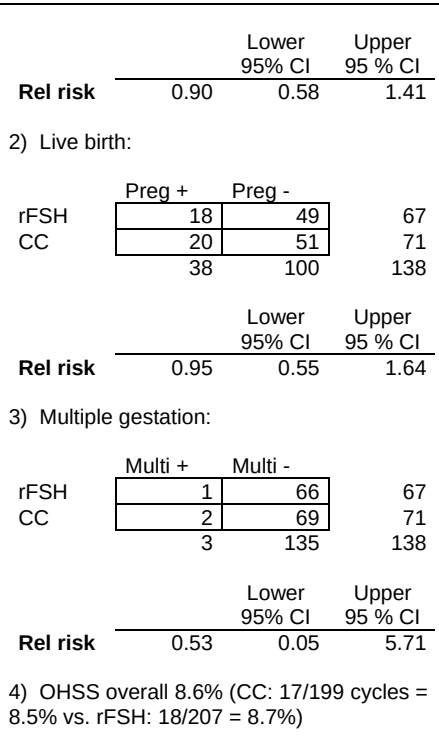
Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Step-up: Puregon 50 IU on day 3-5 x 14 days. If no follicle > 9 mm, increase to 75 IU. Further increments by 25 IU weekly up to 100 IU in 1st cycle. In 2nd and 3rd cycle, start dose of 75 IU if no follicular development before dose of 100 IU and maximum of 125 IU for these cycles. Step down: Puregon 100 IU days 3-5. When follicle > 9 mm, dose decreased to 75 IU for 3 days and then to 50 IU until the day prior to hCG. If no follicular development after 5 days, initial dose increased to 150 IU. After follicle development, decrease to 125 IU for 3 days, 100 IU for 3 days and 75 IU until hCG. Both protocols: hCG 5000 IU IM or SC when leading follicle > 18 mm. hCG withheld if ≥ 4 follicles > 16 mm or estradiol level ≥ 1000 pg/ml.	stromal hypertrophy - Normal prolactin - Serum FSH < 10 IU/l - Normal testosterone - Normal HSG or laparoscopy in past 3 years **Exclusion criteria:** NR		step-down	
Crosignani, Somigliana, and Intrauterine Inseminatio n Study Group, 2007	**Geographical location:** 11 different centers: Amsterdam, Athens, Barcelona, Budapest, Cairo, Hradek Kralove, Lubeck, Milan, Palermo and Prague	**Age:** Mean (SD): rFSH + Ganirelix: 31.3 ± 3.9 rFSH only: 31.2 ± 3.9 **Race/ethnicity (n [%]):** NR	**Definition(s) of outcome(s):** Pregnancy: US visualization of at least 1 intrauterine gestational sac	1) Ongoing pregnancy: Multi + / Multi - rFSH + Ganirelix: 15 / 133 — 148 rFSH: 16 / 135 — 151 31 / 268 — 299	**Comments:** - Patients and physicians were not blinded - Intention to treat analysis was performed **Quality assessment:** Randomization method: +

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#51290	**Study dates:** Jan 2004-Oct 2005 **Size of population (no. of patients):** 299 **Number of cycles analyzed:** 299 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** Population: Unexplained or mild male factor infertility Compare rFSH + Ganirelix vs. rFSH only rFSH only: 50 IU qd starting day 3 rFSH + Ganirelix: rFSH as above and Ganirelix - .25 mg/d when follicle ≥ 13 mm until hCG administered.	**Diagnoses (n [%]):** Unexplained infertility: 209 (70%) Male factor: 90 (30%) **Inclusion criteria:** - Age < 38 years - Primary or secondary infertility for > 2 years - Regular menstrual cycles - BMI ≤ 30 kg/m^2 - Midluteal progesterone > 6ng/ml - Day 3 FSH < 10 IU/ml - Normal uterus and fallopian tubes by HSG and/or laparoscopy - If monolateral tubal occlusion, then normal patent tube by laparoscopy - Normal semen analysis with > 5 million motile after preparation and 5% normal morphology - Male subfertility ≤ 20 million/ml concentration, and/or progressive motility < 25% and/or morphology < 9% - No previous IUI - Stage I-II endometriosis **Exclusion criteria:** - Stage III-IV endometriosis - PID	Ongoing pregnancy: Pregnancy beyond 1st trimester Live birth: NR Multiples: Yes Complications: OHSS definition NR but another reference cited for criteria	2) Twin gestation: Multi + / Multi - rFSH + Ganirelix: 15 / 133 (148) rFSH: 3 / 148 (151) 18 / 281 (299) **Rel risk** 5.10 (Lower 95% CI 1.51, Upper 95% CI 17.26) 3) No cases of OHSS	Blinding: - (patients and physicians not blinded) Dropout rate < 20%: + (12.7% [38/299]) Adequacy of randomization concealment: +
Dankert, Kremer, Cohlen, et al., 2007 **#51370**	**Geographical location:** Nijmegen, Netherlands **Study dates:** Jan 2001-Sep 2004 **Size of population (no.**	**Age:** Mean (SD): Unexplained subfertility: CC: 31.0 rFSH 31.6 Male subfertility:	**Definition(s) of outcome(s):** Pregnancy: + urine pregnancy test; US 7th and 12th week	1) Pregnancy: Preg + / Preg - rFSH: 23 / 44 (67) CC: 27 / 44 (71) 50 / 88 (138)	**Comments:** - Patients not blinded because rFSH SC injection vs. CC which is oral medication - No information regarding blinding of others in the study

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	of patients): 138 **Number of cycles analyzed:** 406 **Number of cycles per patient:** 2.94 **Study type:** RCT **Interventions:** Population: unexplained and male subfertility Compare CC versus low dose recombinant FSH CC: 100 mg/d on days 3-7. If mono-follicular development, then dose increased by 50 mg in next cycle. If excessive follicle development (≥ 3 follices of > 14 mm), then decreased by 50 mg Low dose rFSH: 75 IU/d SC from cycle day 3 until follicular maturation. If no follicle > 10 mm on day 11, increase to 112.5 IU/d. If mono-follicular development, decrease by 37.5 IU in next cycle. If excessive follicle development (≥ 3 follicles, > 14 mm), then decrease by 37.5 IU.	CC: 30.1 rFSH: 31.2 Range: 19.7-38.3 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 68 (49%) Male factor: 70 (51%) **Inclusion criteria:** - Primary subfertility for 24 months - Regular menses cycle 21-35 days - Laparoscopy and/or HSG to confirm tubal patency - Unexplained subfertility defined as no abnormality on: ovulation by basal body temp, ultrasound and/or mid-luteal progesterone, post-coital testing, semen analysis and Chlamydia antibody titer - If + Chlamydia antibodies, then laparoscopy done **Exclusion criteria:** - Age < 18 or > 38 - Anovulation - Prior assisted reproduction attempts - Stage III or IV endometriosis - Contraindication for CC or rFSH - Resisting ovarian cyst (> 19 mm and 1 > 1 month) - Total motile sperm count < 1 million after semen	Live birth: Review patient charts or by phone calls to the patient Multiples: On US Complications: NR	 	**Quality assessment:** Randomization method: + Blinding: - (patients not blinded for reasons above; blinding of other individuals not stated) Dropout rate < 20%: + (18% [24/138]) Adequacy of randomization concealment: - (not discussed)

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		preparation - Cancer of ovaries, breast and/or uterus			
Dehbashi, Vafaei, Parsanezhad, et al., 2006 **#51490**	**Geographical location:** Shiraz, Iran **Study dates:** June 2002 – May 2004 **Size of population (no. of patients):** 78 **Number of cycles analyzed:** 149 **Number of cycles per patient:** Group 1: 71cycles/37 pts = 1.92 Group 2: 78 cycles/41 pts = 1.90 **Study type:** RCT **Interventions:** Population: Women with PCOS Group 1: Compare CC 100mg/d on days 1-5 Group 2: CC 100mg/d on days 5-9	**Age:** Mean (SD): Group 1: 23.1 ± 3.7 Group 2: 23.0 ± 3.5 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 0 Endometriosis: 0 Male factor: 0 Tubal factor: 0 PCOS: 78 (100%) Other (specify): **Inclusion criteria:** - PCOS women defined as anovulatory women with laboratory or clinical evidence of hyperandrogenism but no appreant cause were diagnosed with PCOS. **Exclusion criteria:** - Evaluation included semen analysis, hormonal assays, endometrial biopsy, HSG and any cause of infertility other than PCOS was excluded.	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Pregnancy: Preg + / Preg - / Total CC D1-5: 15 / 22 / 37 CC D5-9: 8 / 33 / 41 23 / 55 / 78 Rel risk: 2.08 (Lower 95% CI 1.00, Upper 95 % CI 4.33)	**Comments:** - No allocation concealment - No information on blinding **Quality assessment:** Randomization method: + Blinding: -, not discussed Dropout rate < 20%: + Adequacy of randomization concealment: -, not discussed
Demirol and Gurgan, 2007 **#51510**	**Geographical location:** Ankara, Turkey **Study dates:** May 2000-May 2004	**Age:** Mean (SD): rFSH: 30.4 ± 2.9 uFSH: 31.5 ± 3.6 hMG: 30.8 ± 3.2	**Definition(s) of outcome(s):** Pregnancy: US 6 wk after IUI	1) Pregnancy: rFSH vs. uFSH Preg + / Preg - / Total	**Comments:** - No information regarding blinding -No adjustment for multiple comparisons **Quality assessment:**

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Size of population (no. of patients): 241 **Number of cycles analyzed:** 241 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** Population: unexplained infertility Compare different gonadotropin preparations: Folitropin α vs. urinary FSH (uFSH) vs. hMG Group 1: rFSH Group 2: uFSH Group 3: hMG For all, day 2-3, 75IU of gonadotrophin if BMI , 25kg/m^2 or 150 IU if BMI ≥ 25kg/m^2	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 241 (100%) **Inclusion criteria:** - Primary infertility > 2 years - Age between 20-40 - Normal ovulatory cycles - Patent tubes by HSG or laparoscopy - Normal sperm count and motility **Exclusion criteria:** - Previous ART - Previous controlled ovarian stimulation (COS)-IUI cycle - History of pelvic surgery	Live birth: NR Multiples: Yes Complications: OHSS (not defined)	uFSH **11** **69** 80 rFSH **21** **60** 81 Total 32 129 161 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.53 0.27 1.03 rFSH vs. hMG Preg + / Preg - / Total hMG **10** **70** 80 rFSH **21** **60** 81 Total 31 130 161 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.48 0.24 0.96 uFSH vs. hMG Preg + / Preg - uFSH 11 69 80 hMG 10 70 80 21 139 160 Lower 95% CI / Upper 95 % CI **Rel risk** 1.10 0.50 2.44 3) Multiple pregnancy: no difference rFSH 2/80 = 10% uFSH 0/80 = 0% hMG 1/80 = 9% 4) No cases of OHSS	Randomization method: + Blinding: - (no information) Dropout rate < 20%: + Adequacy of randomization concealment: +
Elnashar, Abdelmageed, Fayed, et al., 2006 **#51730**	**Geographical location:** Benha, Egypt **Study dates:** March - Dec 2004 **Size of population (no.**	**Age:** Mean (SD): Group 1: 23.4 ± 3.6 Group 2: 25.2 ± 2.4 **Race/ethnicity (n [%]):** NR	**Definition(s) of outcome(s):** Pregnancy: gestational sac on TVUS 1 week after missed period	1) Pregnancy: Preg + / Preg - CC+ dexameth 16 24 40 CC+ placebo 2 38 40	**Comments:** - Placebo pill (folic acid) and dexamethasone may have different appearance **Quality assessment:** Randomization method: +

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	of patients): 80 **Number of cycles analyzed:** 80 as only 1 cycle per patient **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** Population: All patients had previously received CC and diagnosed with CC resistance (failure of ovulation after 3 cycles of CC reaching 150mg/d dose) Group 1: CC 100mg/d day 3-7 + dexamethzone 2mg/d from day 3-12 Group 2: CC 100mg/d day 3-7 + placebo (folic acid tablets) day 3-12	**Diagnoses (n [%]):** Unexplained infertility: Endometriosis: Male factor: Tubal factor: PCOS: 80 (100%) Other (specify): **Inclusion criteria:** - PCOS according to Rotterdam criteria - Age 18-39 - Infertility > 2 years - Normal serum DHEAS (80-400 µg/dl) - No treatment during prior 2 months **Exclusion criteria:** - Pelvic surgery or infertility factor other than anovulation	Live birth: NR Multiples: NR Complications: Side effects Ovulation: disappearance of pre-ovulatory follicle, fluid in the cul-de-sac and/or corpus luteum formation	18 62 80 Lower 95% CI / Upper 95 % CI **Rel risk** 8.00 1.97 32.54 2) No side effects for those on dexamethasone	Blinding: -, placebo pill may look different than dexamethasone pill Dropout rate < 20%: + Adequacy of randomization concealment: +
Fancsovits, Toth, Murber, et al., 2005 **#10230**	**Geographical location:** Budapest, Hungary **Study dates:** March 2000 – July 2003 **Size of population (no. of patients):** 251 **Number of cycles analyzed:** 784 **Number of cycles per patient:** 3.1	**Age:** Mean (SD): Gynetics: 33.1 ± 5.3 Makler 32.2 ± 5.1 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Infertility > 1 year - Male factor, cervical factor, unexplained	**Definition(s) of outcome(s):** Pregnancy: + urine pregnancy test Live birth: NR Multiples: NR Complications: NR	[1) Pregnancy Preg + / Preg - Gynetics 34 88 122 Makler 32 89 121 66 177 243 Lower 95% CI / Upper 95 % CI **Rel risk** 1.05 0.70 1.59	**Comments:** - Patients were blinded; physicians were not as the cannulas are different - Allocation concealment not discussed - No intention to treat in paper; unable to calculate ITT results because no information on allocation of the 8 who dropped out **Quality assessment:** Randomization method: +

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Study type: RCT **Interventions:** Population: Infertile couples undergoing IUI Compare IUI with Gynetics (Belgium) vs Makler cannula (Haifa, Israel)	infertility or any combination of these - Ovulatory - At least 1 open fallopian tube - ≥ 5 x 10^6 progressive motile sperm **Exclusion criteria:** NR			Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: -, not discussed
Farquhar, Williamson, Gudex, et al., 2002 **#58180**	**Geographical location:** Auckland, New Zealand **Study dates:** 1996-1999 **Size of population (no. of patients):** 50 **Number of cycles analyzed:** Unclear; 6 months follow-up after diathermy, up to 3 cycles of gonadotropins **Number of cycles per patient:** > 1.0 **Study type:** RCT **Interventions:** 1) Bilateral laparoscopic diathermy, vs. 2) 3 cycles gonadotropins	**Age:** Mean (SD): Drilling: 29.6 (4.7); gonadotropins 29.6 (4.2) **Race/ethnicity (n [%]):** White: 28 (56%) Maori: 7 (14%) Asian: 10 (20%) Other: 4 (8%) **Diagnoses (n [%]):** PCOS: 50 (100%) **Inclusion criteria:** 20-38 years of age, clomiphene citrate resistance (no ovulation after one or more cycles of 150 mg of clomiphene citrate from day 2 to day 6 each month), infertility of ≥ 12 months duration, polycystic ovaries on ultrasound scan according to accepted criteria (10), a body mass index of ≤ 33 kg/m^2 for women of European descent and of ≤ 35 kg/m^2 for women of Pacific Island or NZ Maori descent, and normal	**Definition(s) of outcome(s):** Pregnancy: Fetal heart on ultrasound Live birth: Birth after 20 weeks Multiples: Yes Complications: NR	1) Clinical pregnancy (within 6 months): Preg + / Pregt - / Total Diathermy: **5** / **24** / 29 Gonadotropins: **5** / **16** / 21 Total: 10 / 40 / 50 Value: **Rel risk** 0.72; Lower 95% CI 0.24; Upper 95% CI 2.19 2) Live birth (6 months): Live birth + / Live birth - / Total Diathermy: **4** / **25** / 29 Gonadotropins: **4** / **17** / 21 Total: 8 / 42 / 50 Value: **Rel risk** 0.72; Lower 95% CI 0.20; Upper 95% CI 2.57 3) Any pregnancy (+ hCG) within 12 months: Preg + / Preg - / Total Diathermy: **9** / **20** / 29 Gonadotropins: **7** / **14** / 21 Total: 16 / 34 / 50	**Comments:** Proportion with BMI ≤ 25 higher in gonadotropin group **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		semen analysis (≥ 20 million per milliliter, ≥ 96% abnormal forms, and ≥ 50% motility) **Exclusion criteria:** Other known causes of infertility, including male factor infertility or known tubal disease		Rel risk: Value 0.93, Lower 95% CI 0.41, Upper 95% CI 2.10 4) No multiples in either group	
Fatemi, Kolibianakis, Tournaye, et al., 2003 **#58190**	**Geographical location:** Brussels, Belgium **Study dates:** Sep 2001-Aug 2002 **Size of population (no. of patients):** 15 **Number of cycles analyzed:** 15 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Clomiphene 100 mg day 3-7 or letrozole 2.5 mg day 3-7, followed by IUI	**Age:** Median: Clomiphene 28.2 Letrozole 28.9 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Age ≤ 39 - BMI 18-29 - Ovulatory cycles - Normal semen analysis - Day 3 FSH ≤ 12 - Normal liver/kidney function - No history of tubal disease **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: + hCG on days 12 and 16 post IUI Live birth: NR Multiples: NR Complications: NR	1) Pregnancy: Out + / Out - / Total Letrozole: **2** / **5** / 7 Clomiphene: **3** / **5** / 8 Total: 5 / 10 / 15 Rel risk: Value 0.76, Lower 95% CI 0.17, Upper 95% CI 3.33	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -
Filicori, Cognigni, Pocognoli, et al., 2003 **#15930**	**Geographical location:** Bologna, Italy **Study dates:** NR **Size of population:** 50 **Number of cycles analyzed:** 50	**Age:** Mean (SD): - rFSH: 31.9 (0.7) - hMG: 32.6 (0.5) Median: NR Range: 22-38 **Race/ethnicity (n [%]):** NR	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Pregnancy rate: Preg + / Preg - / Total rFSH: **4** / **21** / 25 hMG: **7** / **18** / 25 11 / 39 / 50 Value, Lower 95% CI, Upper 95% CI	**Comment:** Underpowered for pregnancy **Quality assessment:** Randomization method: - (NR) Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Number of cycles per patient: 1.0 **Study type:** RCT **Interventions:** 150 IU hMG or 150 IU rFSH in COH/IUI cycle	**Diagnoses (n [%]):** Unexplained infertility: 100% **Inclusion criteria:** Unexplained or mild male factor-related infertility **Exclusion criteria:** NR		**Rel risk** 0.57 0.19 1.71 Duration of treatment and cost significantly lower with hMG	
Fleming, Hopkinson, Wallace, et al., 2002 **#58210**	**Geographical location:** Glasgow, UK **Study dates:** NR **Size of population (no. of patients):** 94 (42 desired pregnancy) **Number of cycles analyzed:** 16 weeks of treatment **Number of cycles per patient:** > 1.0 **Study type:** RCT **Interventions:** Metgormin 850 mg BID x 16 weeks vs. placebo	**Age:** Mean: Metformin: 28.6 Placebo: 29.2 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** PCOS: 100% **Inclusion criteria:** - Age <35 - Oligo- (< 8 cycles/year) or amenorrhea - Polycystic ovaries on transvaginal ultrasound **Exclusion criteria:** - Hyperprolactinemia - Congenital adrenal hyperplasia - Abnormal thyroid function	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Pregnancy (of those seeking pregnancy): Preg + / Preg - / Total Metformin: **4** / **19** / 23 Placebo: **1** / **18** / 19 Total: 5 / 37 / 42 Value / Lower 95% CI / Upper 95% CI **Rel risk** 3.30 0.40 27.13	**Comments:** Not all subjects actively seeking conception **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +
George, George, Chandy, et al., 2007 **#52070**	**Geographical location:** Tamil Nadu and Chennai, India **Study dates:** NR **Size of population (no. of patients):** 180	**Age:** Mean (SD): Group A: 24.7 ± 3.5 Group B: 25.1 ± 4.0 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):**	**Definition(s) of outcome(s):** Pregnancy: + FH on TVUS at 6-7 wk Live birth: Yes Multiples: NR	1) Pregnancy (intention-to-treat): Preg + / Preg - / Lower / Upper CC+hCG: 10 / 80 / 90 CC only: 6 / 84 / 90 16 / 164 / 180	**Comments:** - Blinding issues: 1. Only Group A received hCG; no placebo in Group B 2. After 18 mm follicle, Group A advised to have intercourse 36 hrs after hCG vs. Group B advised to have intercourse frequently - No information about patients who

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		Anovulation 180 (100%)			dropped out - No information about number of cycles total
	Number of cycles analyzed: NR **Number of cycles per patient:** NR **Study type:** RCT **Interventions:** Population: Women receiving CC for anovulation. CC given days 2-6 with a starting dose 100 mg. Increase 50 mg until a response. Max dose was 200 mg. Compare CC with 5000 IU hCG vs. CC alone Group A: CC and 5,000 IU hCG after follicle reached 18 mm Group B: CC only	**Inclusion criteria:** - All women receiving CC for anovulation, defined as cycle length > 35 days or serum progesterone < 10 ng/ml on day 21 for women with 28-day cycles **Exclusion criteria:** NR	Complications: Miscarriage	**Rel risk** 1.67 (95% CI 0.63, 95 % CI 4.39) 2) Live birth (intention-to-treat): CC+hCG: Live birth + 8, Live birth - 82, 90 CC only: Live birth + 5, Live birth - 85, 90 13, 167, 180 **Rel risk** 1.60 (Lower 95% CI 0.54, Upper 95 % CI 4.70) 3) No difference in miscarriage rates (1 in CC+hCG group vs. 1 in CC only)	**Quality assessment:** Randomization method: Blinding: - (Group A received hCG, Group B did not receive placebo; 2 groups given different instructions for timing of intercourse) Dropout rate < 20%: + Adequacy of randomization concealment: +
George, George, Irwin, et al., 2003 **#17420**	**Geographical location:** Tamil Nadu, India **Study dates:** 1999-2001 **Size of population:** 60 (metformin-30; hMG-30) **Number of cycles analyzed:** NR **Number of cycles per patient:** NR **Study type:** RCT **Interventions:** Sequential use of	**Age:** Mean (SD): Metformin: 25.1 (3) hMG: 26 (2.9) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** PCOS: 100% **Inclusion criteria:** - Tubal factor infertility - Male factor infertility - BMI > 35 **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: Yes Multiples: NR Complications: NR	1) Pregnancy rate: Metformin: Out + **5**, Out - **25**, Total 30 hMG: Out + **7**, Out - **23**, Total 30 Total: 12, 48, 60 **Rel risk** Value 0.71 (Lower 95% CI 0.25, Upper 95% CI 2.00) 2) Live birth rate: Metformin: Out + **2**, Out - **28**, Total 30	**Comments:** Cumulative pregnancy rate over multiple cycles **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	metformin for 6 mo followed by Clomid compare to gonadotropin for OI cycle Population: CC-resistance PCOS			hMG **6** **24** 30 Total 8 52 60 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.33 0.07 1.52	
Gerli, Casini, Unfer, et al., 2004 **#11060**	**Geographical location:** Perugia and Rome, Italy **Study dates:** NR **Size of population:** 170 **Number of cycles analyzed:** 379 **Number of cycles per patient:** 2.23 **Study type:** RCT **Interventions:** This study compare the outcome of the ovulation induction using uFSH or rFSH in PCOS pts	**Age:** Mean (SD): uFSH: 28 ± 2.7 rFSH: 29.1 ± 2.4 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** PCOS: 100 **Inclusion criteria:** Women with PCOS and a history of 2 yrs of infertility **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Biochemical pregnancy: small or transient increase in b-HCG concentrations Clinical pregnancy: The visualization of an embryo with cardiac activity at 6-7 wk of pregnancy Live birth: NR Multiples: Yes Complications: NR	1) Clinical pregnancy rate: Preg + / Preg - / Total uFSH **22** **60** 82 rFSH **23** **65** 88 45 125 170 Value / Lower 95% CI / Upper 95% CI **Rel risk** 1.03 0.62 1.69 2) Multiple pregnancy: Preg + / Preg - Study group 3 19 22 Control 3 17 20 6 36 42 Lower 95% CI / Upper 95 % CI **Rel risk** 0.91 0.21 4.00	**Comments:** Cumulative pregnancy rate **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +
Gerli, Gholami, Manna, et al., 2000 **#58240**	**Geographical location:** Perugia, Rome, and Naples, Italy **Study dates:** NR **Size of population (no. of patients):** 64 **Number of cycles analyzed:** 64	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** PCOS: 100% **Inclusion criteria:** - Age 25-35 - 2 years infertility	**Definition(s) of outcome(s):** Pregnancy: Clinical: gestational sac on ultrasound at 6-7 weeks, or hCG > 1400 Ongoing: > 20 weeks Live birth: NR	1) Ongoing pregnancy: Out + / Out - / Total CC + E2 **12** **20** 32 CC **2** **30** 32 Total 14 50 64 Value / Lower 95% CI / Upper 95% CI **Rel risk** 6.00 1.46 24.69	**Comments:** None **Quality assessment:** Randomization method: - Blinding:+ Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Number of cycles per patient: 1.0 **Study type:** RCT **Interventions:** Clomiphene 100 mg x 5 days (day 3-7) + placebo day 8-12, vs. clomiphene days 3-7 + 0.05 mg ethinyl estradiol days 8-12	Oligo- or amenorrhea with positive bleeding to progesterone withdrawal - Normal thyroid, prolactin, testosterone - No prior infertility treatment **Exclusion criteria:** - Abnormal semen analysis -Tubal or uterine pathology - BMI > 25	Multiples: NR Complications: Miscarriage	2) Miscarriage: Out + / Out - / Total CC + E2: **2** / **30** / 32 CC: **6** / **26** / 32 Total: 8 / 56 / 64 Value / Lower 95% CI / Upper 95% CI **Rel risk**: 0.33 / 0.07 / 1.53	
Ghazeeri. Kutteh, Bryer-Ash, et al., 2003 **#17290**	**Geographical location:** Memphis, Tennessee **Study dates:** NR **Size of population (no. of patients):** 25 **Number of cycles analyzed:** NR **Number of cycles per patient:** NR **Study type:** RCT **Interventions:** Population: CC-resistant overweight and obese women with PCOS Compare rosiglitazone with placebo to rosiglitazone with CC Group 1: Rosiglitazone 4 mg bid with placebo on days 5-9 Group 2: Rosiglitzaone 4	**Age:** Mean (SD): Group 1: 28.7 ± 3.5 Group 2: 28.7 ± 4.1 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** PCOS: 25 (100%) **Inclusion criteria:** - PCOS diagnosed by: 1. anovulation with mid-luteal progesterone < 5 mg/ml 2. History of oligomenorrhea with no menses in last 60 days 3. + progestin withdrawal test 4. self-reported hirsutism or total testosterone > 65 ng/dl - Ages 18-40 - BMI > 26 kg/m^2 - Failure to ovulate with 150 mg/d CC **Exclusion criteria:**	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: Yes Multiples: NR Complications: NR	1) Pregnancy: Preg + / Preg - / Total Rosi + CC: 2 / 11 / 13 Rosi + placebo: 1 / 11 / 12 3 / 22 / 25 Lower 95% CI / Upper 95 % CI **Rel risk**: 1.85 / 0.19 / 17.85 2) Live birth: Live birth + / Live birth - / Total Rosi + CC: 1 / 12 / 13 Rosi + placebo: 1 / 11 / 12 2 / 23 / 25 Lower 95% CI / Upper 95 % CI **Rel risk**: 0.92 / 0.06 / 13.18	**Comments:** - Randomization method and allocation concealment were well described - Investigators, study personnel and patients were blinded **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	mg bid with CC on days 5-9	- Diabetes or fasting glucose > 125 mg/dL - CAH or fasting serum 17αOHP > 200 ng/dL - Thyroid disease - Hyperprolactinemia - Congestive heart failure - Hypertension - Hepatic or renal disease - Ovulation induction agent or oral hypoglycemic agent within 30 days			
Gomes, Vieira, Moura, et al., 2007 **#52230**	**Geographical location:** Sao Paulo, Brazil **Study dates:** NR **Size of population (no. of patients):** 51 **Number of cycles analyzed:** 51 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** Population: Patients undergoing controlled ovarian stimulation	**Age:** Mean (SD): hCG: 30.1 hMG: 29.4 rFSH: 29.0 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Male factor: 39 (76%) Tubal factor: 7 (14%) Other: "Association": 5 (10%) **Inclusion criteria:** - Ages 25-35 - Regular menstrual cycles - Normal BMI (20-25 kg/m^2)	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: Yes Complications: Abortion	1) Pregnancy: hCG vs. rFSH Preg + / Preg - / Lower 95% CI / Upper 95 % CI hCG: 9 / 8 / 17 rFSH: 4 / 13 / 17 13 / 21 / 34 **Rel risk**: 2.25 / 0.86 / 5.92 hMG vs. rFSH Preg + / Preg - hMG: 5 / 12 / 17 rFSH: 4 / 13 / 17 9 / 25 / 34	**Comments:** No information about allocation concealment or blinding **Quality assessment:** Randomization method: + Blinding: - (no information) Dropout rate < 20%: + Adequacy of randomization concealment: - (not discussed)

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Compare hCG vs. hMG vs. rFSH in late stage of follicular development All patients: OCPs 1st day of previous menses until 5 days prior to stimulation. Leuprolide acetate 0.5 mg/d started 10 days before induction and continued until day before hCG injection. rFSH 200 IU daily sq until dominant follicle 12-13 mm. Then divided into groups. hCG: 200 IU IM daily until follicles 18-19 mm hMG: 225 IU IM daily rFSH: 200 IU SC daily	- Tubal factor or unexplained or moderate to severe male factor infertility (less than 5 million motile, progressive and normal sperm after washing). **Exclusion criteria:** - PCOS - FSH > 10 IU/mL during early follicular phase - Endometriosis - Uterine myomas - Use of injectable hormonal contraceptive up to 6 months before stimulation - Poor ovarian response to controlled ovarian stimulation in past - Uterine alterations or absence of 1 ovary		Lower 95% CI / Upper 95 % CI **Rel risk** 1.25 0.40 3.87 hCG vs. hMG Preg + / Preg - hCG 9 8 17 hMG 5 12 17 14 20 34 Lower 95% CI / Upper 95 % CI **Rel risk** 1.80 0.76 4.26 3) Multiple gestations: hCG: 3/17 (18%) hMG: 3/17 (18%) rFSH: 0/17 (0%) 4) Abortion: hCG: 3/9 (33%) hMG: 0/5 (0%) rFSH: 1/4 (25%)	
Gomez-Palomares, Julia, Acevedo-Martin, et al., 2005 **#9720**	**Geographical location:** Madrid, Spain **Study dates:** 1/03-6/03 **Size of population:** 82 **Number of cycles analyzed:** 82 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** The aim of this study is to	**Age:** Mean (SD): GnRHa: 33.9 (2.6) Control: 32.05 (3.3) Median: NR Range: 18-38 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: GnRHa: 30 (75) Control: 28 (67) Endometriosis: 0 Male factor: 0 Tubal factor: 0	**Definition(s) of outcome(s):** Pregnancy: - Clinical pregnancy:+ hCG and + heart beat on u/s - Biochemical pregnancy: + hCG alone Live birth: NR Multiples: Yes Complications: SAB	1) Clinical pregnancy rate: Preg + / Preg - Study group 15 25 40 Control 6 36 42 21 61 82 Lower 95% CI / Upper 95 % CI **Rel risk** 2.63 1.13 6.09 2) No miscarriage noted in both groups There is no difference in the Singleton and Multiple pregnancy rate between 2 grps Singleton	**Comment:** - Grp 1 had stat significantly greater # of follicles compared to Grp 2: 2.4 vs. 1.7, p = 0.02 - 1 pt excluded from each grp due to excessive follicle # **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: - (NR)

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	assess the efficacy of a GnRH antagonist in IUI cycles. Control: rFSH Alone Experiment grp : rFSH+ GnRH antagonist (Ganirelix)	PCOS: 0 Other (specify): Anovulation GnRHa: 10 (25) Control: 14 (33) **Inclusion criteria:** - age 18-38 - Regular period - Infertility lasting > or= 12 mos - Normal prolactin - Normal thyroid function tests - Normal uterine cavity - Bilateral tubal petency **Exclusion criteria:** - FSH > 10 - PCOS		GnRHa 93% (14/15) Control : 100% (6/6) Multiple pregnancy 1 pt in GnRHa None in Control 2) Multiples: Grp 1: 6.6% Grp 2: 0 3) SAB: Grp 1: 0 Grp 2: 14%	
Grigoriou, Makrakis, Konidaris, et al., 2005 **#10260**	**Geographical location:** Athens, Greece **Study dates:** May 2002-Oct 2003 **Size of population (no. of patients):** 52 **Number of cycles analyzed:** 133 **Number of cycles per patient:** 2.6 **Study type:** RCT **Interventions:** Ovarian stimulation was CC days 3-7, hCG 10,000 U when lead follicle ≥18mm. IUI 34-	**Age:** Mean (SD): PAF: 30.6 ± 3.1 NonPAF: 31.8 ± 4.1 Median: NR Range: NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Population: Couples with unexplained infertility and candidates for IUI - Infertility ≥1 year - Regular menstrual cycles 26-32 days - Ovulatory basal body temperature chart	**Definition(s) of outcome(s):** Pregnancy: gestational sac with fetal pole on US Live birth: NR Multiples: NR Complications: NR	1) Pregnancy (intention to treat): - Only data from 1st 3 cycles before cross over Preg + / Preg - PAF: 14 / 12 — 26 nonPAF: 6 / 20 — 26 20 / 32 — 52 Rel risk: 2.33 (Lower 95% CI 1.06, Upper 95% CI 5.13)	**Comments:** - Patients were crossed over if they failed the 1st assigned treatment after 3 cycles - Only data from the 1st 3 cycles is presented - No information regarding blinding **Quality assessment:** Randomization method: + Blinding: -, no information Dropout rate < 20%: + Adequacy of randomization concealment: -, not discussed

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	38 hrs after hCG Compare sperm treatment with exogenous platelet – activating factor (PAF) PAF: sperm for IUI treated with PAF (10^{-7} mol/L) for 3 cycles nonPAF: direct swim-up technique for 3 cycles If no pregnancy after first 3 cycles, then cross over design. Only data from 1st 3 cycles presented.	- Midluteal serum P levels ≥32ng/ml - Normal levels of FSH, LH, androstenedione and DHEAS - Normal prolactin on day 3 - Normal thyroid function tests - Nonsignificant results from TVUS - Normal HSG - Nonsignificant results at laparoscopy - Normal semen analysis on 2 occasions **Exclusion criteria:** NR			

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
International Recombinant Human Chorionic Gonadotropin Study Group, 2001 **#5150**	**Geographical location:** Multicenter **Study dates:** Mar 1996-May 1999 **Size of population:** 198 **Number of cycles analyzed:** 198 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Compare the use of recombinant 250 ug hCG (Ovidrel) and 5000 IU of uhCG for surrogate LH surge in COH cycle. COH protocol: rFSH step up protocol. No GnRH agonist used. Each pt either received 2 SQ injections (1 injection of hCG and one injection of placebo to study side effect when criteria met - One follicle with mean diameter ≥18 mm - No more 3 follicle with mean diameter ≥16 mm - No more 4 follicle 11-15 mm - Estradiol level appropriate for the number of follicles but not higher than 5500 pmol/L (1500 pg/ml) Insemination was via IUI	**Age:** Mean (SD): rhCG 29.2 (3.7) uhCG 28.5 (3.5) All 28.8 (3.6) Range: 20-38 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovulatory dysfunction 100%: **Inclusion criteria:** - Infertility due to ovulatory dysfunction - Spontaneous menses, menses induced by CC therapy, or a positive progesterone-withdrawal bleeding within the previous year - No more than 10 previous cycles of gonadotropins or clomiphene citrate, the last cycle of which should not have been within 2 months of the study - Acceptable pretreatment hormone levels in blood samples withdrawn within 3 months of the start of treatment, that is: (a) FSH (≥ 3 IU/L and ≤ 12 IU/L) (b) Progesterone< 10 nmole/L) (c) Prolactin (<800 mIIU/L) (d) Testosterone <6.0 nmol.L) (e) DHEAS <20.0 umol/L (f) 17 OHP (<14.4 nmol/L) (g) TSH (0.3-4.1 mIUlL)	**Definition(s) of outcome(s):** Pregnancy and clinical pregnancy: Not defined Live birth: Yes Multiples: NR Complications: Local adverse reactions (redness, pain, itching, swelling, bruising) OHSS (not defined)	1) Pregnancy: Preg + / Preg - rhCG: 26 / 73 — 99 uhCG: 31 / 68 — 99 57 / 141 — 198 Rel risk: 0.84 (Lower 95% CI 0.54; Upper 95 % CI 1.30) 2) Clinical pregnancy: Preg + / Preg - rhCG: 22 / 77 — 99 uhCGl: 29 / 70 — 99 51 / 147 — 198 Rel risk: 0.76 (Lower 95% CI 0.47; Upper 95 % CI 1.22) 3) Live birth rate: LB + / LB - rhCG: 14 / 85 — 99 uhCG: 20 / 79 — 99 34 / 164 — 198 Rel risk: 0.70 (Lower 95% CI 0.38; Upper 95 % CI 1.31) 4) Local side effects: Pts with uhCG reports more side effects than rhCG (0.0002). When looking into the detailed of the local side effect, the only thing that has statistically between the 2 grps is redness (p < 0.0001) 5) There were 3 OHSS reported in rhCG grp (all are moderate OHSS). None were reported in uhCG group.	**Comments:** None **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	or home intercourse.	(h) Free thyroxine 11-24 pmol/L - Two patent tubes - Normal uterine cavity - BMI ≥18 and ≤ 35 - Male partner with SA within acceptable value within the past 6 mo: (a) .10 M/ml (b) 25% with linear progression and normal morphology according to the local laboratory (c) No significant infection within the last 6 mo **Exclusion criteria:** - Clinically significant condition - Positive HIV serology - Positive Hep B surface antigen serology, unless vaccinated - Abnormal gynecological bleeding of unknown origin - History of severe OHSS - Active substance abuse		6) Pts in rhCG grp had overall higher luteal phase progesterone when compared to uhCG	
Karlstrom,	**Geographical location:**	**Age:**	**Definition(s) of**	1) GnRHa+hMG vs. hMG: pregnancy rate:	**Comments:**

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Bergh, and Lundkvist, 2000 **#8810**	Uppsala, Sweden **Study dates:** NR **Size of population:** 161 **Number of cycles analyzed:** 161 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** 1) study the usage of GnRH agonist during hMG treatment VS. hMG alone in IUI cycle 2) Study the efficacy of one vs. two insemination per cycle GnRH agonist used: Busereline 300 ug intranasal q 4-6 hr., start on the fist day of the menstrual period. hMG started with E2 less than 100 pmol/L	Mean (SD): NR GnRHa + hMG:31.9 (0.4) hMG 32.4 (0.4) one IUI:32.1 (0.4) two IUI: 32.4 (0.4) Median: NR Range: NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 88 Endometriosis: 39 Male factor: 21 Tubal factor: 0 PCOS: 0 Other (specify): Cervical factor 24 **Inclusion criteria:** -h/o failed 1 cycle of CC or hMG combined with IUI or home intercourse -non-tubal infertility -normal ovulatory function **Exclusion criteria:** -cycle length >35 days	**outcome(s):** Pregnancy: u/s showed gestational sac Live birth: Yes Multiples: Yes Complications: Miscarriage	<table><tr><th></th><th>Out +</th><th>Out -</th><th>Total</th></tr><tr><td>GNRha+ hMG</td><td>10</td><td>71</td><td>81</td></tr><tr><td>Hmg</td><td>7</td><td>63</td><td>80</td></tr><tr><td>Total</td><td>17</td><td>134</td><td>151</td></tr></table><table><tr><th></th><th>Value</th><th>Lower 95% CI</th><th>Upper 95% CI</th></tr><tr><td>**Rel risk**</td><td>1.23</td><td>0.50</td><td>3.07</td></tr></table>2) 2 vs. one IUI, pregnancy rate:<table><tr><th></th><th>Out +</th><th>Out -</th><th>Total</th></tr><tr><td>2 IUI</td><td>6</td><td>59</td><td>65</td></tr><tr><td>one IUI</td><td>10</td><td>77</td><td>87</td></tr><tr><td>Total</td><td>16</td><td>136</td><td>152</td></tr></table><table><tr><th></th><th>Value</th><th>Lower 95% CI</th><th>Upper 95% CI</th></tr><tr><td>**Rel risk**</td><td>0.80</td><td>0.31</td><td>2.10</td></tr></table>3) GnRHa+hMG vs. hMG: live birth rate:<table><tr><th></th><th>Out +</th><th>Out -</th><th>Total</th></tr><tr><td>GNRha+ hMG</td><td>8</td><td>73</td><td>81</td></tr><tr><td>hMG</td><td>7</td><td>63</td><td>80</td></tr><tr><td>Total</td><td>15</td><td>136</td><td>151</td></tr></table><table><tr><th></th><th>Value</th><th>Lower 95% CI</th><th>Upper 95% CI</th></tr><tr><td>**Rel risk**</td><td>0.99</td><td>0.38</td><td>2.59</td></tr></table>4) No difference in multiple gestation on miscarriage rate	2x2 factorial design **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +
Kocak,	**Geographical location:**	**Age:**	**Definition(s) of**	1) Pregnancy:	**Comments:**

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Caliskin, Simsir, et al., 2002 **#58300**	Ankara, Turkey **Study dates:** NR **Size of population (no. of patients):** 56 **Number of cycles analyzed:** 112 **Number of cycles per patient:** 2 **Study type:** RCT? **Interventions:** 1 cycle of metformin or placebo, followed by 2nd cycle of metformin or placebo + 100 mg CC days 3-7	Mean (SD): Metformin: 26.2 ± 3.7 Placebo: 27.1 ± 4.5 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** PCOS: 56 (100%) **Inclusion criteria:** - Clomiphene resistance: failure to have an ovarian response for three consecutive cycles on transvaginal ultrasonographic examination with concomitant failure of E2 levels to increase after treatment with CC, 150 mg daily for 5 days - Oligomenorrhea (< 6 menstrual periods in the preceding year) with hirsutism, hyperandrogenemia, or presence of multiple subcapsular follicles by vaginal - Ultrasound during the first 3 days of spontaneous menstrual bleeding **Exclusion criteria:** - Abnormal endocrine profile, pelvic anatomy - Diabetes - Use of OCPs or anti-diabetics within preceding 2 months	**outcome(s):** Pregnancy: "confirmed by ultrasound" Live birth: NR Multiples: NR Complications: NR	 Preg + / Preg - / Total Metformin: 4 / 24 / 28 Placebo: 0 / 28 / 28 Total: 4 / 52 / 56 Rel risk: Value 9.00; Lower 95% CI 0.51; Upper 95% CI 159.70	Unclear whether true RCT; + allocation concealment, but based on admission numbers, not true randomization **Quality assessment:** Randomization method: - Blinding: - Dropout rate < 20%: - Adequacy of randomization concealment: +
Leader and Monofol-	**Geographical location:** Ontario, Canada	**Age:** Mean (SD):	**Definition(s) of outcome(s):**	1) Pregnancy (intention-to-treat):	**Comments:** - Patients not blinded as they

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
licular Ovulation Induction Study Group, 2006 **#53480**	**Study dates:** June 2000-Jan 2002 **Size of population (no. of patients):** 161 **Number of cycles analyzed:** 1 cycle per patient but only 118 completed the trial **Number of cycles per patient:** As above **Study type:** RCT **Interventions:** Population: Anovulatory or oligo-ovulatory women Compare two low-dose rFSH step-up protocols Both start with 50 IU for 7 days. At weekly intervals, daily dose increased by 25 IU for one group vs. 50 IU for the other if no follicle at least 12 mm. Treatment continued until 1 follicle ≥ 18 mm, then hCG 10,000 IU SC or IM.	25 IU: 29.5 ± 4.0 50 IU: 29.9 ± 4.4 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Other (specify): 158 (100%) Anovulatory or oligo-ovulatory women **Inclusion criteria:** - WHO group II infertility; anovulatory or oligo-ovulatory - Infertile > 1 year - No ovulation or conception during at least 3 preceding CC cycles - No CC or gonadotropins within 30 days prior to study treatment - Age 18-39 - BMI 18-33 kg/m^2 - Normal uterine cavity by hysteroscopy, HSG or sonohyst within 3 years - Normal testosterone - Normal semen analysis **Exclusion criteria:** - Pregnant or lactating - Prior hospitalization for OHSS - Untreated hyperprolactinemia - Tumors of ovary, breast, uterus, pituitary or hypothalamus - GYN condition incompatible with pregnancy (severe fibroids or sexual organ malformation) - Undiagnosed vaginal	Pregnancy: + hCG and US Live birth: NR Multiples: Yes Complications: OHSS (definition NR)	2) Multiple gestations (intention-to-treat): 3) Ovarian hyper-response (intention-to-treat):	injected themselves - Drop-out 27% (43/161) - No information about allocation concealment **Quality assessment:** Randomization method: + Blinding: - (patients not blinded and no additional information about blinding of others) Dropout rate < 20%: - (27%) Adequacy of randomization concealment: - (not discussed)

	Preg +	Preg -	
50 IU	10	68	78
25 IU	16	67	83
	26	135	161

		Lower 95% CI	Upper 95 % CI
Rel risk	0.67	0.32	1.38

	Multi +	Multi -	
50 IU	0	78	78
25 IU	2	81	83
	2.49	159	161

		Lower 95% CI	Upper 95 % CI
Rel risk	0.26	0.01	5.80

	OHSS +	OHSS -	
50 IU	16	62	78
25 IU	4	79	83
	20	141	161

		Lower 95% CI	Upper 95 % CI
Rel risk	4.26	1.49	12.18

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		bleeding - Primary ovarian failure - Current or recent drug or EtOH abuse			
Legro, Barnhart, Schlaff, et al., 2007 **#42670**	**Geographical location:** 12 centers in the U.S. including Hershey, PA; Durham, NC; Houston, TX; Detroit, MI; Dallas, TX; Denver, CO; Philadelphia, PA; Newark, NJ; Palo Alto, CA; Birmingham, AL; Richmond, VA; and Pittsburgh, PA **Study dates:** NR **Size of population:** 626 infertile women **Number of cycles analyzed:** 2925 **Number of cycles per patient:** 4.67 **Study type:** RCT **Interventions:** Metformin extended-release (Glucophage XR) 1000 mg bid x 6 cycles or 30 wk Clomiphene citrate 50 mg x 5 d beginning on day 3 of menses (dose maintained if adequate ovulation was documented; in non- or poor responders, dose increased to 100 mg/d and then 150 mg/d)	**Age:** Mean (SD): 28.1 (4.0) **Race/ethnicity (n [%]):** White 435 (69.5%) Black 109 (17.4%) Asian 17 (2.7%) Other 72 (11.5%) **Diagnoses (n [%]):** PCOS: 100% **Inclusion criteria:** PCOS based on unexplained hyperandrogenic chronic anovulation, using the 1990 NIH criteria: oligomenorrhea with a history of ≤ 8 spontaneous menses/yr and hyperandrogenemia based on an elevated testosterone level documented within 1 yr; with normal uterine cavity; ≥ 1 pt fallopian tube; partner with ≥ 20 x 10^6/mL sperm concentration **Exclusion criteria:** - Cause of infertility other than PCOS (PRL excess, thyroid disease, and nonclassic congenital adrenal hyperplasia) - Poor health - Any major medical illness	**Definition(s) of outcome(s):** Pregnancy: NR Live birth: Yes Multiples: Yes Complications: Various (see at right) (Also NR in methods paper, Legro RS et al, Fertility and Sterility, 2006)	1) Rate of live birth: Metformin vs. no metformin (clomiphene or combination): Out + / Out - / Total Exp + 15 / 193 / 208 Exp - 103 / 315 / 418 Total 118 / 508 / 626 Value 0.29 (95% CI 0.17 – 0.49) Clomiphene vs. no clomiphene (metformin or combination): Out + / Out - / Total Exp + 47 / 162 / 209 Exp - 71 / 346 / 417 Total 118 / 508 / 626 Value 1.32 (95% CI 0.95 – 1.84) 2) Rate of singleton pregnancy: Metformin vs. no metformin (clomiphene or combination): Out + / Out - / Total Exp + 18 / 190 / 208 Exp - 110 / 308 / 418 Total 128 / 498 / 626 Value 0.33 (95% CI 0.21 – 0.53)	**Comment:** Cumulative pregnancy rate **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: - (dropout rates were 26% C; 35% M; 23% C+M; despite the fact that dropout rates exceeded 20%, they were fairly similarly high between groups) Adequacy of randomization concealment: + Also Q1b

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Metformin + clomiphene Pt w/o recent menses had withdrawal bleed induced with PO medroxyprogesterone acetate			Clomiphene vs. no clomiphene (metformin or combination): Out + / Out - / Total Exp +: 47 / 162 / 209 Exp -: 81 / 336 / 417 Total: 128 / 498 / 626 Rel risk: Value 1.16; Lower 95% CI 0.84; Upper 95% CI 1.59 3) Multiple gestation –observed only with clomiphene-treated pts - twins were observed in 2 of 50 pregnancies with clomiphene alone, and 2 of 65 pregnancies with clomiphene + metformin; triplets were observed in 1/50 pregnancies (clomiphene alone) 4) Complications – no significant differences between treatment grps were reported for pregnancy losses (among pts who conceived), 1st trimester losses, ectopic pregnancy, or 2nd-3rd trimester losses.	
Lewis, Queenan, Hoeger, et al., 2006 **#53610**	**Geographical location:** Brockport, New York **Study dates:** NR **Size of population (no. of patients):** 150 **Number of cycles analyzed:** NR **Number of cycles per patient:** more than 1 cycle per patient but actual number of cycles was NR **Study type:** RCT	**Age:** Mean (SD): LH: 33.5 ± 3.9 hCG: 34.0 ± 3.9 Range: 23-42 **Race/ethnicity (n [%]):** Caucasian 130 (87%) African-American 13 (9%) Hispanic 5 (3%) Asian 2 (1%) **Diagnoses (n [%]):** Unexplained infertility: 97 (65%) Endometriosis: 14 (9%) Male factor: 19 (13%) Tubal factor: 14 (9%)	**Definition(s) of outcome(s):** Pregnancy: rising hCG and then viable when fetal pole with cardiac activity seen on US Live birth: NR Multiples: Yes Complications: NR	1) Viable pregnancy (intention-to-treat): Preg + / Preg - hCG: 19 / 56 / 75 LH surge: 11 / 64 / 75 30 / 120 / 150 Rel risk: 1.73; Lower 95% CI 0.88; Upper 95 % CI 3.38 2) Multiple gestation (intention-to-treat): Multi + / Multi - hCG: 3 / 72 / 75 LH surge: 2 / 73 / 75 5 / 145 / 150	**Comments:** - Patients and physicians unblended after informed consent and baseline US performed - No information about allocation concealment **Quality assessment:** Randomization method: + Blinding: -, as above, patients an physicians unblended after consent and US performed Dropout rate < 20%: -, overall drop out 31/150 = 20.6%. LH surge 11% vs hCG 31%. Adequacy of randomization concealment: -, not stated

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results				Comments/Quality Scoring
		PCOS: NR Cervical factor 6 (4%)				Lower 95% CI	Upper 95 % CI	
	Interventions: Population: Patients treated with CC 100mg on days 5-9 Compare two different methods of intrauterine insemination (IUI) timing LH surge group: IUI day after home test for LH surge was positive hCG group: hCG 10,000 units when at least 1 follicle 2-mm and endometrial thickness > 8mm; IUI 33-40 hours later	**Inclusion criteria:** - Ovulatory patients who had infertility, defined by at least 1 year of unprotected intercourse or 3 failed cycles of donor IUI - Ovulatory if monthly menses and biphasic basal body temperature charts or a h/o of positive ovulation predictor kids or midluteal serum progesterone in ovulatory range - At least 1 normal, patent fallopian tube and a functional ipsilateral ovary **Exclusion criteria:** - Elevated FSH on day 3 - Severe endometriosis - Recurrent pregnancy loss - Previous use of superovulation and IUI - Severe male factor infertility (< 4 million motile sperm)		**Rel risk**	1.50	0.26	8.72	
Malkawi and Qublan, 2002	**Geographical location:** Amman, Jordan **Study dates:** Jan 2001-	**Age:** Mean (SD): NR, but stated no significant	**Definition(s) of outcome(s):** Pregnancy: gestational	1) Pregnancy:	Preg +	Preg -	Total	**Comments:** None **Quality assessment:**
				Metformin	9	7	16	

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#58360	July 2001 **Size of population (no. of patients):** 28 **Number of cycles analyzed:** 168 **Number of cycles per patient:** 6 **Study type:** RCT **Interventions:** Metformin 850 mg BID or placebo, plus CC 50 mg days 5-9; CC dose increased in subsequent cycles if no response	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** PCOS: 28 (100%) **Inclusion criteria:** - Presence of polycystic ovaries on vaginal ultrasound - Examination combined with 3 or more of the following criteria: oligo-menorrhea (< 6 menstrual periods in the preceding year); hirsutism (when Ferriman-Gallwey score >7); hyperandrogenemia (elevated free estosterone, androstenedione, dehydroepiandrosterone sulfate, [DHEAS]), and elevated concentrations [LH]); or LH: follicle stimulating hormone (FSH) ratio>2. Congenital adrenal hyperplasia, Cushing's syndrome, hyperprolactinemia and thyroid disease were excluded by appropriate tests. Clomiphene citrate resistance was defined as failure to ovulate or to conceive after CC treatment up to a daily dose of 150 mg from cycle day 5-9 for at least 3 consecutive cycles. **Exclusion criteria:** Abnormal pelvic anatomy, abnormal semen analysis	sac on ultrasound Live birth: NR Multiples: NR Complications: OHSS	Placebo 2 10 12 Total 11 17 28 Value / Lower 95% CI / Upper 95% CI **Rel risk** 3.38 / 0.89 / 12.85 2) OHSS: OHSS + / OHSS - / Total Metformin 0 16 16 Placebo 2 10 12 Total 2 26 28 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.15 / 0.01 / 2.92	Randomization method: - Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: -
Matorras,	**Geographical location:**	**Age:**	**Definition(s) of**	1) Pregnancy rate:	**Comment:**

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Recio, Corco-stegui, et al., 2000 **#7800**	Viscaya, Spain **Study dates:** Sep 1997-Sep 1998 **Size of population:** 91 **Number of cycles analyzed:** 345 **Number of cycles per patient:** 3.79 **Study type:** RCT **Interventions:** Compares rFSH and uFSH in IUI with husband's spermatozoa	Range: 18-40 **Race/ethnicity (n [%]):** NR **Diagnoses (%):** Endometriosis: - rFSH: 28.9 - uFSH: 34.7 Male factor: - rFSH: 57.77 - uFSH: 58.69 Tubal factor: - rFSH: 22.2 - uFSH: 20.0 Other (specify): Ovulation disorder: - rFSH: 11.1 - uFSH: 13.6 **Inclusion criteria:** - At least one normal tube - Failure to obtain pregnancy in six cycles of programmed intercourse, under ovarian stimulation with gonadotropins **Exclusion criteria:** NR	**outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	Preg + / Preg - / Total uFSH 24 / 22 / 46 rFSH 25 / 20 / 45 Total 49 / 42 / 91 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.94 / 0.64 / 1.37 2) Pregnancy rate: rFSH / uFSH Per woman (%) 45 / 46 Per intention-to-treat PR 57.8 (26/45) / 52.2 (24/46) Corrected PR 56.8 (25/44) / 52.2 (24/46) Cumulative PR 69.9 / 61 No statistically significant differences between the 2 grps. 3) Cancellation rate: 14.7% / 14.8% No statistically significant difference between the 2 grps.	Cumulative pregnancy rate **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +
Moll, Bossuyt, Korevaar, et al., 2006	**Geographical location:** Netherlands (20 sites) **Study dates:** June 2001-May 2003	**Age:** Mean (SD): CC + metformin: 27.9 (3.7) CC only: 28.4 (4.7)	**Definition(s) of outcome(s):** Pregnancy: Not defined	1) Ongoing pregnancy per randomized subject: Preg + / Preg - / Total Metformin + CC 44 / 67 / 111	**Comments:** None **Quality assessment:** Randomization method: +

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results				Comments/Quality Scoring
#60030			Live birth: NR	CC only	51	63	114	Blinding: +
	Size of population (no. of patients): 225	**Race/ethnicity (n [%]):** NR	Multiples: NR	Total	95	130	225	Dropout rate < 20%: +
								Adequacy of randomization concealment: +
	Number of cycles analyzed: Up to 6 cycles per patient	**Diagnoses (n [%]):** PCOS: 225 (100%)	Complications: NR		Value	Lower 95% CI	Upper 95% CI	
				Rel risk	0.89	0.65	1.20	
	Number of cycles per patient: > 1.0	**Inclusion criteria:** - Chronic anovulation (menstrual cycle ≥ 35 days, WHO type II, normogonadotropic, normoestrogenic, oligoanovulation or anovulation) - Polycystic ovaries diagnosed by transvaginal ultrasonography - Wanted to conceive						
	Study type: RCT							
	Interventions: Randomized to metformin (1000 mg/day) + clomiphene (dose increased as needed) vs clomiphene + placebo	**Exclusion criteria:** - Other causes of anovulation - Age > 40 years - Liver, kidney, or heart disease or failure - Partner's sperm quality indicated male factor subfertility (total motile count < 10×10^6)						
Ng, Makkar, Yeung, et al., 2003	**Geographical location:** Hong Kong	**Age:** Mean (SD): SIUI: 32.7± 2.4	**Definition(s) of outcome(s):**	1) Ongoing pregnancy :				**Comments:** - DIUI regimen is different which affects blinding - No allocation concealment
	Study dates: NR	DIUI: 32.9 ± 2.7	Pregnancy: + hCG and US to confirm intrauterine pregnancy or products of	- Compare FSP vs SIUI				
#15610		FSP: 32.9 ± 3.1			Preg +	Preg -		
	Size of population (no.			FSP	15	15	30	

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	of patients): 90 **Number of cycles analyzed:** 204 **Number of cycles per patient:** 2.3 cycles/patient **Study type:** RCT **Interventions:** Population: Patients undergoing ovarian stimulation Compare single IUI (SIUI) to double IUI (DIUI) to fallopian tube sperm perfusion (FSP) SIUI: 38 hrs after hCG FSP: 38 hrs after hCG DIUI: 18 and 42 hrs after hCG	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 19 (21%) Endometriosis: 37 (41%) Male factor: 34 (38%) **Inclusion criteria:** - Age < 40 - Infertility > 2 years - Regular ovulatory cycles based on midluteal progesterone nmol/L - Bilateral tubal patency and absence of peritubal adhesions by laparoscopy with chromotubation - Total motile speramatozoa ≥ 10million **Exclusion criteria:** - Previous artificial insemination cycles - Total motile sperm < 10 million	conception on histology for miscarriages; ongoing if beyond 10-12 weeks Live birth: US to confirm number of gestational sacs Multiples: US to confirm number of gestational sacs Complications: NR	SIUI 7 23 30 22 38 60 Lower 95% CI / Upper 95 % CI **Rel risk** 2.14 1.02 4.49 - Compare DIUI vs FSP Preg + / Preg - FSP 15 15 30 DIUI 5 25 30 20 40 60 Lower 95% CI / Upper 95 % CI **Rel risk** 3.00 1.25 7.21 - Compare DIUI vs SIUI Preg + / Preg - DIUI 5 25 30 SIUI 7 23 30 12 48 60 Lower 95% CI / Upper 95 % CI **Rel risk** 0.71 0.25 2.00 2) Multiple gestations: no difference SIUI: 2/30 (6.6%) DIUI: 1/30 (3.3%) FSP: 5/30 (16.6%)	**Quality assessment:** Randomization method: + Blinding: -, DIUI different regimen Dropout rate < 20%: + Adequacy of randomization concealment: -, not discussed
Ng, Wat, and Ho, 2001 **#58450**	**Geographical location:** Hong Kong, China **Study dates:** Jan 1999-Dec 1999	**Age:** Mean (SD): Median: Range:	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR	1) Pregnancy: Out + / Out - / Total Metfor-min 1 9 10 Placebo 2 8 10	**Comments:** None **Quality assessment:** Randomization method: + Blinding: +

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Size of population (no. of patients): 20 **Number of cycles analyzed:** 20 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Metformin 500 mg TID or placebo x 3 cycles, with CC added if no ovulation after 3 cycles	**Race/ethnicity (n [%]):** Asian: 20 (100%) **Diagnoses (n [%]):** PCOS: 20 (100%) **Inclusion criteria:** - Age < 40 - PCOS with no response to 100 mg CC over 3 cycles - Normal tubes, uterus **Exclusion criteria:** -Smoking - Renal impairment - Use of sex steroids past 3 months	Multiples: NR Complications: NR	Total 3 17 20 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.50 0.05 4.67	Dropout rate < 20%: + Adequacy of randomization concealment: +
Ortega-Gonzalez, Luna, Hernandez, et al., 2005 **#10460**	**Geographical location:** Mexico City, Mexico **Study dates:** NR **Size of population (no. of patients):** 52 **Number of cycles analyzed:** NR, but treated for 6 months **Number of cycles per patient:** [please calculate] >1.0 **Study type:** RCT **Interventions:** Population: Women with PCOS Group 1: pioglitazone (30mg/d)for 24 wks	**Age:** Mean (SD): Pioglitazone: 28.8 ± 0.9 Metformin: 29.0 ± 0.8 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: Endometriosis: Male factor: Tubal factor: PCOS: 52 (100%) Other (specify): **Inclusion criteria:** - PCOS defined as at least 2 of 3 of the following: i) oligomenorrhea or amenorrhea ii) serum androstenedione > 2.9ng/ml iii) serum testosterone > 2.5pg/ml iv) polycystic ovaries by	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: Yes Multiples: NR Complications: Metformin: 4 women discontinued therapy secondary to severe gastrointestinal side effects	1) Pregnancy (intention to treat) Preg + / Preg - / Total Pioglitazone 5 20 25 Metformin 3 24 27 8 44 52 Lower 95% CI / Upper 95 % CI **Rel risk** 1.80 0.48 6.76 2) Live birth (intention to treat) Live birth + / Live birth - / Total Pioglitazone 2 23 25 Metformin 2 25 27 4 48 52 Lower 95% CI / Upper 95 % CI **Rel risk** 1.08 0.16 7.10	**Comments:** - Not blinded because pioglitazone was daily dosing vs metformin was tid - No intention to treat analysis. In fact, one criterion for exclusion was loss to follow-up. - Overall dropout was 9/52 = 17% but dropout for metformin group was 6/27 = 22%. **Quality assessment:** Randomization method: + Blinding: - because daily vs tid dosing for Group 1 vs 2 Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Group 2: metformin (850mg tid) for 24 wks	US **Exclusion criteria:** - Impaired glucose tolerance test or Type II diabetes mellitus - Hyperprolactinemia - Thyroid disorders - Late-onset CAH - Cushing's syndrome - No CC, OCPs, antiandrogens or medications for appetite control during previous 6 months			
Palomba, Falbo, Orio, et al., 2005 **#39590**	**Geographical location:** Naples, Italy **Study dates:** May 2002-June 2003 **Size of population:** 70 **Number of cycles analyzed:** 172 **Number of cycles per patient:** 2.45 **Study type:** RCT **Interventions:** Randomized controlled trial evaluating metformin pretreatment and co-administration in non-obese insulin-resistant women with PCOS who undergoing COH plus timed intercourse or IUI. Each pt received Metformin or placebo for 12 prior to start COH	**Age:** Mean (SD): Metformin 26.2 (2.7) Control 26.9 (2.8) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** PCOS: 100% **Inclusion criteria:** -PCOS diagnosed using NIH criteria -Failed CC treatment **Exclusion criteria:** - Age < 20 or > 34 - BMI < 18 or > 30 - Medical conditions (neoplastic, metabolic exclude glucose intolerance, hepatic, cardiovascular, hypothyroidism, CAH, Cushing's syndrome, abuse of alcohol, current - Use of OCP, glucocorticoids,	**Definition(s) of outcome(s):** Pregnancy: US showed evidence of intrauterine gestational sac Live birth: Percentage of women with baby alive/women who achieve a pregnancy Multiples: Yes Abortion: Percentage of early pregnancy losses (within the first 12 wk of gestation)/total pregnancies Complications: OHSS	1) Pregnancy rate: Preg + / Preg - / Total Metform: 18 / 17 / 35 Placebo: 14 / 21 / 35 32 / 38 / 70 Rel risk: 1.29 (Lower 95% CI 0.77; Upper 95 % CI 2.16) 2) Abortion rate: Abort + / Abort - / Total Met: 1 / 17 / 18 Placebo: 2 / 12 / 14 Total: 3 / 29 / 32 Rel risk: Value 0.39 (Lower 95% CI 0.04; Upper 95% CI 3.87) 3) Live birth rate: LB + / LB - / Total Met: 17 / 18 / 35 Placebo: 12 / 23 / 35 29 / 41 / 70	**Comment:** - Underpowered for primary outcome of multiple pregnancy rate - Cumulative pregnancy rate **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

cycle using low dose gonadotropins.

antiandrogens, antidiabetic, anti-obesity and other hormone drugs
- Organic pelvic diseases
  Previous pelvic surgery,
- Suspected peritoneal factor infertility,
- Tubal infertility
- Male factor infertility
- Intended to start a diet or a specific program of physical activity

		Lower 95% CI	Upper 95% CI
Rel risk	1.42	0.80	2.51

4) OHHS:

	OHSS +	OHSS -	Total
Met	0	85	85
Placebo	1	86	87
Total	1.5	171	172.5

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.51	0.02	14.97

5) Multiple pregnancy rate:

	Multi preg +	Multi preg -	Total
Met	2	16	18
Placebo	5	9	14
Total	7	25	32

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.31	0.07	1.37

Palomba, Orio, Balbo, et al., 2005

#60060

Geographical location: Catanzaro, Italy

Study dates: Apr 2003-Sep 2003

Size of population (no.

Age:
Mean (SD):
Metformin: 26.4 (2.9)
Clomiphene: 25.9 (2.7)

Race/ethnicity (n [%]):
NR

Definition(s) of outcome(s):

Pregnancy: Gestational sac on ultrasound

Live birth: Yes

1) Pregnancy per randomized subject:

	Preg +	Preg -	Total
Metformin	31	19	50
CC	16	34	50
Total	47	53	100

Comments:
None

Quality assessment:
Randomization method: +
Blinding: +
Dropout rate < 20%: +

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	of patients): 100 **Number of cycles analyzed:** Up to 6 per patient **Number of cycles per patient:** > 1.0 **Study type:** RCT **Interventions:** Metformin 850 mg/day + placebo for 5 days, or clomiphene 150 mg/day for 5 days + placebo	**Diagnoses (n [%]):** PCOS: 100% **Inclusion criteria:** PCOS by WHO criteria **Exclusion criteria:** - Age < 20 or > 34 - BMI > 30 kg/m^2 - Neoplastic, metabolic (including glucose intolerance), hepatic, and cardiovascular disorders or other concurrent medical illnesses - Hypothyroidism, hyperprolactinemia, Cushing's syndrome, or nonclassical congenital adrenal hyperplasia - Current or previous (within the last 6 months) use of oral contraceptives, glucocorticoids, antiandrogens, ovulation induction agents, antidiabetic and antiobesity drugs, or other hormonal drugs - No uterine bleeding after progesterone challenge test - Organic pelvic diseases - Previous pelvic surgery - Suspected peritoneal factor infertility - Tubal or male factor infertility - Planning a diet	Multiples: NR Complications: NR	Lower Upper Value 95% CI 95% CI **Rel risk** 1.94 1.22 3.06 2) Live birth per randomized subject: Preg + Preg - Total Metformin **26** **24** 50 CC **9** **41** 50 Total 35 65 100 Lower Upper Value 95% CI 95% CI **Rel risk** 2.89 1.51 5.53	Adequacy of randomization concealment: +
Palomba, Orio, Falbo, et al., 2005	**Geographical location:** Naples, Italy **Study dates:** NR (article	**Age:** Mean (SD): Metformin: 27.2 (2.2) Ovarian drilling: 25.4 (2.4)	**Definition(s) of outcome(s):** Pregnancy: Appropriate	1) Pregnancy: Out + Out - Total Metform **6** **2** 8	**Comments:** None **Quality assessment:**

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#39110	did state that the investigators followed pts for 6 mo) **Size of population:** 28 **Number of cycles analyzed:** 110 **Number of cycles per patient:** 3.9 **Study type:** RCT **Interventions:** Pts with CC-resistant PCOS were previously randomized to Metformin + diagnostic laparoscopy vs. Laparoscopic ovarian drilling+placebe. Pts who had not ovulated after 6 mo of the treatments were then enrolled in this study. Everyone received Clomid 150 mg x 5 d from D3-7 each month. Ovulation, pregnancy, abortion rate, and live-birth rates were evaluated in each grp	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 0 Endometriosis: 0 Male factor: 0 Tubal factor: 0 PCOS: 0 Other (specify): 0 **Inclusion criteria:** - Anovulation after 6 mo of - Metformin or ovarian drilling **Exclusion criteria:** NR	increase of hCG and +gestational sac on US Live birth: Percentage of women with baby alive/women who achieve a pregnancy Multiples: NR Complications: Abortion rate; percentage of miscarriage during the first 12 wk of gestation/total pregnancy	Ovarian drilling: 12 / 8 / 20 Total: 18 / 10 / 28 Value 1.25; Lower 95% CI 0.73; Upper 95% CI 2.14 **Rel risk** 2) Live birth rate: Out + / Out - / Total Metform: 4 / 4 / 8 Ovarian drilling: 7 / 13 / 20 Total: 11 / 17 / 28 Value 1.43; Lower 95% CI 0.57; Upper 95% CI 3.57 **Rel risk** 3) Abortion rate: Out + / Out - / Total Metform: 2 / 4 / 6 Ovarian drilling: 5 / 7 / 12 Total: 7 / 11 / 18 Value 0.80; Lower 95% CI 0.21; Upper 95% CI 2.98 **Rel risk** 4) No difference in ovulation rate between 2 groups	Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +
Palomba, Orio, Nardo, et al., 2004 **#12340**	**Geographical location:** Catanzaro, Italy **Study dates:** Oct 2001-Dec 2002 **Size of population (no. of patients):** 120	**Age:** Mean (SD): LOD + metformin: 26.8 ± 2.2 LOD: 27.5 ± 2.4 **Race/ethnicity (n [%]):** NR	**Definition(s) of outcome(s):** Pregnancy: rising β-hcg and intrauterine gestational sac on US Live birth: Baby alive	1) Pregnancy (intention-to-treat): Preg + / Preg - LOD + metformin: 39 / 21 / 60 LOD + placebo: 31 / 29 / 60 70 / 50 / 120	**Comments:** - No intention-to-treat analysis - Metformin and multivitamin may have different appearance **Quality assessment:** Randomization method: + Blinding: +

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Number of cycles analyzed: 441 **Number of cycles per patient:** 120/441 = 0.27 **Study type:** RCT **Interventions:** Population: overweight CC-resistant women with PCOS Comparison of laparoscopic ovarian diathermy (LOD) + metformin vs LOD only Group A: Diagnostic laparoscopy f/b 6 months metformin cloridrate (850 mg bid) Group B: Laparoscopic ovarian diathermy f/b 6 months of multivitamins	**Diagnoses (n [%]):** PCOS: 120 (100%) But PCOS with glucose intolerance was excluded **Inclusion criteria:** - PCOS defined by NIH criteria - CC resistance defined as failure to ovulate during ≥ 3 consecutive cycles using CC 150 mg qd from d3-7. - Overweight defined as BMI 25-30 kg/m^2 **Exclusion criteria:** - Age < 22 or > 34 - PCOS with glucose intolerance - Hypothyroidism - Hyperprolactinemia - Cushing's syndrome - Nonclassical CAH - Use of the following within the last 6 mos: OCPs, Glucocorticoids, Antiandrogens, Ovulation induction agents, Antidiabetic or Antiobesity medications, Other hormonal drugs - Neoplastic, metabolic, hepatic, cardiovascular disorders or other concurrent medical illness (i.e. diabetes, renal disease or malabsorptive disorders). - Diet or physical activity program - Organic pelvic disease, previous pelvic surgery, suspected peritoneal factor infertility and tubal or male factor infertility	Multiples: NR Complications: Drug-related adverse event = diarrhea, flatulence and nausea; abortion rate	 2) Live birth (intention-to-treat): Live birth+ / Live birth- / LOD + metformin: 32 / 28 / 60 LOD + placebo: 20 / 40 / 60 52 / 68 / 120 Rel risk: 1.26 (Lower 95% CI 0.93, Upper 95 % CI 1.71) Rel risk: 1.60 (Lower 95% CI 1.04, Upper 95 % CI 2.46) 3) Abortion rate (no. abortions / no. pregnancies): LOD + metformin: 15.4% LOD + placebo: 29.0% 4) Drug-related adverse events: LOD + metformin: 22.2% LOD + placebo: 5.5%	Dropout rate < 20%: + (9%) Adequacy of randomization concealment: +

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		- Smoking or drinking alcoholic beverages			
Perez-Medina, Bajo-Arenas, Salazar, et al., 2005 **#41940**	**Geographical location:** Madrid, Spain **Study dates:** Jan 2000 – Feb 2004 **Size of population (no. of patients):** 215 **Number of cycles analyzed:** NR but multiple cycles per patient **Number of cycles per patient:** unable to calculate because total number of cycles NR **Study type:** RCT **Interventions:** Population: Infertile women with endometrial polyps diagnosed on US undergoing IUI Compare hysteroscopic polypectomy with scissors and forceps to diagnostic hysteroscopy and polyp biopsy (no additional details on how biopsy was performed)	**Age:** Mean (SD): Polypectomy 30.8 ± 4.1 Biopsy: 30.9 ± 4.4 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** - Some cases have multiple factors Unexplained infertility: 105 (49%) Endometriosis: 23(11%) Male factor: 46 (21%) Tubal factor: 0 PCOS: Other (specify): Ovulatory 71 (33%) Cervical 24 (11%) - No difference in mean size (16mm) of polyps between groups **Inclusion criteria:** - Infertility > 24 months - US diagnosis of endometrial polyp - Candidate for IUI **Exclusion criteria:** - Age > 39 - Anovulation - Azoospermia - Uncorrected tubal disease - Previous unsuccessful use of rFSH	**Definition(s) of outcome(s):** Pregnancy: + hCG followed by TVUS 2 weeks later Live birth: NR Multiples: NR Complications: NR	1) Pregnancy (intention to treat): Preg + / Preg - Polypectomy: 64 / 43 / 107 Biopsy: 29 / 79 / 108 93 / 122 / 215 Rel risk: 2.23 (Lower 95% CI 1.57; Upper 95 % CI 3.15)	Comments: - No intention to treat analysis - No information about blinding **Quality assessment:** Randomization method: + Blinding: -, not discussed Dropout rate < 20%: +, 5% (11/215) Adequacy of randomization concealment: +

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Revelli, Poso, Gennarelli, et al., 2006 **#55220**	**Geographical location:** Torino, Italy **Study dates:** NR **Size of population (no. of patients):** 260 **Number of cycles analyzed:** 260 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** Low-dose step up regimen Randomized to highly purified urinary FSH vs. recombinant FSH Ovulation triggered with hCG, timed intercourse Ovulation only triggered if 1 follicle	**Age:** Mean (SD): 32.7 (4.3) Range: 28-38 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 184 (70.8%) PCOS: 76 (29.2%) This table only includes data for PCOS patients, all clomiphene-resistant **Inclusion criteria:** - > 1 year infertility - Good general health - Normal tubes/uterus - Normal semen analysis **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Gestational sac at 7 weeks Live birth: Yes Multiples: NR Complications: NR	1) Live birth: Preg + / Preg - / HP- uFSH: 4 / 35 / 39 rFSH: 7 / 30 / 35 11 / 65 / 74 Rel risk: 0.51 (Lower 95% CI 0.16, Upper 95% CI 1.63) 2) Lower number of vials of rFSH used; lower overall costs in cost minimization analysis	**Comments:** - This table only includes data for PCOS patients, all clomiphene-resistant - Subgroup analysis of combined study of both unexplained infertility and PCOS; overall RR for uFSH vs. rFSH 0.76 (95% CI 0.39, 1.51) **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +
Rizk, Bedaiwy, and Al-Inany, 2005 **#10620**	**Geographical location:** Cairo, Egypt **Study dates:** Mar 2002-Nov 2003 **Size of population (no. of patients):** 150 **Number of cycles analyzed:** 150	**Age:** Mean (SD): Group 1: 28.9 ± 4.7 Group 2: 28.4 ± 5.7 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** PCOS: 150 (100%)	**Definition(s) of outcome(s):** Pregnancy: Viable pregnancy at least 12 weeks after hCG administration Live birth: NR Multiples: Yes	1) Pregnancy: Preg + / Preg - / NAC NAC: 14 / 61 / 75 placebo: 0 / 75 / 75 14.49 / 136 / 150 Rel risk: 28.76 (Lower 95% CI 1.70, Upper 95% CI 487.61)	**Comments:** With sugar as the placebo, questionable blinding if there is a different taste between NAC and sugar **Quality assessment:** Randomization method: + Blinding: + (physicians blinded but patients may not be because placebo [sugar] may have a

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Number of cycles per patient: 1 **Study type:** RCT **Interventions:** Population: CC-resistant PCOS women Compare N-acetyl-cysteine (NAC) vs. placebo Group 1: NAC 1.2 g/d with CC 100 mg/d days 3-7 Group 2: placebo (sugar) with CC 100 mg/d days 3-7	**Inclusion criteria:** - PCOS definition: bilaterally normal or enlarged ovaries with at least 7-10 peripheral cysts - CC resistance defined as lack of ovulation after CC 100 mg for 5 days in 3 consecutive cycles - Ages 18-29 - 1 patent fallopian tube by HSG or laparoscopy - Normal semen analysis **Exclusion criteria:** - Hyperprolactinemia - Clinical evidence of hypercorticism - Thyroid dysfunction - Hormonal medication except for progesterone 2 months prior	Complications: OHSS	2) Multiple gestation: Multi + / Multi - NAC: 5 / 70 (75) placebo: 0 / 75 (75) 5.49 / 145 (150) Rel risk: 10.27 (Lower 95% CI 0.56, Upper 95% CI 189.78) 3) No cases of OHSS	different taste than NAC) Dropout rate < 20%: + Adequacy of randomization concealment: +
Roudebush, Toledo, Kort, et al., 2004 **#12880**	**Geographical location:** Atlanta, Georgia **Study dates:** Jan 2001 – Dec 2002 **Size of population (no. of patients):** 165 **Number of cycles**	**Age:** Mean (SD): Normal study arm: 1. Control 36.2 ± 4.2 2. PAF: 35.9 ± 4.9 Male factor arm: 1. Control: 35.8 ±4.5 2. PAF: 34.1 ± 4.4 **Race/ethnicity (n [%]):**	**Definition(s) of outcome(s):** Pregnancy: + hCG and fetal heartbeat on US Live birth: NR Multiples: Yes	1) Pregnancy: - Overall (both CC and gonadotropin stimulation), PAF vs control Preg + / Preg - PAF: 28 / 36 (64) Control: 22 / 59 (81) 50 / 95 (145)	**Comments:** - No intention to treat analysis - Cycle stimulation was done with either CC or gonadotropins and outcome could be affected by stimulation method and not necessarily PAF. Thus results presented as overall, CC stimulation only and gonadotropin only.

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	analyzed: 346 **Number of cycles per patient:** 2.1 **Study type:** RCT **Interventions:** Population: Patients with infertility underoing IUI. Cycle stimulation with CC or gonadotropins. If CC, 50-150mg CC for 5 days. IUI based on LH surge or US timed hCG administration. If gonadotropins, stimulations started on day 3 with 75-225 IU daily. IUI 12-18 hrs and then 36-38 hrs after hCG. Compare use of platelet activating factor (PAF) vs no PAF in control groups PAF treatment at the time of semen washing right before IUI For analysis, groups also divided by normal vs male factor study arm; also CC vs gonadotropin	NR **Diagnoses (n [%]):** Unexplained infertility: 8 (5.5%) Endometriosis: 12 (8.3%) Male factor: 84 (57.9%) Tubal factor: 2 (1.4%) PCOS: Other (specify): Anovulatory: 35 (24.1%) **Inclusion criteria:** - Healthy, infertile patients with nontubal factor infertility - Infertility diagnoses included anovulatory, endometriosis, idiopathic, tubal (single or fibroids), cervical factor and male factor - Male factor if failed to meet 1 or more reference standards - Basal FSH < 15mIU/mL - Normal uterine cavity - No contraindication to pregnancy **Exclusion criteria:** NR	Complications: NR	Lower 95% CI / Upper 95 % CI **Rel risk** 1.61 (1.02 – 2.53) - Only CC simulation, PAF vs control Preg + / Preg - / Total PAF: 8 / 14 / 22 Control: 11 / 20 / 31 19 / 34 / 53 Lower 95% CI / Upper 95 % CI **Rel risk** 1.02 (0.49 – 2.12) - Only gonadotropin simulation, PAF vs control Preg + / Preg - / Total PAF: 17 / 23 / 40 Control: 11 / 39 / 50 28 / 62 / 90 Lower 95% CI / Upper 95 % CI **Rel risk** 1.93 (1.02 – 3.64) 3) Multiple gestations: no difference - Control 7/22 (31.8%) - PAF 7/28 (25.0%)	- No allocation concealment **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: - , not discussed
Rouzi and Ardawi, 2006 **#55350**	**Geographical location:** Jeddah, Saudi Arabia **Study dates:** April 2002 – April 2004 **Size of population (no. of patients):** 25 **Number of cycles analyzed:** >1	**Age:** Rosiglitazone: Mean: 28.6±3.7 Range: 23-36 Metformin: Mean: 27.4±4.3 Range: 23-35 **Race/ethnicity (n [%]):** NR	**Definition(s) of outcome(s):** Pregnancy: positive serum hcg followed by US Live birth: Yes Multiples: NR Complications: Drug-	1) Pregnancy: Preg + / Preg - / Total Rosiglitazone: 6 / 6 / 12 Metformin: 5 / 8 / 13 11 / 14 / 25 Lower 95% CI / Upper 95 % CI	**Comments:** - Rosiglitazone dose was bid versus metformin dose was tid which affects blinding - GI side effects associated with metformin may also affect blinding **Quality assessment:** Randomization method:+ Blinding: -, dosing was different between the two groups

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	- more than 1 cycle per patient but total number of cycles analyzed was not recorded **Number of cycles per patient:** Unable to calculate given cycle numbers NR **Study type:** RCT **Interventions:** Population: CC-resistant PCOS. Rosiglitazone and CC: - Rosiglitazone 4mg bid - CC 100mg x 5 days starting on day 3 Metformin and CC: - Metformin 500mg tid - CC 100mg x 5 days starting on day 3	**Diagnoses (n [%]):** PCOS: 25 (100%) **Inclusion criteria:** - Ages 20-40 - Primary infertility & PCOS - PCOS diagnosis based on the following: 1. Oligomenorrhea (interval ≥ 35 days) or amenorrhea (absence of menses x 6 mos) 2. Hirsutism 3. Enlarged ovaries with multiple follicles (> 10 measuring 2-8mm) arranged peripherally on TVUS 4. Elevated serum testosterone - Failure to ovulate with CC 150mg/d for 5 days starting on day 3 - Patent tubs by HSG - No other infertility factor **Exclusion criteria:** - Adrenal dysfunction - Cushing's syndrome - CAH - Androgen producing tumor - Hyperprolactinemia - Thyroid dysfunction - Diabetes - Taking medication that could influence carbohydrate metabolism - Hypertension - Prior use of gonadotropins - H/o ovarian drilling - Prior IVG - Abnormal renal or liver function tests	related adverse events: diarrhea, nausea and abdominal bloating	**Rel risk** 1.30 (0.53, 3.17) 2) Live birth: Rosiglitazone: Live birth + 5, Live birth - 7, 12 Metformin: Live birth + 4, Live birth - 9, 13 9, 16, 25 **Rel risk** 1.35 (Lower 95% CI 0.47, Upper 95 % CI 3.89) 3) Multiple gestation: Rosiglitazone: AE + 1, AE - 11, 12 Metformin: AE + 0, AE - 13, 13 1.49, 24, 25 **Rel risk** 2.29 (Lower 95% CI 0.08, Upper 95 % CI 63.98) 4) Drug-related adverse events: Rosiglitzaone 0% vs Metformin 31% (4/13)	Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Sakhel, Khedr, Schwark, et al., 2007 **#72400**	**Geographical location:** Saginaw, Rochester Hills, and Flint, MI **Study dates:** Apr 2003-Mar 2004 **Size of population (no. of patients):** 284 **Number of cycles analyzed:** 284 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** GnRH antagonist with rFSH COH, randomized to (a) urinary hCG, or (b) recombinant hCG , followed by IUI	**Age:** Mean (SD): 32.3 (4.5) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Age 22-44 years - Non-tubal infertility **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Gestational sac on ultrasound 4 weeks after transfer Live birth: Yes Multiples: Yes Complications: NR	1) Clinical pregnancy: Preg + / Preg - / Total rhCG: 38 / 102 / 140 uhCG: 41 / 103 / 144 Total: 79 / 205 / 284 Rel risk: Value 0.95; Lower 95% CI 0.66; Upper 95% CI 1.39 2) Ongoing/live birth: Out + / Out - / Total rhCG: 31 / 109 / 140 uhCG: 36 / 108 / 144 Total: 67 / 217 / 284 Rel risk: Value 0.89; Lower 95% CI 0.58; Upper 95% CI 1.35 3) Multiple rates similar	**Comments:** No IRB oversight **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -
Sharma, Kriplani, and Agarwal, 2006 **#58520**	**Geographical location:** New Delhi, India **Study dates:** NR **Size of population (no. of patients):** 20 **Number of cycles analyzed:** NR, but 6-month followup	**Age:** Mean: Unipolar: 27.3 Bipolar: 25.5 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** PCOS: 20 (100%) **Inclusion criteria:**	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Pregnancy: Preg + / Preg - / Total Bipolar: 7 / 3 / 10 Unipolar: 5 / 5 / 10 Total: 12 / 8 / 20 Rel risk: Value 1.40; Lower 95% CI 0.67; Upper 95% CI 2.94	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Number of cycles per patient: > 1.0 **Study type:** RCT **Interventions:** Unipolar or bipolar electrocautery of ovaries; no treatment for 3 months, CC if no ovulation	- PCOS - "Resistant" after 6 cycles of CC - Patent tubes - Normal semen analysis **Exclusion criteria:** NR			
Tartagni, Cicinelli, De Pergola, et al., 2007 **#56100**	**Geographical location:** Bari, Italy **Study dates:** NR **Size of population (no. of patients):** 50 **Number of cycles analyzed:** NR; ?50 **Number of cycles per patient:** ?1.0 **Study type:** RCT **Interventions:** All scheduled for stimulation with rFSH; randomized to (a) 0.05 mg ethinyl estradiol TID for 2 weeks prior to stimulation vs. (b) placebo	**Age:** Mean (SD): E2 32.9 (3.9); placebo 32.5 (4.8) Range: 24-39 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Other: All with premature ovarian failure **Inclusion criteria:** - Aamenorrhea ≥ 6 months - Serum FSH ≥ 40 mIU/mL - E2 ≤ 25 pg/mL at two separate measurements in the preceding 2 months - Normal prolactin, chromosome - No history of radiotherapy or chemotherapy - Normal laboratory and physical - No oral contraceptives or other hormone therapy within last 6 mo **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Pregnancy: Preg + / Preg - Estradiol **12** / **13** — 25 Placebo **0.5** / **25** — 25 12.5 / 38 — 50 Rel risk 24.00 (Lower 95% CI 1.50; Upper 95 % CI 384.61)	**Comments:** None **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: -
Timmer-	**Geographical location:**	**Age:**	**Definition(s) of**	1) Pregnancy, intention to treat:	**Comments:**

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
man-van Kessel, Cikot, Dargel-Donkers, et al., 2000 **#58590**	Eindhoven, the Netherlands **Study dates:** NR **Size of population (no. of patients):** 30 **Number of cycles analyzed:** 65 **Number of cycles per patient:** 2.1 **Study type:** RCT **Interventions:** PCOS, randomized to clomiphene days 3-7 vs. 3 weeks GnRH agonist suppression, followed by daily pulsatile IV GnRH	Median (range): GnRH: 26 (22-31) CC: 27 (21-31) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** PCOS: 30 (100%) **Inclusion criteria:** - Age < 40 - Primary infertility - Oligo/amenorrhea - LH > 6.5 and/or LH/FSH > 1.5 - Normal semen analysis **Exclusion criteria:** NR	**outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	<table><tr><th></th><th>Preg +</th><th>Preg -</th><th>Total</th></tr><tr><td>GnRH</td><td>4</td><td>12</td><td>16</td></tr><tr><td>CC</td><td>4</td><td>10</td><td>14</td></tr><tr><td>Total</td><td>8</td><td>22</td><td>30</td></tr></table> <table><tr><th></th><th>Value</th><th>Lower 95% CI</th><th>Upper 95% CI</th></tr><tr><td>Rel risk</td><td>0.88</td><td>0.27</td><td>2.86</td></tr></table> 2 CC patients did not receive treatment – per protocol RR 0.75	None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -
Tsai, Lin, Chen, et al., 2004 **#12800**	**Geographical location:** Tainan, Taiwan **Study dates:** January 2002-Oct 2002 **Size of population (no. of patients):** 121 **Number of cycles analyzed:** 121 **Number of cycles per**	**Age:** Mean (SD): Percoll 30.7 (3.8); PureSperm 31.6 (4.0) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** PCOS: 121 (100%) **Inclusion criteria:** Clomiphene resistance	**Definition(s) of outcome(s):** Pregnancy: Gestational sac with + FHR Live birth: NR Multiples: NR Complications: NR	1) Clinical pregnancy: <table><tr><th></th><th>Preg +</th><th>Preg -</th><th></th></tr><tr><td>PureSperm</td><td>7</td><td>49</td><td>56</td></tr><tr><td>Percoll</td><td>9</td><td>56</td><td>65</td></tr><tr><td></td><td>16</td><td>105</td><td>121</td></tr></table> <table><tr><th></th><th></th><th>Lower 95% CI</th><th>Upper 95 % CI</th></tr><tr><td>**Rel risk**</td><td>0.90</td><td>0.36</td><td>2.27</td></tr></table>	**Comments:** Randomization method not described **Quality assessment:** Randomization method: - Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	patient: 1.0 **Study type:** RCT **Interventions:** Superovulation with clomiphene + rFSH, hCG trigger Fresh semen prepared by gradient separation, randomized to one of 2 media: Percoll vs PureSperm	**Exclusion criteria:** NR			
Unfer, Casini, Constabile, et al., 2004 **#11280**	**Geographical location:** Rome, Italy **Study dates:** NR **Size of population:** Total: 134 CC + phytoestrogen (PE): 65 CC alone: 69 **Number of cycles analyzed:** 134 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Compares pregnancy rate in pts receiving CC + PE + IUI versus CC + IUI Also looks at endometrial thickness, uterine pulsatility index and SAB rate.	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** PCOS: 134 (100%) **Inclusion criteria:** - Age 25-35 - 2 yr primary infertility - Normal levels of TSH, prolactin and testosterone **Exclusion criteria:** - Previous infertility treatment - Male factor or tubal factor infertility - BMI > 25	**Definition(s) of outcome(s):** Pregnancy: Biochemical Ongoing > 20 wk EGA Live birth: NR Multiples: NR Complications: SAB	1) Ongoing pregnancy rate: |	Ongoing preg +	Ongoing preg -	Total
---	---	---	---
CC + PE	13	52	65
CC	3	66	69
Total	16	118	134 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Rel risk	4.60	1.37	15.41 | 2) Biochemical pregnancy rate: |	Biochem preg +	Biochem preg -	Total
---	---	---	---
CC + PE	3	62	65
CC	4	65	69
Total	7	127	134 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Rel risk	0.80	0.19	3.42 | 3) SAB rate: |	SAB +	SAB -	Total
---	---	---	---
CC + PE	2	63	65
CC	6	63	69		**Comment:** - Low numbers - Does not give age or weight of subjects in each grp, but does exclude BMI > 25 **Quality assessment:** Randomization method: - Blinding: + Dropout rate < 20%: - (NR) Adequacy of randomization concealment: +

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Total 8 126 134 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.35 / 0.07 / 1.69 4) No significant difference between groups in endometrial thickness or pulsatility index	
Vander-molen, Ratts, Evans, et al., 2001 **#58610**	**Geographical location:** Richmond and Charlottesville, VA; St. Louis, MO **Study dates:** NR **Size of population (no. of patients):** 27 **Number of cycles analyzed:** Up to 6 **Number of cycles per patient:** > 1 **Study type:** RCT **Interventions:** Metformin 500 mg TID vs. placebo x 7 weeks, followed by CC up to 6 cycles	**Age:** Mean (SD): Metformin 29 (± 1.2) Placebo 30 (± 1.0) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - 18–35 years of age - Wanted to become pregnant - Anovulatory in response to a 5-day course of CC, 150 mg/day (anovulation documented by failure to menstruate by cycle day 35 and a negative result on a pregnancy test or by a midluteal P level , 4 ng/mL) -Oligoovulation (< 6 menstrual periods annually) - Hyperandrogenism (by laboratory assay of androstenedione, free T, or total T or by clinical evidence of hirsutism) - Normal levels of TSH, PRL, and 17-hydroxyprogesterone (< 200 ng/dL)	**Definition(s) of outcome(s):** Pregnancy: Gestational sac on ultrasound Live birth: NR Multiples: NR Complications: NR	1) Pregnancy: Preg + / Preg - / Total Metformin + CC: **6** / **6** / 12 Placebo + CC: **1** / **14** / 15 Total: 7 / 20 / 27 Value / Lower 95% CI / Upper 95% CI **Rel risk** 7.50 / 1.04 / 54.12	**Comments:** None **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		Normal renal function (serum creatinine concentration < 1.4 mg/dL) - Normal results on liver function tests **Exclusion criteria:** - Nonpatent tubes - Abnormal semen analysis - Diabetes			
Wu, Wang, Cheng, et al., 2007 **#56740**	**Geographical location:** Changhua, Taiwan **Study dates:** June – November 2004 **Size of population (no. of patients):** 33 **Number of cycles analyzed:** NR **Number of cycles per patient:** NR **Study type:** RCT **Interventions:** Anastrozole (AI) 1mg qd versus clomiphene citrate (CC) 100mg qd from cycle day 3-7	**Age:** Mean (SD): AI group: 33.2 ± 3.3 CC group: 32.7 ± 4.2 Range: 25-41 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: NR Endometriosis: NR Male factor: NR Tubal factor: NR PCOS: NR Other (specify): Primary infertility: 22 (67%) Secondary infertility: 11 (33%) **Inclusion criteria:** - Primary or secondary infertility < 1 year **Exclusion criteria:** - Bilateral tubal obstruction diagnosed by either HSG or laparoscopy - Severe male-factor infertility - Pre-existing ovarian cysts at US on cycle day 3	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Pregnancy (intention to treat): Preg + / Preg - Anastrozole: 2 / 12 — 14 CC: 0 / 19 — 19 2.49 — 31 — 33 Rel risk: 5.68 (Lower 95% CI 0.27, Upper 95 % CI 119.72)	**Comments:** - Randomization not well-described; "Randomization by computer" - No allocation concealment - No discussion regarding blinding **Quality assessment:** Randomization method: -, no details Blinding: -, not discussed Dropout rate < 20%: + Adequacy of randomization concealment: -, not discussed

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		- Day 3 blood estradiol ≥ 100pmol/l or FSH ≥ 10 IU/l - + βhCG - Before enrollment: 1. No use of OCP or CC within 1 month 2. No use of gonadotropin-releasing hormone agonist within 3 months 3. No use of depot medroxyprogesterone within 6 months			
Yarali, Yildiz, Demirol, et al., 2002 **#2820**	**Geographical location:** Ankara, Turkey **Study dates:** NR **Size of population:** Recruited 32, 16 to metformin, 16 to placebo. 6 removed from metformin due to ovulation, 1 removed from placebo due to ovulation. Final number receiving FSH: Metformin: 10 Placebo: 15 **Number of cycles analyzed:** 25 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Compares pregnancy rates and biochemical changes in women treated with metformin or	**Age:** Mean (SD): Metformin: 29.7 ± 5.6 Placebo: 28.4 ± 5.1 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** PCOS: 32 (100%) **Inclusion criteria:** - PCOS by clinical, biochemical and ultrasound criteria - Refractory to previous CC for 6 mo - Normal HSG or laparoscopy within 6 mo - Normal glucose tolerance by OGTT **Exclusion criteria:** - Previous gonadotropin treatment - Diabetes, CAH, Cushings, hyperprolactinemia, hypothyroid, or any other infertility factor - Previous genital surgery	**Definition(s) of outcome(s):** Pregnancy: + hcg Live birth: NR Multiples: NR Complications: NR	1) Total pregnancy rate in the 2 grps including observation time and 1 cycle rFSH: Preg + / Preg - / Total Met: 5 / 11 / 16 Placebo: 1 / 14 / 15 Total: 6 / 25 / 31 Rel risk: Value 4.69, Lower 95% CI 0.62, Upper 95% CI 35.63 2) Pregnancy rate in the observation period prior to rFSH: Preg + / Preg - / Total Met: 2 / 4 / 6 Placebo: 0 / 1 / 1 Total: 2 / 5 / 7 Rel risk: Value 1.43, Lower 95% CI 0.11, Upper 95% CI 19.20 3) Pregnancy rate with 1 cycle rFSH: Preg + / Preg - / Total Met: 3 / 7 / 10 Placebo: 1 / 14 / 15 Total: 4 / 21 / 25	**Comment:** Low numbers **Quality assessment:** Randomization method: - (NR) Blinding: - (NR) Dropout rate < 20%: + Adequacy of randomization concealment: - (NR)

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	placebo for 6 wk followed by rFSH.				

	Value	Lower 95% CI	Upper 95% CI
Rel risk	4.50	0.54	37.38

4) Spontaneous ovulation rate prior to rFSH:

	Ovul +	Ovul -	Total
Met	6	10	16
Placebo	1	15	16
Total	7	25	32

	Value	Lower 95% CI	Upper 95% CI
Rel risk	6.00	0.81	44.35

5) Ovulation rate with rFSH:

	Ovul +	Ovul -	Total
Met	9	1	10
Placebo	11	4	15
Total	20	5	25

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.23	0.85	1.77

Yilmaz, Kelekci, Savan, et al., 2006

#56800

Geographical location: Ankara, Turkey

Study dates: May 2002-Apr 2004

Size of population (no. of patients): 133

Number of cycles analyzed: 1 cycle per patient and 8 lost to f/u, so 125 cycles

Number of cycles per patient: 1

Age:
Mean (SD):
Group A: 26.7 ± 3.2
Group B: 26.2 ± 3.4

Race/ethnicity (n [%]): NR

Diagnoses (n [%]):
PCOS: 100%

Inclusion criteria:
- WHO class II ovarian dysfunction
- Normal prolactin
- Normal gonadotropins
- Primary infertility with

Definition(s) of outcome(s):

Clinical pregnancy: + hCG and +FH on US at 7 weeks

Live birth: NR

Multiples: Yes

Complications: NR

1) Pregnancy:

	Preg +	Preg -	
CC+hCG	20	40	60
CC only	18	47	65
	38	87	125

		Lower 95% CI	Upper 95 % CI
Rel risk	1.20	0.71	2.05

2) Twin gestation:

	Twin +	Twin -	
CC+hCG	2	58	60
CC only	1	64	65
	3	122	125

Comments:
- Unable to calculate intention-to-treat. 8 lost to follow-up but no information regarding the distribution of these patients.
- Only group B received hCG IM, affecting blinding
- Ultrasonographers were blinded

Quality assessment:
Randomization method: +
Blinding: - (only group B received hCG)
Dropout rate < 20%: + (6% [8/133])
Adequacy of randomization concealment: +

Evidence Table 1. Question 2 – Ovulation Induction without Assisted Conception (continued)

Study	Study Design	Patients	Clinical Presentation	Results				Comments/Quality Scoring
	Study type: RCT **Interventions:** Population: Women with WHO class II anovulation Group A: 50 mg CC on days 5-9 Group B: 50 mg CC plus hCG (Pregnyl 10,000 IU IM) when 1 or more follicles reached 18 mm	oligo/amenorrhea - Ages 20-40 - Primary infertility 2 years - No h/o ovulation induction treatment and thyroid disease - Normal HSG - Normal semen analysis **Exclusion criteria:** See above				Lower 95% CI	Upper 95 % CI	
				Rel risk	2.17	0.20	23.29	

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Aboulghar, Mansour, Serour, et al., 2004 **#12050**	**Geographical location:** Cairo, Egypt **Study dates:** 2002 **Size of population:** 151 **Number of cycles analyzed:** 151 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** Investigated whether increasing the dose of gonadotrophins on the date of GnRH antagonist administer would increase the pregnancy rate. The study grp received an extra dose of 75 units per day from the date of GnRH antagonist (Cetrorllixix) administer until TVOR. Randomization at time of study intervention with sealed envelopes	**Age:** Mean (SD): Control: 31.9 (6.1) Study group: 32.8 (5.1) **Race/ethnicity (n [%]):** Egyptian 100% **Diagnoses (n [%]):** NR **Inclusion criteria:** - Female - Age < 40 - Infertility **Exclusion criteria:** - History of poor responses - General contraindication for pregnancy - Clinically significant systemic disease - More than 3 failed cycles	**Definition(s) of outcome(s):** Clinical pregnancy: Presence of fetal cardiac activity 3 wks after embryo transfer Live birth: NR Multiples: Yes Complications: NR	1) Clinical pregnancy rate: Note: numbers imputed from reported rates Preg + / Preg - / Standard + 75: 29 / 50 / 79 Standard: 23 / 49 / 72 52 / 99 / 151 Rel risk: 1.15 (Lower 95% CI 0.74, Upper 95 % CI 1.79) 2) Multiple pregnancy rate: Note: numbers imputed from reported rates Multiples / Single-ton / Standard + 75: 11 / 18 / 29 Standard: 9 / 14 / 23 20 / 32 / 52 Rel risk: 0.97 (Lower 95% CI 0.49, Upper 95 % CI 1.93)	**Comments:** Unclear if reported analysis was intent-to-treat **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Albano, Felberbaum, Smitz, et al., 2000 **#8590** ***and*** **Ludwig, Felberbaum, Devroey, et al., 2000** **#6990 (OHSS results only)**	**Geographical location:** Brussels, Belgium; Lubeck and Frankfurt, Germany **Study dates:** NR **Size of population:** 273 **Number of cycles analyzed:** 273 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** Compared the use of GnRH agonist (buserelin) and GnRH antagonist (cetrorelix) in ovarian stimulation with HMG	**Age:** Mean (SD): Cetrorelix: 31.9 (3.7) Buserelin: 31.6 (3.8) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Age ≤ 39 - Regular menstrual cycle ranging 24d-35d - Normal ovarian function (detected by FSH ≤ 10 IU/L) - Normal ovarian morphology - Normal uterus - No more than three previous IVF or ICSI **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Clinical Pregnancy: u/s showed gestational sac and fetus with cardiac activity Live birth: NR Multiples: Yes Complications: Miscarriage, ectopic pregnancies, OHSS (using WHO criteria OHSS II: Moderate OHSS III: Severe)	1) Clinical pregnancy rate: Preg + / Preg - / Total Cetrorelix: 42 / 146 / 188 Buserelin: 22 / 66 / 88 64 / 212 / 276 Rel risk: 0.89 (Lower 95% CI 0.57; Upper 95 % CI 1.40) 2) Number of deliveries (patients): Del + / Del - / Total Cetrorelix: 34 / 154 / 188 Buserelin: 19 / 69 / 88 53 / 223 / 276 Rel risk: 0.84 (Lower 95% CI 0.51; Upper 95 % CI 1.38) 3) Outcomes of all pregnancies: Cetrorelix / Buserelin / P-value Clinical preg: 42 / 22 / NS Miscarriage: 7 / 2 Ectopic preg: 1 / 0 No of deliveries: 34 / 19 / NS Singletons: 26 / 17 Twins: 8 / 2 No. children born: 42 / 21 4) OHSS rate: OHSS + / OHSS - / Total Cetrorelix: 2 / 186 / 188 Buserelin: 5 / 80 / 85 Total: 7 / 266 / 273 Rel risk: Value 0.18 (Lower 95% CI 0.04; Upper 95% CI 0.91)	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				5) One pt in Buserelin group had severe OHSS 6) 3 (1.6%) pts in Cetrorelix and 6 (5.9%) in Buserelin grp did not get hCG trigger due to threatened OHSS. Significantly higher E2 on the date of hCG trigger was noted in Buserelin grp.	
Alleyassin, Khademi, Aghahos-seini, Safdarian, et al., 2006 **#50130**	**Geographical location:** Tehran, Iran **Study dates:** January 2004 to January 2005 **Size of population (no. of patients):** 160 **Number of cycles analyzed:** 160 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** Bilateral transfer of injected oocytes into fallopian tubes Unilateral transfer of injected oocytes into fallopian tube	**Age:** Mean (SD): 30 (4.3) Range: 16 - 39 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Male factor: 160 (100%) **Inclusion criteria:** Female < 40 years old; primary infertility; male factor infertility (the candidate couples for percutaneous epididymal sperm aspiration or testicular sperm extraction were not allowed to enter to the study); basal levels of FSH ≤ 10 IU/L and basal levels of E2 < 80 pg/mL at the initiation of the ovarian stimulation, and > 4 metaphase 2 (MII) normal-shaped oocytes obtained by ovum puncture. **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Pregnancy was defined by the detection of a positive serum β-hCG (≥ 200 mIU/mL) 18–19 days after MIFT. Clinical intrauterine pregnancy was confirmed by detection of a gestational sac in the uterus 2–3 weeks later by transvaginal ultrasound. Live birth: NR Multiples: Yes Complications: Pregnancy with unknown location: either a discriminatory zone ≥ 1,500 mIU/mL of serum hCG level or a suboptimally rising serum hCG over 48 hours	1) Pregnancy: Preg + / Preg - / Total Bilateral transfer: **32** / **48** / 80 Unilateral transfer: **40** / **40** / 80 Total: 72 / 88 / 160 **Rel risk**: Value 0.80, Lower 95% CI 0.57, Upper 95% CI 1.13 2) Clinical intrauterine pregnancy Same as pregnancy. 3) Multiples: Bilateral, 4 multiples in 32 pregnancies; unilateral, 7 multiples in 40 pregnancies. 4) One pregnancy of unknown location in each group	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Anderson, Devroey, and Arce, 2006 **#50170**	**Geographical location**: 37 centers in Belgium, France, Finland, Czech Republic, Poland, Denmark, Sweden, Israel, Slovenia Spain **Study dates:** Feb 2004-Dec 2004 **Size of population (no. of patients):** 731 **Number of cycles analyzed:** 731 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** **-** Long protocol GnRH agonist, randomized to either highly purified human menopausal gonadotropin (HP-hmG) or recombinant FSH (rFSH), both with standard dose of 225 IU s.c for 1st 5 days, adjusted afterwards to maximum of 450 IU daily dose and 20 days maximum duration of treatment - 1-2 embryos transferred	**Age:** Mean (SD): HP-hMG: 30.8 (3.2), rFSH 30.9 (3.3) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 317 (43.4%) Male factor:86 (11.6%) Tubal factor: 256 (35.0%) Other (specify): (includes endometriosis) 72 (9.8%) **Inclusion criteria:** (i) women with good physical and mental health, aged 21–37 years with regular menstrual cycles of 21–35 days and presumed to be ovulatory; (ii) tubal or unexplained infertility, including endometriosis stage I/II and mild male factor, eligible for IVF treatment; (iii) infertility for ≥1 year before randomization, except for proven bilateral tubal infertility; (iv) BMI of 18–29 kg/m2 at the time of randomization; (v) hysterosalpingography, hysteroscopy or transvaginal ultrasound documenting a uterus consistent with expected normal function (e.g. no clinically interfering uterine fibroids) within 3 years before randomization; (vi) transvaginal ultrasound documenting	**Definition(s) of outcome(s):** Pregnancy: Ongoing pregnancy: at least 1 viable fetus 10-11 weeks after embryo transfer Live birth: At least one live born neonate Multiples: Yes Complications: Moderate/severe OHSS	1) Ongoing pregnancy (intention-to-treat): Preg + / Preg - hMG: 97 / 266 — 363 rFSH: 82 / 286 — 368 179 / 552 — 731 Rel risk: 1.20 (Lower 95% CI 0.93; Upper 95 % CI 1.55) 2) Live birth: Preg + / Preg - hMG: 96 / 267 — 363 rFSH: 82 / 286 — 368 178 / 553 — 731 Rel risk: 1.19 (Lower 95% CI 0.92; Upper 95 % CI 1.53) 3) Moderate/severe OHSS: Preg + / Preg - hMG: 8 / 355 — 363 rFSH: 8 / 360 — 368 16 / 715 — 731 Rel risk: 1.01 (Lower 95% CI 0.38; Upper 95 % CI 2.67) 4) Singleton delivery rates similar (21% HP-hMG, 17% rFSH):	**Comments:** None **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		the presence of both ovaries, without evidence of abnormality (e.g. no endometrioma) and normal adnexa (e.g. no hydrosalpinx) within 6 months before randomization; (vii) early follicular phase serum FSH levels of 1–12 IU/l; (viii) willing to accept transfer of one or two embryos; (ix) male partner with sperm quality compatible with fertilization via IVF procedure (results obtained within 12 months before randomization) or previous clinical pregnancy; (x) confirmation of down-regulation before randomization, defined as either menstrual bleeding and transvaginal ultrasound showing a shedded endometrium with a thickness of < 5 mm and no ovarian cysts or serum estradiol (E2) levels of < 50 pg/ml (local laboratory) and transvaginal ultrasound showing no ovarian cysts; (xi) signed informed consent form before screening. **Exclusion criteria:** (i) polycystic ovarian syndrome, endometriosis stage III/IV or severe male factor requiring ICSI; (ii)			

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		more than three previously consecutive unsuccessful IVF cycles; (iii) previous poor response in an IVF cycle, defined as >20 days of gonadotrophin stimulation, cancellation due to limited follicular response or less than four follicles of ≥15 mm diameter; (iv) previous IVF cycle with unsuccessful fertilization, defined as fertilization of ≤30% of the retrieved oocytes; (v) history of recurrent miscarriage; (vi) severe ovarian hyperstimulation syndrome (OHSS) in a previous IVF cycle; (vii) any significant systemic disease, endocrine or metabolic abnormalities (pituitary, thyroid, adrenal, pancreas, liver or kidney); (viii) use of any non-registered investigational drug during the 3 months before screening or previous participation in the study and any concomitant medication that would interfere with the evaluation of the study medication (non-study hormonal therapy, except thyroid medication, anti-psychotics, anxiolytics, hypnotics, sedatives and need for continuous use of prostaglandin inhibitors); (ix) treatment with clomiphene citrate, metformin, gonadotrophins or GnRH analogues within			

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		1 month before randomization; (x) pregnancy, lactation or contraindication to pregnancy; (xi) current or past (3 months) smoking habit of >10 cigarettes per day; (xii) current or past (last 12 months) abuse of alcohol or drugs; (xiii) a history of chemotherapy (except for gestational conditions) or radiotherapy; (xiv) undiagnosed vaginal bleeding; (xv) tumours of the ovary, breast, adrenal gland, pituitary or hypothalamus and malformation of sexual organs incompatible with pregnancy and (xvi) hypersensitivity to any trial product.			

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Ata, Isiklar, Balaban, et al., 2007 **#50290**	**Geographical location:** Istanbul, Turkey **Study dates:** April-May 2006 **Size of population (no. of patients):** 260 **Number of cycles analyzed:** 260 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Randomized to Labotect (stiff outer sheath, no need for stylet) or Wallace embryo transfer catheter	**Age:** Mean (SD): Wallace: 33.2 (3.7) Labotect: 33.5 (5.2) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 29 (11%) Endometriosis: 18 (7%) Male factor: 142 (55%) Tubal factor: 33 (13%) Other: "Ovarian factor" 38 (15%) **Inclusion criteria:** 1st ART cycle **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Visualization of a gestational sac by ultrasound at 4-6 weeks after embryo transfer Ongoing: Viable pregnancy after 20 weeks Live birth: NR Multiples: NR Complications: NR	1) Clinical pregnancy (ITT): Preg+ / Preg - / Total Labotect: **45** / **85** / 130 Wallace: **58** / **72** / 130 Total: 103 / 157 / 260 Rel risk: Value 0.78; Lower 95% CI 0.57; Upper 95% CI 1.05 2) Ongoing pregnancy (ITT): Preg + / Preg - / Total Labotect: **36** / **94** / 130 Wallace: **50** / **80** / 130 Total: 86 / 174 / 260 Rel risk: Value 0.72; Lower 95% CI 0.51; Upper 95% CI 1.02	**Comments:** None **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: Adequacy of randomization concealment: +
Avrech, Orvieto, Pinkas, et al., 2004 **#11000**	**Geographical location:** Tel Aviv, Israel **Study dates:** NR **Size of population (no. of patients):** 219 **Number of cycles analyzed:** 219 (11 cycles cancelled, not analyzed in paper) **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:**	**Age:** Mean (SD): 42.0 (2.1) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - 40-48 years - normal menstrual cycles - normal hormonal profile - normal ultrasound **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Clinical pregnancy: Not defined Live birth: Yes Multiples: NR Complications: NR	1) Clinical pregnancy, both GnRH agonist groups vs control (data not provided for individual groups): Preg + / Preg - / Total GnRH a: 11 / 135 / 146 Control: 8 / 65 / 73 19 / 200 / 219 Rel risk: 0.69; Lower 95% CI 0.29; Upper 95 % CI 1.63 2) Live birth, both GnRH agonist groups vs control: Preg + / Preg - / Total GnRH a: 7 / 139 / 146 Control: 3 / 70 / 73	**Comments:** None **Quality assessment:** Randomization method: - (NR) Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: - (NR)

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	- Short protocol COH - All had hMG - Randomized to (a) hMG only (b) hMG plus buserelin 200 micrograms 3x/day (c) hMG plus buserelin 300 micrograms/day from cycle day 2 until injection of hCG			10 209 219 Lower 95% CI / Upper 95 % CI **Rel risk** 1.17 0.31 4.38	
Babayof, Margalioth, Huleihel, et al., 2006 **#50320**	**Geographical location:** Beer-Sheva, Israel **Study dates:** Apr 2004 to Jan 2005 **Size of population (no. of patients):** 28 **Number of cycles analyzed:** 28 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** rHCG: Recombinant HCG (Ovitrelle 250 µg, Serono) GnRH agonist: (Decapeptyl 0.2 mg, Ferring Ltd, Herzliya, Israel).	**Age:** Mean (SEM): 30 (1.5) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** PCOS: 28 [100%] **Inclusion criteria:** PCOS (diagnosed as 10 or more follicles with a diameter of < 9 mm, Adams *et al*., 1985) undergoing IVF treatment **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: Yes Multiples: Yes Complications: Moderate to severe OHSS, not defined	1) Pregnancy: Preg + / Preg - / Total GnRH 5 10 15 rHCG 4 9 13 Total 9 19 28 Value / Lower 95% CI / Upper 95% CI **Rel risk** 1.08 0.37 3.21 2) Live birth: Live birth + / Live birth - / Total GnRH 1 14 15 rHCG 2 11 13 Total 3 25 28 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.43 0.04 4.25 One live birth of twins in the GnRH group. 3) OHSS: OHSS + / OHSS - / Total GnRH 0 15 15 rHCG 4 9 13 Total 4 24 28	**Comments:** None **Quality assessment:** Randomization method: - Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.10 / 0.01 / 1.65	
Bahceci, Ulug, Ben-Shlomo, et al., 2005 **#10400**	**Geographical location:** Istanbul, Turkey and Haifa, Israel **Study dates:** Nov 2001-Nov 2002 **Size of population (no. of patients):** 148 **Number of cycles analyzed:** 129 cycles secondary to drop out **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** Population: Women with PCOS undergoing controlled ovarian hyperstimulation (COH) for assisted reproductive technology (ART) Compare gonadrotropin-releasing hormone antagonists (Cetrorelix) versus agonists (leuprolide acetate (LA)) All patients OCP for 21 days LA 0.5 mg daily on starting on day 14. Gonadotropins on day 3.	**Age:** Mean (SD): LA: 29.4 ± 4.3 Cetrorelix: 30.1 ± 4.8 Median: LA: 29 Cetrorelix: 30 Range: LA: 21-38 Cetrorelix: 21-38 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** PCOS: 148 (100%) Other: 61(41%) of partners had oligasthenoteratospermia as coexisting infertility factor **Inclusion criteria:** - PCOS defined as primary infertility, oligomenorrhea, clinical hyperandrogenism (hirsutism Feriman-Galwey score > 7), reversed FSH/LH ratio, polycystic appearance of ovaries on US - No previous ART **Exclusion criteria:** - Male factor due to nonobstructive	**Definition(s) of outcome(s):** Pregnancy: Gestational sac and fetal heart activity on US Live birth: NR Multiples: Yes Complications: OHSS (not defined), miscarriage (not defined)	1) Pregnancy (intention-to-treat): Preg + / Preg - / Total Cetrorelix: 34 / 39 / 73 LA: 41 / 34 / 75 75 / 73 / 148 Value / Lower 95% CI / Upper 95 % CI **Rel risk** 0.85 / 0.62 / 1.17 2) Multiple gestation (intention-to-treat): Multi + / Multi - / Total Cetrorelix: 20 / 53 / 73 LA: 22 / 53 / 75 42 / 106 / 148 Value / Lower 95% CI / Upper 95 % CI **Rel risk** 0.93 / 0.56 / 1.56 3) No difference in OHSS (7.1% LA vs. 5.0% Cetrorelix) 4) No difference in miscarriage (12.1% LA vs. 5.8% Cetrorelix)	**Comments:** - No intention-to-treat analysis - LA vs. Cetrorelix regimens were different affecting blinding - No information regarding allocation concealment **Quality assessment:** Randomization method: + Blinding: - (different regimens for 2 groups) Dropout rate < 20%: + (12.8% [19/148] total; 6.6% [5/75] from LA group and 19.1% [14/73] from Cetrorelix group) Adequacy of randomization concealment: - (not discussed)

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	LA dropped to 0.25 mg when gonadotropins started. Gonadotropin dose fixed for first 4 days and then adjusted according to response. When at least 2 follicles reached 18 mm, hCG given. Cetrorelix: gonadotropins on day 3 as above. Cetrorelix 0.25 mg/d s.c. given when leading follicle 14 mm. Cetrorelix continued daily until hCG injection.	azoospermia - Hyperprolactinemia - Thyroid abnormalities			
Bahceci, Ulug, Ciray, et al., 2006 **#50340**	**Geographical location:** Istanbul, Turkey **Study dates:** June 2004-Dec 2004 **Size of population (no. of patients):** 272 **Number of cycles analyzed:** 272 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Randomized to (a) embryo assessment and transfer day 2, or (b) embryo assessment and transfer day 3	**Age:** Mean (SD): Day 2:36.5 (0.8); Day 3: 36.6 (0.8) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 53 (19.6%) Male factor: 66 (24.3%) Other (specify): "Female": 131 (48.3%) Combined: 31 (11.4%) **Inclusion criteria:** - Undergoing COH, with ≤5 oocytes - Fresh ejaculated semen **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Gestational sac with increasing hCG Ongoing pregnancy: Viable beyond 12 weeks Live birth: NR Multiples: Yes Complications: NR	1) Clinical pregnancy: Preg + / Preg - / Lower 95% CI / Upper 95 % CI Day 2: **51** / **86** / 137 Day 3: **29** / **106** / 135 80 / 192 / 272 **Rel risk**: 1.73 (1.17, 2.56) 2) Ongoing pregnancy: Preg + / Preg - / Lower 95% CI / Upper 95 % CI Day 2: **38** / **99** / 137 Day 3: **22** / **113** / 135 60 / 212 / 272 **Rel risk**: 1.70 (1.07, 2.72) 3) Multiple pregnancy: Preg + / Preg - Day 2: **9** / **42** / 51	**Comments:** Powered to detect 15% absolute difference in pregnancy rates **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Day 3	

	7	**22**	29
	16	64	80

		Lower 95% CI	Upper 95 % CI
Rel risk	0.73	0.30	1.76

Balaban, Yakin, Isiklar, et al., 2007

#50410

Geographical location: Istanbul, Turkey

Study dates: Mar 2004-May 2005

Size of population (no. of patients): 396 frozen cycles, thawing in 197 (not explict whether # couples = # cycles)

Number of cycles analyzed: 197

Number of cycles per patient: 1.0?

Study type: RCT

Interventions: Cryopreservation of embryos using either (a) conventional or (b) high-security straws (HSS) (designed to prevent cross-contamination), followed by thawing and embryo transfer

Age: Mean (SD): Conventional 32.1 (3.3); HSS: 31.8 (3.6)

Race/ethnicity (n [%]): NR

Diagnoses (n [%]): Diagnoses for all frozen cycles (thawed cycles not reported):
Unexplained infertility: 16 (4.0%)
Male factor: 173 (43.7%)
Combined: 107 (27.0%)

Inclusion criteria: NR

Exclusion criteria: Testicular sperm extraction, percutaneous epididymal aspiration

Definition(s) of outcome(s):

Pregnancy: Gestational sac on ultrasound

Live birth: NR

Multiples: Yes (twins)

Complications: NR

1) Clinical pregnancy:

	Preg +	Preg -	
HSS	43	57	100
Control	30	66	96
	73	123	196

		Lower 95% CI	Upper 95 % CI
Rel risk	1.38	0.95	2.00

2) Multiple pregnancies (twins):

	Twins +	Twins -	
HSS	18	83	101
Control	5	91	96
	23	174	197

		Lower 95% CI	Upper 95 % CI
Rel risk	3.42	1.32	8.85

Comments:
Unclear whether # cycles/patient = 1; 92 (HSS) and 96 (conventional) cycles reported as not

Quality assessment:
Randomization method: +
Blinding: -
Dropout rate < 20%: +
Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Balasch, Creus, Fabregues, et al., 2001 **#58030**	**Geographical location:** Barcelona, Spain **Study dates:** NR **Size of population (no. of patients):** 30 **Number of cycles analyzed:** 30 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** GnRH agonist down-regulation, randomized to rFSH alone or rFSH + fixed dose rLH	**Age:** Mean (SD): rFSH alone: 33.6 (0.8) rFSH + rLH: 34.8 (0.8) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Age 29-40 - Regular menses - FSH < 11 **Exclusion criteria:** - > 2 previous ART attempts - PCOS	**Definition(s) of outcome(s):** Pregnancy: NR Live birth: NR Multiples: NR Complications: NR	1) Pregnancy (per randomized subject): Preg + / Preg - / Total rFSH + rLH: 0 / 16 / 16 rFSH: 2 / 12 / 14 Total: 2 / 28 / 30 Rel risk: Value 0.18; Lower 95% CI 0.01; Upper 95% CI 3.39	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: - Adequacy of randomization concealment: +
Barmat, Chantilis, Hurst, et al., 2005 **#10670**	**Geographical location:** Abington, PA; Dallas, TX; Charlotte, NC; New Orleans, LA **Study dates:** NR **Size of population (no. of patients):** 80 **Number of cycles analyzed:** 80 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** Agonist: OC on cycle day 2-4 to day 14-28.	**Age:** Mean (SD): 32.5 (3.5) Range: 28-38 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Couples undergoing IVF with or without ICSI, < 39 years, day-3 FSH <=10, E2 <60 pg/mL, basal antral follicle > 5 with a menstrual cycle range of 26 to 34 days, no more than one previous failed IVF or IVF/ICSI cycle, BMI 19 to 32 kg/m2, no hydorsalpinx by	**Definition(s) of outcome(s):** Pregnancy: Biochemical based on β-hCG measured 14 dys after oocyte retrieval; "ongoing" based on U/S at 6 weeks with sacs with fetal heart motion. Live birth: NR Multiples: NR Complications: NR	1) Delivered pregnancy: Preg + / Preg - / Total Antagonist: 12 / 26 / 38 Agonistt: 17 / 24 / 41 29 / 50 / 79 Rel risk: Value 0.76; Lower 95% CI 0.42; Upper 95 % CI 1.38 Excludes one pregnancy at 37 weeks. 2) Biochemical pregnancy: Preg + / Preg - / Total Antagonist: 14 / 25 / 39 Agonist: 18 / 23 / 41 32 / 48 / 80	**Comments:** None **Quality assessment:** Randomization method: - (NR) Blinding: - (none) Dropout rate < 20%: + Adequacy of randomization concealment: - (open label)

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	About 5 days before completing OCs, leuprolide 0.5 mgm/d started. In 5 days, if adequate pituitary desensitization demonstrated, FSH 300 IU/d SC in the abdominal wall with dose adjusted of 75-150 IU based on patients' response by US and hormonal assay; leuprolide reduced to 0.25 mgm/d. If E2 >pg/mL or a cyst > 20 mm continued leuprolide another week; if E2 still elevated, patient dropped. Antagonist: Same OC regimen; patients with E2 > 60 pg/mL started on FSH. Cancelled if cyst > 20mm. Ganirelix 250 µgm/evening when a follicle obtained of 12-14 mm.	hysterosalpingogram, laparoscopy or ultrasound in previous year, nonobstructive azoospermia **Exclusion criteria:** NR		Lower 95% CI / Upper 95 % CI **Rel risk** 0.82 0.47 1.41 3) Ongoing pregnancy: Ongoing preg + / Ongoing preg - / Total Antagonist 14 25 39 Agonist 18 23 41 32 48 80 Lower 95% CI / Upper 95 % CI **Rel risk** 0.82 0.47 1.41	
Baruffi, Mauri, Petersen, et al., 2000 **#58050**	**Geographical location:** Sao Paolo, Brazil **Study dates:** NR **Size of population (no. of patients):** 103 **Number of cycles analyzed:** 103 **Number of cycles per patient:** 1.0 **Study type:** RCT	**Age:** Mean (SD): Zona thinning: 31.8 (3.6) No thinning: 31.4 (3.6) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Male factor: 100% **Inclusion criteria:** - Age ≤ 37 - Scheduled for ICSI for male factor	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Pregnancy: Preg + / Preg - / Total Zona thinning 17 34 51 No zona thinning 21 31 52 Total 38 65 103 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.83 0.50 1.37	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Interventions: ICSI; randomized to laser zona thinning or no zona thinning	**Exclusion criteria:** NR			
Baruffi, Mauri, Petersen, et al., 2003 **#14340**	**Geographical location:** Sao Paulo, Brazil **Study dates:** NR **Size of population (no. of patients):** 103 **Number of cycles analyzed:** 103 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** 400 mg vaginal progesterone beginning at (a) day of oocyte retrieval vs (b) day of embryo transfer (day 2)	**Age:** Mean (SD): Retrieval 34.2 (4.6); transfer: 34.8 (4.9) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** NR **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Gestational sac with + FHR at 6 weeks Live birth: NR Multiples: NR Complications: NR	1) Clinical pregnancy: Preg + / Preg - / total Day of retrieval: 14 / 37 / 51 Day of transfer: 15 / 37 / 52 29 / 74 / 103 Rel risk: 0.95 (Lower 95% CI 0.51; Upper 95 % CI 1.76)	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -
Baruffi, Mauri, Petersen, et al., 2003 **#15470**	**Geographical location:** Sao Paulo, Brazil **Study dates:** NR **Size of population:** 106 **Number of cycles analyzed:** 106 **Number of cycles per patient:** 1 **Study type:** RCT	**Age:** Mean (SD): Day 2: 33.1 (4.5) Day 3: 32.7 (4.4) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** NR **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Clinical pregnancy: Presence of gestational sac and embryo with a heart beat at 6 wks gestation Live birth: NR Multiples: NR Complications: NR	1) Clinical pregnancy rate: Preg + / Preg - / total Day 2: 23 / 30 / 53 Day 3: 22 / 31 / 53 Total: 45 / 61 / 106 Rel risk: Value 1.05 (Lower 95% CI 0.67; Upper 95% CI 1.63)	**Comments:** None **Quality assessment:** Randomization method: + ("randomization list") Blinding: - Dropout rate < 20%: - Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Interventions: Compared implantation and pregnancy rates between day 2 and day 3 embryo transfer after ICSI				
Battaglia, Regnani, Marsella, et al., 2002 **#2670**	**Geographical location:** Modena, Italy **Study dates:** NR **Size of population (no. of patients):** 37 **Number of cycles analyzed:** 37 (5 cancellations) **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** - IVF cycles - COH with triptorelin, purified FSH - Randomized to 16 g/day L-arginine (nitric oxide stimulant) or placebo	**Age:** Mean (SD): 33.8 (3.1) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Tubal factor: 37 (100%) **Inclusion criteria:** - Tubal infertility - Scheduled for IVF - Bilateral ovaries - Normal ovulation **Exclusion criteria:** - Concurrent illness - BMI>30 - Endometriosis - Regular exercise - Smoking > 10 cigs/day - Hypertension	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Ongoing pregnancy (intention-to-treat): Preg + / Preg - / Lower 95% CI / Upper 95 % CI Study drug: 3 / 15 / 18 Control: 6 / 13 / 19 9 / 28 / 37 **Rel risk** 0.53 (0.15 – 1.80) 2) Ongoing pregnancy (as reported in paper): Preg + / Preg - / Lower 95% CI / Upper 95 % CI L-arginine: 3 / 13 / 16 Placebo: 6 / 10 / 16 9 / 23 / 32 **Rel risk** 0.50 (0.15 – 1.66)	**Comments:** - Study powered on difference in number of follicles >17 mm diameter - Timing of beginning/end of L-arginine not specified - Paper states significant difference in pregnancy rates, but difference not statistically significant in either ITT population or analyzed population (n = 32) **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Beckers, Laven, Eijkemans, et al., 2000 **#58060**	**Geographical location:** Rotterdam, the Netherlands **Study dates:** NR **Size of population (no. of patients):** 60 **Number of cycles analyzed:** 60 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** (a) Long protocol GnRH agonist = hMG + hCG for luteal support; (b) Cessation of GnRH on day 3 of hMG, no luteal support; (c) GnRH until hCG for ovarian maturation , no luteal support	**Age:** Mean: 32-33 in all groups (total for randomized patients not given) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Age < 39 - Scheduled for IVF - Regular menses - No hormonal abnormalities **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: + pregnancy test Live birth: NR Multiples: NR Complications: Hyper-response	1) Pregnancy (all randomized subjects), GnRH + hMG + luteal support vs. early cessation GnRH: Preg + / Preg - / Total Early cessation: **3** / **17** / 20 GnRH + support: **4** / **16** / 20 Total: 7 / 33 / 40 Rel risk: Value 0.75, Lower 95% CI 0.19, Upper 95% CI 2.93 2) Pregnancy (all randomized subjects), GnRH + hMG + luteal support vs. no support: Preg + / Preg - / Total No support: **0** / **20** / 20 GnRH + support: **4** / **16** / 20 Total: 4 / 36 / 40 Rel risk: Value 0.11, Lower 95% CI 0.01, Upper 95% CI 1.94 3) Cancellation for hyper-response: Early cessation vs. standard protocol: 0.71 (0.27, 1.88) No support vs. standard protocol: 1.43 (0.68, 3.00)	**Comments:** Subjects withdrawn for hyper-response not included in reported analysis **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: - Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Bellver, Munoz, Ballesteros, et al., 2003 **#15060**	**Geographical location:** Valencia, Spain **Study dates:** Mar 1999-Feb 2002 **Size of population (no. of patients):** 988 (605 patients and 383 oocyte donors); only patients reported here **Number of cycles analyzed:** 605 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Albumin: 40 g human albumin Control: No albumin	**Age:** Mean (SD): 32 (4.3) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** PCOS: 122 (20%) **Inclusion criteria:** Collection of > 20 oocytes during oocyte retrieval **Exclusion criteria:** None specified	**Definition(s) of outcome(s):** Pregnancy: Pregnancy, biochemical pregnancy, and ongoing pregnancy reported as %, numerator and denominator not defined Live birth: Yes Multiples: NR Complications: OHSS (by Golan et al. 1989 criteria)	1) Pregnancy (derived from reported percentages): Preg + / Preg - / Total Albumin: 138 / 160 / 298 No albumin: 166 / 141 / 307 Total: 304 / 301 / 605 Rel risk: Value 0.86, Lower 95% CI 0.73, Upper 95% CI 1.00 2) OHSS (derived from reported percentages): OHSS + / OHSS- / Total Albumin: 24 / 274 / 298 No albumin: 21 / 286 / 307 Total: 45 / 560 / 605 Rel risk: Value 1.18, Lower 95% CI 0.67, Upper 95% CI 2.07	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -
Ben-Yosef, Amit, Azem, et al., 2004 **#10970**	**Geographical location:** Tel Aviv, Israel **Study dates:** Nov 1999 - Apr 2000 **Size of population:** 349 **Number of cycles analyzed:** 375 **Number of cycles per patient:** 1.07 **Study type:** RCT	**Age:** Mean (SD): P1: 35.2 (6.2) Cook: 35.4 (5.9) **Race/ethnicity (n [%]):** NR **Diagnoses (%):** Unexplained infertility: P1: 25.7 Cook: 20.7 Endometriosis and anovulation: P1: 4.5	**Definition(s) of outcome(s):** Clinical pregnancy: Presence of a gestational sac, CRL, and fetal heart beat at u/s performed at 6-7 wks after ET Live birth: Yes Multiples: Yes Complications: NR	1) Clinical pregnancy rate: Preg + / Preg - / P1: 38 / 144 / 182 Cook: 23 / 144 / 167 61 / 288 / 349 Rel risk: 1.52, Lower 95% CI 0.94, Upper 95 % CI 2.43 2) Live birth: Preg + / Preg - P1: 32 / 150 / 182 Cook: 20 / 147 / 167	**Comments:** - Randomization by "Table", but all patients on a given day received intervention; patients with multiple cycles apparently had same media in each cycle - No a priori sample size estimation **Quality assessment:** Randomization method: - Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Interventions: Compares 2 embryo culture systems: P1 Medium by Irvine scientific and the Cook IVF Medium	Cook: 0 Male factor: P1: 27.9 Cook: 35.5 Tubal factor: P1: 27.9 Cook: 19.5 **Inclusion criteria:** - Age < 45 - D3 FSH < 12 mIU/mL - NI uterine cavity - Presence of at least 2 follicles ≥ 16 mm in diameter on the day of hCG administration **Exclusion criteria:** NR		52 297 349 Lower 95% CI / Upper 95 % CI **Rel risk** 1.47 0.87 2.46 2) Multiples: Preg + / Preg - Study group 16 22 38 Control 6 14 20 22 36 58 Lower 95% CI / Upper 95 % CI **Rel risk** 1.40 0.65 3.02	
Berk-kanoglu, Isikoglu, Seleker, et al., 2006 **#50630**	**Geographical location:** Antalya, Turkey **Study dates:** NR **Size of population (no. of patients):** 240; 180 include in analysis **Number of cycles analyzed:** 181 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** - Embryo transfer on day 2, all under U/S guidance - All had cervical irrigation with IVF culture media	**Age (mean [SD]):** Flushing: 31.3 (0.5) Control: 31.5 (0.5) Unclear what means were for all randomized **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** NR **Exclusion criteria:** Women with "difficult transfer, uterine anomalies, or inadvertent flushing of endometrial cavity during cervical irrigation" were excluded after randomization	**Definition(s) of outcome(s):** Pregnancy: Clinical pregnancy if positive fetal heart rate on ultrasound Ongoing pregnancy: > 12 weeks gestation Live birth: NR Multiples: NR Complications: NR	1) Pregnancy – all randomized: Preg + / Preg - Flushing 33 87 120 No Flushing 56 64 120 89 151 240 Lower 95% CI / Upper 95 % CI **Efficacy** 0.59 0.42 0.83 2) Ongoing pregnancy – all randomized: Preg+ / Preg - Flushing 34 86 120 No Flushing 51 69 120 85 155 240 Lower 95% CI / Upper 95 % CI **Efficacy** 0.67 0.47 0.95 3) Reported rates, based on analyzed patients	**Comments:** - Much larger number of subjects excluded from flushing arm (n=48), compared to no flushing (n=12); discrepancy this large unlikely to be random - By intention to treat, flushing significantly worse than no flushing - Randomization method not specified ("computer-generated") **Quality assessment:** Randomization method: - Blinding: - Dropout rate < 20%: - Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	- Transabdominal U/S used to assess whether any cervical irrigation entered endometrial cavity – subjects excluded if yes - Flushing group: endometrial cavity irrigated with 0.4 ml culture media under ultrasound guidance - Embryo transfer			(n = 73 for flushing, n = 108 for control): Clinical pregnancy: 45.2% flushing, 51.4% control Ongoing pregnancy: 47.9% flushing, 47.2% control	
Bhatta-charya, Hamilton, Shaaban, et al., 2001 **#4750**	**Geographical location:** UK (multicenter study) **Study dates:** NR **Size of population:** 415 **Number of cycles analyzed:** 435 **Number of cycles per patient:** 1.05 **Study type:** RCT **Interventions:** Compares the conventional IVF VS ICSI for the treatment of non-male factor infertility	**Age:** Mean (SD): IVF: 30.9 (4.1) ICSI: 31.6 (3.2) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: IVF: 21 ICSI: 25 Endometriosis: IVF: 9 ICIS: 7 Male factor (mild) IVF: 11 ICSI: 11 Tubal factor: IVF: 47 ICSI: 48 Ovulation dysfunction: IVF: 9 ICSI: 10 **Inclusion criteria:** - Female partner age < 37	**Definition(s) of outcome(s):** Clinical Pregnancy: Presence of fetal heart activity shown by transvaginal u/s Live birth: NR Multiples: Yes Complications: NR	1) Clinical pregnancy rate: (Note: per cycle, not per patient) Preg + / Preg - / Total IVF: 72 / 147 / 219 ICSI: 53 / 151 / 204 125 / 298 / 423 Rel risk: Value 1.27, Lower 95% CI 0.94, Upper 95% CI 1.71 2) Multiple pregnancy rate: Preg + / Preg - / Total IVF: 17 / 55 / 72 ICSI: 16 / 37 / 53 33 / 92 / 125 Rel risk: Value 0.78, Lower 95% CI 0.44, Upper 95% CI 1.40	**Comments:** - 20 couples re-randomized after failure of 1st cycle - Not true "per-patient" rates **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		- Minimal acceptable semen characteristics - density 20 millions/ml - progressive motility 40% - acceptable morphology per local lab (variable between 10%-20%) **Exclusion criteria:** - Fertilization rate in a previous IVF cycle < 20% - Baseline FSH > 12 mIU/L - More than 3 previous IVF cycles - Abnormal semen analysis, require ICSI treatment			
Bjuresten, Hreinsson, Fridstrom, et al., 2003 **#16670**	**Geographical location:** Stockholm, Sweden **Study dates:** NR **Size of population (no. of patients):** 102 **Number of cycles analyzed:** 102 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** - 1 or 2 embryo transfer under ultrasound guidance (no difference in number of embryos, embryo score) - Usually on day 2 (no difference between groups)	**Age (mean [SD]):** Midwife: 32.8 (3.3) Physician: 33.1 (3.8) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** NR **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Clinical pregnancy: + heartbeat Live birth: NR Multiples: NR Complications: NR Other: Anonymous questionnaire rating experience	1) Clinical pregnancy rate: Preg + / Preg - Midwife: 16 / 35 — 51 MD: 15 / 36 — 51 31 / 71 — 102 Rel risk: 1.07 (Lower 95% CI 0.59, Upper 95 % CI 1.92) 2) Proportion of respondents who rated experience “excellent” was similar in both groups (100% midwives, 90% gynecologists), although response rate was higher in midwife group (86% vs. 59%).	**Comments:** - More ICSI cycles in midwife group (57% vs 41%) - Response rate to questionnaire much higher for midwives **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	- Catheters varied, but no difference between groups - Gynecologist called if midwife unable to complete transfer				
Born and Mannaerts, 2000 **#58070**	**Geographical location:** Multiple sites in 10 countries: Belgium, Denmark, France, Germany, Greece, the Netherlands, Norway, Spain, Sweden, UK **Study dates:** NR **Size of population (no. of patients):** 730 (701 in analysis) **Number of cycles analyzed:** 701 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Ganirelix or buserelin for downregulation	**Age:** Mean (SD): Ganirelix: 31.9 (3.6) Buserelin: 31.9 (3.8) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 16% Male factor: 40% Tubal factor: 29% **Inclusion criteria:** - Age 18-39 - BMI 18-29 - Regular menstrual cycle 25-35 days - Scheduled for IVF **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: OHSS	1) Ongoing pregnancy: Preg + / Preg - / Total Ganirelix: 94 / 369 / 463 Buserelin: 61 / 177 / 238 Total: 155 / 546 / 701 Value / Lower 95% CI / Upper 95% CI **Rel risk**: 0.79 / 0.60 / 1.05 2) OHSS: OHSS + / OHSS - / Total Ganirelix: 11 / 452 / 463 Buserelin: 14 / 224 / 238 Total: 25 / 676 / 701 Value / Lower 95% CI / Upper 95% CI **Rel risk**: 0.40 / 0.19 / 0.88	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: - Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Branigan, Estes, Walker, et al., 2006 **#50730**	**Geographical location:** Bellingham, WA **Study dates:** NR **Size of population (no. of patients):** 64 (94 randomized but 31 dropped after randomization and not analyzed.) **Number of cycles analyzed:** NR **Number of cycles per patient:** Cannot be calculated **Study type:** RCT **Interventions:** Group 1: Thorough sonographic oocyte retrieval (SER) Group 2: Routine SER	**Age:** Mean (SD): 30 (4) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** PCOS: 64 (100%) **Inclusion criteria:** Amenorrheic or severely oligomenorrheic, hyperandrogenism either clinical (hirsutism, acne) and/or biochemical (elevated testosterone level, >1.0 ng/mL), unresponsive to clomophene in any dose either with or without adjuvant therapy (oral contraceptives, metformin, dexamethasone), longstanding infertility of > 18 mo and absence of other infertility factors other than anovulation, absence of other androgen excess or ovulation disorders, planning to undergo IVF, did not conceive during the IVF cycle (note that patients who did conceive during IVF cycle were randomized but dropped and not analyzed) **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: serum HCG elevation and 7-week gestational ultrasound scans Live birth: NR Multiples: NR Complications: NR	1) Pregnancy: Preg + / Preg - / Total Thorough SER: 8 / 26 / 34 Routine SER: 0 / 30 / 30 Total: 8 / 56 / 64 Value / Lower 95% CI / Upper 95% CI **Rel risk**: 15.06 / 0.91 / 250.34	**Comments:** None **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: - Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Brook, Khalaf, Coomara-samy, et al., 2006 **#50750**	**Geographical location:** London, UK **Study dates:** Apr 2004-Mar 2005 **Size of population (no. of patients):** 350 **Number of cycles analyzed:** 350 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Treatment arm: 750 mg co-amoxiclav tablets night before embryo transfer (day 2, 3, or 4), 750 mg 2 hours prior to transfer Control: No tablets (no placebo used)	**Age (mean [SD]):** Treatment: 34.7 (4.1) Control: 34.4 (4.4) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 26.3% Endometriosis: 3.4% Male factor: 51.4% Tubal factor: 9.1% PCOS: 1.1% Other (PGD): 6.3% **Inclusion criteria:** Scheduled to undergo transvaginal oocyte retrieval and embryo transfer **Exclusion criteria:** Contraindications to antibiotics; not planning on embryo transfer; required antibiotics based on history of prior infection or high risk	**Definition(s) of outcome(s):** Pregnancy: Gestational sac with positive FHR Live birth: NR Multiples: NR Complications: NR Other: Catheter transfer tips cultured for bacteria, difference in contamination rates	1) Clinical pregnancy: Preg + / Preg - / Co-amoxiclav: 64 / 114 / 178 Control: 61 / 111 / 172 125 / 225 / 350 Rel risk: 1.01 (Lower 95% CI 0.77; Upper 95 % CI 1.34) 2) Bacterial contamination: Culture + / Culture - / Co-amoxiclav: 76 / 78 / 154 Control: 81 / 49 / 130 157 / 127 / 284 Rel risk: 0.79 (Lower 95% CI 0.64; Upper 95 % CI 0.98) 3) Pregnancy rates significantly lower with positive cultures in logistic regression	**Comments:** Excellent reporting of study details **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +
Bungum, Bungum, Humaidan, et al., 2003 **#15740**	**Geographical location:** Skive, Denmark **Study dates:** Dec 2001 – May 2002 **Size of population:** 118 Day 3 ET: 57 Day 5 ET: 61 **Number of cycles analyzed:** 118	**Age:** Mean: Day 3 ET Grp: 31.3 Day 5 ET Grp: 31.2 Range: Day 3 ET Grp: 22.0-39.0 Day 5 ET Grp: 22.5-39.3 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR Note: Day 3 ICSI cycles	**Definition(s) of outcome(s):** Pregnancy: - Biochemical: + hCG - Clinical: USD with + FCM Live birth: NR Multiples: NR Complications: NR	1) Clinical pregnancy: Preg + / Preg - / Day 5: **32** / **29** / 61 Day 3: **36** / **21** / 57 68 / 50 / 118 Rel risk: 0.83 (Lower 95% CI 0.61; Upper 95 % CI 1.13) 2) A statistically greater number of patients had embryos frozen on Day 3 vs. Day 5.	**Comments:** - Low power of 0.32 for clinical pregnancy - % of pts receiving ICSI was higher in Day 5 grp - Diagnoses NR **Quality assessment:** Randomization method: NR Blinding: NR Dropout rate < 20%: NR Adequacy of randomization concealment: NR

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		51%, day 5 64%			
	Number of cycles per patient: 1.0 **Study type:** RCT **Interventions:** Pts undergoing IVF/ICSI randomized to Day 3 vs. Day 5 ET. All pts in Day 3 grp had 2 embryos transferred, whereas 2 pts in Day 5 group only had one embryo transferred.	**Inclusion criteria:** - 3 or more 8-cell embryos on Day 3 with < 20% fragmentation - Age < 40 - BMI < 30 - FSH < 12 - Received standard luteal phase down regulation with rFSH treatment **Exclusion criteria:** NR			
Cerne, Bergh, Borg, et al., 2006 **#50920**	**Geographical location:** Goteborg and Stockholm, Sweden **Study dates:** Oct 2004 to Jan 2005 **Size of population (no. of patients):** 183 **Number of cycles analyzed:** 183 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Preovarian block (POB) Paracervical block (PCB)	**Age:** Mean (SD): POB: 34.5 (3.9) PCB: 34.3 (4.4) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Swedish speaking **Exclusion criteria:** Participated previously in this study, lidocaine allergy, only one ovary or abnormal position of ovaries (i.e. reachable only when passing the aspiration needle through uterus) and coasting more than 1 day because of high risk of ovarian hyperstimulation syndrome.	**Definition(s) of outcome(s):** Pregnancy: Biochemical pregnancy: positive urinary HCG test 14 days after embryo transfer Clinical pregnancy: ultrasound verification of fetal heartbeat at least 5 weeks after embryo transfer. Live birth: NR Multiples: NR Complications: Pain, adverse effects	1) Biochemical pregnancy: Biochem preg + / Biochem preg - / Total POB: 28 / 68 / 96 PCB: 30 / 57 / 87 Total: 58 / 125 / 183 Value / Lower 95% CI / Upper 95% CI **Rel risk**: 0.85 / 0.55 / 1.29 2) Clinical pregnancy: Clinical preg + / Clinical preg - / Total POB: 23 / 68 / 91 PCB: 24 / 63 / 87 Total: 47 / 131 / 178 Value / Lower 95% CI / Upper 95% CI **Rel risk**: 0.92 / 0.56 / 1.50 3) No difference in pain scores 4) No adverse effects	**Comments:** None **Quality assessment:** Randomization method: - Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Cha and Wirth, 2001 **#10**	**Geographical location:** Seoul, South Korea **Study dates:** Dec 1998-March 1999 **Size of population (no. of patients):** 199 **Number of cycles analyzed:** 199 (30 not analyzed due to cancellation) **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** - COH with GnRH agonist/gonadotropins (not specified) - Intervention: Intercessory prayer (individuals praying for either general benefit or specific outcome—conception—in other individual) vs no intercessory prayer	**Age:** Mean (SD): 33.9 (4.7) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Age 26-46 - Candidates for IVF **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: Yes Complications: NR	1) Pregnancy – intention to treat: Preg + / Preg - Prayer: 44 / 56 (100) No Prayer: 21 / 78 (99) 65 / 134 (199) Rel risk: 2.07 (Lower 95% CI 1.34; Upper 95 % CI 3.22) 2) Higher multiple pregnancy rate in prayer group	**Comments:** - No informed consent - Complex intervention allocation of both directed and non-directed prayer—ultimate allocations not reported **Quality assessment:** Randomization method: - Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Chakravarty, Shirazee, Dam, et al., 2005 **#39460**	**Geographical location:** West Bengal, India **Study dates:** Jan 2002 – June 2003 **Size of population:** Grp 1: 351 vaginal micronized progesterone Grp 2: 79 oral dydrogesterone **Number of cycles analyzed:** 430 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** IVF/ICSI cycles randomized to vaginal micronized progesterone vs. oral dydrogesterone	**Age:** Range: 25-42 Age distribution given and same for each group **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Grp 1: - Unexplained infertility: 67 [19.1] - Endometriosis: 34 [9.7] - Male factor: 135 [38.7] - Tubal factor: 114 [32.5] - PCOS: 0 - Other (specify): 0 Grp 2: - Unexplained infertility: 12 [15.2] - Endometriosis: 12 [15.2] - Male factor: 21 [26.6] - Tubal factor: 34 [43] - PCOS: 0 - Other (specify): 0 **Inclusion criteria:** IVF or ICSI with endometrial thickness of 7-12mm and no endometrial pathology **Exclusion criteria:** - Previous failed IVF/ICSI - PCOS - Advanced endometriosis - Dense pelvic adhesions - Genital TB	**Definition(s) of outcome(s):** Pregnancy: NR Live birth: Yes Multiples: NR Complications: NR	1) Live birth: Preg + / Preg - Study drug: **19** / **60** (79) Control: **80** / **271** (351) 99 / 331 (430) **Rel risk** 1.06 (Lower 95% CI 0.68, Upper 95 % CI 1.63)	**Comments:** - Intentional 5:1 randomization - Low numbers in oral group **Quality assessment:** Randomization method: NR Blinding: NR Dropout rate < 20%: + Adequacy of randomization concealment: NR

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Chan, Ng, Chan, et al., 2006 **#50950**	**Geographical location:** Hong Kong, China **Study dates:** Feb 2001-June 2003 **Size of population (no. of patients):** 22 **Number of cycles analyzed:** 227 (184 analyzed due to withdrawals after randomization) **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** - All subjects underwent IVF with COH (GnRH agonist and hMG) - Randomized to no intervention or Eastern Body-Mind-Spirit (EBMS) counseling sessions, focusing on 1. mini-lectures on Traditional Chinese Medicine, which views health as a state of mind-body harmony; 2. stress-reduction training coupled with tai-chi exercises, meditation, and breathing techniques; 3. activities, such as singing, journal writing, and drawing, to encourage the discovery of positive	**Age:** Mean (SD): EBMS: 36.0 (3.3) Control: 35.0 (3.5) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR for entire randomized population **Inclusion criteria:** 1st IVF cycle **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Main outcome: State-Trait Anxiety Scale score Pregnancy: Presence of gestational sac or Live birth: NR Multiples: NR Complications: NR	1) Pregnancy (intention-to-treat): Preg + / Preg - / Total EBMS: 20 / 81 / 101 Control: 16 / 110 / 126 36 / 191 / 227 Rel risk: 1.56 (95% CI 0.85 – 2.85) 2) Ongoing pregnancy (intention-to-treat): Preg + / Preg - / Total EBMS: 13 / 88 / 101 Control: 13 / 113 / 126 26 / 201 / 227 Rel risk: 1.25 (95% CI 0.61 – 2.57) Study drug: 13 / 88 / 101 3) Significant reduction in state anxiety, but not trait anxiety, in intervention group analyzed	**Comments:** - More male factor, more single embryo transfers in control group - Drop-out rate higher in intervention group - 2 spontaneous pregnancies in intervention **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: - (NR)

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	meaning from negative experiences; and 4. reading materials excerpted from ancient Chinese philosophical writings on suffering and the meaning of life. 4 weekly sessions of 3 hours each, done prior to initiation of first IVF cycle				
Chang, Kenley, Burns, et al., 2001 **#58080**	**Geographical location:** 20 centers in U.S. in Alabama, California, Florida, Illinois, Maryland, Massachusetts, Missouri, New Jersey, North Carolina, Pennsylvania, Rhode Island, South Carolina **Study dates:** NR **Size of population (no. of patients):** 275 **Number of cycles analyzed:** 275 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Long protocol GnRH, uFSH stimulation, randomized to (a) 250 µg rhCG (b) 500 µg rhCG (c) 10000 IU uhCG	**Age:** Mean (SD): 250 rhCG: 32.6 (3.7) 500 rhCG: 31.7 (3.5) uhCG: 32.2 (3.7) **Race/ethnicity (n [%]):** White: 80% African-American: 7% Hispanic: 6% Other: 7% **Diagnoses (n [%]):** Unexplained infertility: Endometriosis: 22% Male factor: 18% Tubal factor: 60% **Inclusion criteria:** - Age 18 to 38 - Both ovaries present - Regular menstrual cycles of 25-35 days - Either ≥ 2-year history of infertility or had tubal disease - Non-obese (BMI < 30 kg/m^2) - No more than one previous ART attempt	**Definition(s) of outcome(s):** Pregnancy: Gestational sac on ultrasound Live birth: Yes Multiples: NR Complications: NR	1) Pregnancy, 250 ug rhCG vs uhCG: Preg + / Preg - / Total 250 ug rhCG: 33 / 61 / 94 uhCG: 33 / 59 / 92 Total: 66 / 120 / 186 Rel risk: Value 0.98; Lower 95% CI 0.66; Upper 95% CI 1.44 2) Pregnancy, 500 ug rhCG vs uhCG: Preg + / Preg - / Total 500 ug rhCG: 32 / 57 / 89 uhCG: 33 / 59 / 92 Total: 65 / 116 / 181 Rel risk: Value 1.00; Lower 95% CI 0.68; Upper 95% CI 1.48 3) Live birth, 250 ug rhCG vs uhCG: Birth + / Birth - / Total 250 ug rhCG: 29 / 65 / 94 uhCG: 28 / 64 / 92 Total: 57 / 129 / 186	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		Exclusion criteria: NR			

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.01	0.66	1.56

4) Live birth, 500 ug rhCG vs uhCG:

	Birth +	Birth -	Total
500 ug rhCG	27	62	89
uhCG	28	64	92
Total	55	126	181

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.00	0.64	1.55

Check, Check, Choel, et al., 2004

#9470

Geographical location: NR

Study dates: NR

Size of population (no. of patients): 60 randomized

Number of cycles analyzed: 69 (or 76)

Number of cycles per patient: 1.15 (or 1.27)

Study type: RCT

Interventions:
Agonist: SQ 0.5 mg/d leuprolide for 10 days from mid-leuteal phase, then 0.25 mg once gonatotropins were started (300 IU in divided doses) IM or SC after suppression was

Age:
Mean: 36

Race/ethnicity (n [%]): NR

Diagnoses (n [%]): NR

Inclusion criteria:
Couples requiring IVF or intracytoplasmic sperm injection

Exclusion criteria: NR

Definition(s) of outcome(s):

Pregnancy: Not defined

Live birth: NR

Multiples: NR

Complications: NR

1) Clinical pregnancy:

	Clinical Preg +	Clinical Preg -	
Antagonist	6	13	19
Agonist	12	16	28
	18	29	47

		Lower 95% CI	Upper 95 % CI
Rel risk	0.74	0.34	1.62

2) Viable pregnancy:

	Viable Preg +	Viable Preg -	
Antagonist	6	13	19
Agonist	9	19	28
	15	32	47

		Lower 95% CI	Upper 95 % CI
Rel risk	0.98	0.42	2.31

Comments:
None

Quality assessment:
Randomization method: - (NR)
Blinding: - (none)
Dropout rate < 20%: - (14/60 [23%] couples not clearly accounted for)
Adequacy of randomization concealment: - (open label)

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	observed Antagonist: 250 µgm of ganirelix beginning with observation of at least one dominant follicle with diameter >= 14 mm in conjunction with a serum estradiol E2 level >= 1000 pg/mL. Gonadotropin 300 IU in divided doses beginning day 3 of cycle. In both groups, the gonadotropins included 300 IU of follitropin beta or 150 follitropin beta and 150 hMG, depending on financial situation.				
Chen and Kattera, 2006 **#51040**	**Geographical location:** Singapore **Study dates:** June 2002-June 2004 **Size of population (no. of patients):** 330 **Number of cycles analyzed:** 330 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Embryo selection for transfer randomized to (a) day 3 morphology + progression + Day 1 pronuclear morphology	**Age:** Mean (SD): Morphology 35.7 (3.7), cleavage 35.5 (3.4) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** NR **Exclusion criteria:** - Azoospermia - Poor response to COH - Mixed classification of embryos transferred	**Definition(s) of outcome(s):** Pregnancy: + hCG with rising titer Live birth: NR Multiples: NR Complications: NR	1) Pregnancy (all randomized subjects): Preg + / Preg - / Lower 95% CI / Upper 95 % CI Cleavage: **41** / **124** / 165 Morphology: **47** / **118** / 165 88 / 242 / 330 **Rel risk**: 0.87 / 0.61 / 1.25 Similar results when divided by score	**Comments:** Denominators for reported rates unclear **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	(A: nucleoli large or medium in size and aligned between the two pronuclei (polarized); B: nucleoli llarge or medium and without any particular alignment; C: nucleoli were small or pinpoint with any type of nucleolar alignment.) (b) day 3 morphology and progession + day 1 early zygote cleavage status (A: 2 cells at 26 h; B: PN breakdown had occurred but cleavage had not occurred. C: PN were still intact.				
Cheung, Lam, Lok, et al., 2005 **#9190**	**Geographical location:** Hong Kong, China **Study dates:** Apr 2001 – Dec 2003 **Size of population:** 66 - GnRH antagonist: 31 (2 dropouts) - GnRH agonist: 32 (1 dropout) **Number of cycles analyzed:** 66 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Compares women	**Age:** Mean (SD): Antagonist grp: 36.0 (2.6) Agonist grp: 36.3 (3.0) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Antagonist group: - Unexplained infertility: 3 (9.7%) - Endometriosis: 6 (19.4%) - Male factor: 4 (12.9%) - Tubal factor: 18 (58.0%) Agonist group: - Unexplained infertility: 7 (21.9%) - Endometriosis: 6 (18.8%)	**Definition(s) of outcome(s):** Pregnancy: Clinical – defined as sac on USD Live birth: NR Multiples: NR Complications: NR	1) Clinical pregnancy rate: Preg + / Preg - / Total Antag +: 5 / 26 / 31 Agon -: 3 / 29 / 32 Total: 8 / 55 / 63 Rel risk: Value 1.72; Lower 95% CI 0.45; Upper 95% CI 6.59	**Comments:** - Number of embryos transferred statistically greater in antagonist group -Sample size based on expected number of oocytes - Low power - Not intent-to-treat analysis **Quality assessment:** Randomization method: + (computer-generated random numbers) Blinding: - (investigators blinded, not subjects) Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	undergoing IVF/ICSI treated with GnRH antagonist starting on day 6 and a GnRH agonist started in the luteal phase	- Male factor: 5 (15.6%) - Tubal factor: 13 (40.6%) - Other (specify): 1 (3.1%) **Inclusion criteria:** - History of poor ovarian response with history of < 3 mature follicles with previous IVF using luteal agonist, or pts with basal FSH > 10 **Exclusion criteria:** PCOS			
Coroleu, Barri, Carreras, et al., 2002 **#790**	**Geographical location:** Barcelona, Spain **Study dates:** NR **Size of population:** 184 - USD grp: 93 - Touch grp: 91 **Number of cycles analyzed:** 184 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** In women undergoing frozen embryo transfer, compares ultrasound-guided transfer vs. clinical touch transfer	**Age:** Mean (SD): USD grp: 36.6 (3.4) Touch grp: 36.2 (3.0) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Previous IVF with both luteal down-regulation or flare cycles - Had frozen embryos for transfer **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Clinical – sac on USD Live birth: NR Multiples: Yes Complications: SAB rate	1) Clinical pregnancy rate: Preg + / Preg - / Total USD: 32 / 61 / 93 Touch: 18 / 73 / 91 Total: 50 / 134 / 184 Rel risk: Value 1.74; Lower 95% CI 1.06; Upper 95% CI 2.87 2) SAB rate: SAB + / SAB - / Total USD: 7 / 25 / 32 Touch: 4 / 14 / 18 Total: 11 / 39 / 50 Rel risk: Value 0.98; Lower 95% CI 0.33; Upper 95% CI 2.91 3) Multiple rate: Mult + / Mult - / Total USD: 6 / 26 / 32 Touch: 6 / 12 / 18 Total: 12 / 38 / 50	**Comments:** None **Quality assessment:** Randomization method: + (computer-generated table) Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.56	0.21	1.49

Coroleu, Barri, Carreras, et al., 2006

#51260

Geographical location: Barcelona, Spain

Study dates: Sep 2004-Jan 2005

Size of population (no. of patients): 193

Number of cycles analyzed: 193

Number of cycles per patient: 1.00

Study type: RCT

Interventions:
Soft Wallace catheter (standard) or echogenic catheter (SureView)

Age:
Mean (SD):
Echogenic catheter: 35.9 (2.8); standard 35.5 (3.5)

Race/ethnicity (n [%]):
NR

Diagnoses (n [%]):
Unexplained infertility: 32 (16.3%)
Endometriosis: 28 (14.5%)
Male factor: 70 (36.2%)
Tubal factor: 43 (22.2%)

Inclusion criteria:
Age 25-43, scheduled for IVF/ICSI

Exclusion criteria: NR

Definition(s) of outcome(s):

Pregnancy: Gestational sac at 6 weeks

Live birth: NR

Multiples: Yes

Complications: NR

1) Clinical pregnancy:

	Preg +	Preg -	
Echogenic	53	45	98
Standard	39	56	95
	92	101	193

		Lower 95% CI	Upper 95 % CI
Rel risk	1.32	0.97	1.78

2) Twin (compared to singletons) among pregnancies:

	Twins	Single-ton	
Echogenic	17	36	53
Standard	3	36	39
	20	72	92

		Lower 95% CI	Upper 95 % CI
Rel risk	4.17	1.31	13.24

3) Mean transfer time significantly shorter with echogenic catheter (42.6 seconds vs. 60.2 seconds).

Comments:
None

Quality assessment:
Randomization method: +
Blinding: -
Dropout rate < 20%: +
Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Coroleu, Carreras, Veiga, et al., 2000 **#8550**	**Geographical location:** Barcelona, Spain **Study dates:** Oct 1998-Jan 1999 **Size of population (no. of patients):** 362 **Number of cycles analyzed:** 362 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** All interventions similar until embryo transfer U/S group: Catheter visualized, embryos released when tip within 1.5 cm of fundus, confirmation that embryos expelled Clinical touch: Embryos transferred based on clinician's judgment – as close as possible to fundus without touching	**Age (mean [SD]):** Ultrasound: 34.6 (4.0) Clinical touch: 34.5 (4.1) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 33 (9.1%) Endometriosis: 23 (6.4%) Male factor: 131(36.2%) Tubal factor: 99 (27.3%) Multiple diagnoses: 76 (21.0%) Distributions similar between arms **Inclusion criteria:** NR **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Ultrasound at 6-8 weeks of amenorrhea (not stated if FHR required) Ongoing pregnancy: Viable pregnancy at 12-16 weeks Live birth: NR Multiples: NR Complications: NR	1) Clinical pregnancy: Preg + / Preg - / Total U/S guidance: 91 / 91 / 182 Clinical touch: 61 / 119 / 180 152 / 210 / 362 Rel risk: 1.48 (Lower 95% CI 1.15; Upper 95 % CI 1.90) 2) Ongoing pregnancy: Preg + / Preg - / Total U/S guidance: 85 / 97 / 182 Clinical touch: 52 / 128 / 180 137 / 225 / 362 Rel risk: 1.62 (Lower 95% CI 1.23; Upper 95 % CI 2.13) 3) In subgroup analysis, no difference in outcomes with single embryo transfer, but numbers small (n = 13 in U/S group, n = 15 in clinical touch group).	**Comments:** Randomization method NR **Quality assessment:** Randomization method: - (NR) Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Dal Prato, Borini, Cattoli, et al., 2002 **#1990**	**Geographical location:** Bologna, Italy **Study dates:** Apr 1999 - Sep **Size of population (no. of patients):** 296 **Number of cycles analyzed:** 296 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** GnRH agonist: Single IM injection of depot GnRH administered in the mid-luteal phase of the cycle. At the onset of menses, 17β-estradiol transdermal patches applied at increasing doses for at least 12 days, from 100 µgm to 300µgm. No GnRH agonist: On day 1 of menstrual cycle 200µgm 17 β-estradiol transdermal, increased to 300µgm after 7 days.	**Age:** Mean (SD): 34.25 (3.5) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Women with normal ovarian function for frozen-thawed embryo transfer. **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Presence of one or more gestational sacs on ultrasonography, performed at least 4 weeks after embryo transfer Live birth: NR Multiples: NR Complications: NR	1) Pregnancy: Preg + / Preg - / Total GnRH agonist: **28** / **118** / 146 No GnRH agonist: **34** / **116** / 150 Total: 62 / 234 / 296 Rel risk: Value 0.85; Lower 95% CI 0.54; Upper 95% CI 1.32	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - (not clear if U/S assessment of pregnancy was blinded) Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Dal Prato, Borini, Coticchio, et al., 2004 **#11250**	**Geographical location:** Bologna, Italy **Study dates:** Sep 2000 – Sep 2002 **Size of population:** 180 - ½-dose GnRH grp: 90, 85 received ET - Full-dose GnRH grp: 90, 79 received ET **Number of cycles analyzed:** 180 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** Women undergoing IVF randomized to ½ dose GnRH agonist (1.87 mg Depot triptorelin) in the luteal phase vs. full dose GnRH agonist (3.75 ng triptorelin) in luteal phase with pFSH stimulation	**Age:** Mean (SEM): ½ dose: 33.2 (0.29) Full dose: 33.7 (0.33) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Age 25-38 - First IVF attempt **Exclusion criteria:** - Active endometriosis - Previous ovarian surgery - FSH > 15	**Definition(s) of outcome(s):** Pregnancy: Clinical – sac on USD Live birth: NR Multiples: NR Complications: SAB rate	1) Clinical pregnancy rate per randomized patient (fresh cycles): Preg + / Preg - / Total ½ dose: **33** / **57** / 90 Full dose: **20** / **70** / 90 Total: 53 / 127 / 180 Rel risk: Value 1.65; Lower 95% CI 1.03; Upper 95% CI 2.65 2) Cumulative pregnancy rate per patient, including transfer of frozen/thawed embryos: Preg + / Preg - / Total Study group: **49** / **41** / 90 Control: **29** / **61** / 90 78 / 102 / 180 Rel risk: 1.69; Lower 95% CI 1.19; Upper 95 % CI 2.41 3) SAB rate: SAB + / SAB - / Total ½ dose: **2** / **31** / 33 Full dose: **2** / **18** / 20 Total: 4 / 49 / 53 Rel risk: Value 0.61; Lower 95% CI 0.09; Upper 95% CI 3.97 4) Statistically greater cancellation rate in full dose grp due to lack of stimulation. 5) Statistically greater number of oocytes and embryos, and lower number of days of stimulation and dose of FSH, in ½-dose grp compared to full-dose grp.	**Comments:** - Diagnoses NR - ½-dose group had better quality embryos - Results not reported on intent-to-treat; pregnancy rate significantly higher by intent-to-treat compared to reported analysis **Quality assessment:** Randomization method: + (sequential numbering of opaque envelopes) Blinding: + (both pt and physician) Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Dal Prato, Borini, Trevisi, et al., 2001 **#4910**	**Geographical location:** Bologna, Italy **Study dates:** 9/1998 – 9/1999 **Size of population:** 132 Depot agonist grp: 66, 63 had ET, 2 no retrieval, 1 no transfer Daily agonist grp: 66, 63 had ET, 2 no retrieval, 1 no transfer **Number of cycles analyzed:** 132 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Women undergoing IVF/ICSI, compares down-regulation with luteal depot agonist (3.75 mg depot triptorelin) vs. luteal daily agonist (triptorelin 100 ug from luteal til menses then 50 ug until hCG). Stimulation with pFSH.	**Age:** Mean (SD): Depot grp: 33 ± 3.6 Daily grp: 33.8 ± 3.1 Median: NR Range: NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Age 25-38 - Tubal, male factor or unknown infertility **Exclusion criteria:** - Active endometriosis - Previous ovarian surgery - FSH > 15 - Previous poor response or known history of ovarian hyperstimulation	**Definition(s) of outcome(s):** Pregnancy: Clinical – sac on USD Live birth: NR Multiples: NR Complications: SAB rate, ectopic rate	1) Clinical pregnancy rate per randomized pt: Preg + / Preg - / Total Daily: **22** / **44** / 66 Depot: **24** / **42** / 66 46 / 86 / 132 Rel risk: 0.92 (Lower 95% CI 0.57, Upper 95 % CI 1.46) 2) Clinical pregnancy rate per pt with ET: Preg + / Preg - / Total Depot: **24** / **39** / 63 Daily: **22** / **41** / 63 Total: 46 / 80 / 126 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.09 / 0.69 / 1.73 3) SAB rate: SAB + / SAB - / Total Depot: **2** / **22** / 24 Daily: **2** / **20** / 22 Total: 4 / 42 / 46 Value / Lower 95% CI / Upper 95% CI Rel risk: 0.92 / 0.14 / 5.96 4) Ectopic pregnancy: Ect preg + / Ect preg - / Total Depot: **1** / **23** / 24 Daily: **0** / **22** / 22 Total: 1 / 45 / 46 Value / Lower 95% CI / Upper 95% CI Rel risk: 2.76 / 0.12 / 64.42	**Comments:** - Diagnoses not reported - Low power for pregnancy difference **Quality assessment:** Randomization method: + (sequentially numbered opaque envelopes) Blinding: + (patients and physicians) Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Dale, Fiorentino, de Simone, et al., 2002 **#620**	**Geographical location:** Naples, Italy **Study dates:** 3/1998 – 2/1999 **Size of population:** 407 Zygote grp: 205, 203 had ET Embryo grp: 202, 183 had ET **Number of cycles analyzed:** 407 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Women undergoing IVF/ICSI were randomized to receive zygote transfer at 2 PN stage vs. embryo transfer on day 2 or 3	**Age:** Mean (SD): Zygote grp: 33.8 ± 4.5 Embryo grp: 32.7 ± 3.5 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** *Zygote group:* Unexplained infertility: 31 (15.1%) Endometriosis: 35 (17.1%) Male factor: 97 (47.3%) Tubal factor: 20 (9.7%) *Embryo grp:* Unexplained infertility: 30 (14.8%) Endometriosis: 31 (15.3%) Male factor: 78 (38.6%) Tubal factor: 29 (14.4%) **Inclusion criteria:** First cycle of IVF/ICSI **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Clinical – not defined Live birth: Yes Multiples: Yes Complications: NR	1) Clinical pregnancy rate per randomized pt: Preg + / Preg - Zygote: 74 / 131 (205) Embryo: 77 / 125 (202) 151 / 256 (407) Rel risk: 0.95 (Lower 95% CI 0.74, Upper 95 % CI 1.22) 2) Multiple pregnancy rate: Multi preg + / Multi preg - Zygote: **23** / **51** (74) Embryo: **40** / **37** (77) Total: 63 / 88 (151) Rel risk: 0.60 (Lower 95% CI 0.40, Upper 95% CI 0.89)	**Comments:** - Greater number of zygotes transferred compared to embryos - No SAb's reported—unusual (clinical pregnancy rate=live birth) **Quality assessment:** Randomization method: + (computer-generated random number table) Blinding: NR Dropout rate < 20%: + Adequacy of randomization concealment: NR
De Camargo	**Geographical location:**	**Age (mean [SD]):**	**Definition(s) of**	1) Pregnancy:	**Comments:**

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Martins, Baruffi, Mauri, et al., 2004 **#9960**	São Paolo, Brazil **Study dates:** NR **Size of population (no. of patients):** 100 **Number of cycles analyzed:** 100 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** - All underwent ICSI - Mock transfer performed cycle prior to transfer - Frydman catheter used in all patients - U/S group: Embryos expelled when catheter tip within 0.5-1.5 cm of fundus, confirmed by U/S - Control: Embryos expelled at catheter length determined in previous cycle	U/S: 32.1 (4.1) Control: 32.0 (3.2) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Transfer judged to be easy (no need for cervical manipulation) during mock transfer in previous cycle **Exclusion criteria:** NR	**outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: Miscarriage	Preg + / Preg - / Lower 95% CI / Upper 95 % CI Ultrasound: 21 / 29 / 50 Clinical touch: 15 / 35 / 50 36 / 64 / 100 **Rel risk** 1.40 (0.82, 2.39) 3) Miscarriage rate higher in control group, but denominator not reported.	- No a priori sample size calculation - Authors acknowledge study underpowered **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -
De Placido,	**Geographical location:**	**Age:**	**Definition(s) of**	1) Ongoing pregnancy rate:	**Comments:**

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Alviggi, Perino, et al., 2005 **#9690**	Italy (multicenter) **Study dates:** Feb 2003 – Dec 2003 **Size of population:** 130 **Number of cycles analyzed:** 130 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Compared the use of combine rLH and rFSH vs. rFSH step-up protocol for pts who initially have inadequate ovarian response to rFSH Grp a = combine rLH and rFSH Grp b = rFSH step-up protocol	Mean (SD): Grp a: 31.5 (3.9) Grp b: 30.4 (4.1) Range: 18-37 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Male factor: - Grp a: 51.5 - Grp b: 48.4 Tubal factor: - Grp a: 21.7 - Grp b: 25.6 Combined male and tubal factor: - Grp a: 20.1 - Grp b: 21.8 **Inclusion criteria:** - Age 18-37 - Menstrual cycle ranging from 24d-35d - Day3 FSH ≤ 9 IU/L - Hysteroscopic evidence of a normal uterine cavity within the last 6 mos - Using GnRH agonist long protocol **Exclusion criteria:** - BMI < 18 or > 28 - Biochemical and/or ultrasonographic evidence of PCOS - Stage III-IV endometriosis - Chromosomal abnormalities - Endocrinological and/or autoimmune disorder - More than 2 previously unsuccessful IVF or ICSI - Presence of only 1 ovary	**outcome(s):** Ongoing pregnancy: Pregnancy reaching wk 12 Live birth: NR Multiples: NR Complications: NR	Preg + / Preg - rLH: 19 / 46 (65) rFSH: 13 / 52 (65) 32 / 98 (130) Rel risk: 1.46 (Lower 95% CI 0.79, Upper 95 % CI 2.71)	- Results not reported as intent-to-treat (cancelled cycles not included) - Reported rates do not match calculated rates **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
De Placido, Mollo, Alviggi, et al., 2001 **#4320**	**Geographical location:** Naples, Italy **Study dates:** Nov 1999 – July 2000 **Size of population:** 43 **Number of cycles analyzed:** 43 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Investigated the effects of adding hMG during ovarian stimulation (for IVF) in normoovulatory normogonadotrophic pts showing an initial suboptimal response to standard long protocol using rFSH. Group A: rFSH is substituted by HMG Group B: dose of rFSH increased from 150 to 375 IU	**Age:** Mean (SD): Grp A: 31.65 (3.80) Grp B. 30.44 (3.84 **Race/ethnicity (n [%]):** Caucasian (Italian) 100 **Diagnoses (n [%]):** Male factor: - Grp A: 35 - Grp B: 34.8 Tubal factor: - Grp A: 35 - Grp B: 30.4 Combined male and tubal factors - Grp A: 10 - Grp B: 21.7 **Inclusion criteria:** - Menstrual cycle range 24d-35d - Normal uterine cavity (by hysteroscopy) **Exclusion criteria:** -Basal FSH. 10 IU/L - Age ≥ 37 yr - BMI .29 - Biochemical and/or u/s evidence of PCOS - Stage III-IV endometriosis - Autoimmune disease - Thyroid disease - Chromosomal abnormality - One ovary	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Pregnancy rate: Preg + / Preg - / Total hMG: **10** / **10** / 20 rFSH: **8** / **15** / 23 Total: 18 / 25 / 43 Value (Lower 95% CI, Upper 95% CI) **Rel risk**: 1.44 (0.71, 2.93)	**Comments:** - Low power for pregnancy **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +
De Placido, Mollo, Clarizia, et	**Geographical location:** Naples, Italy	**Age:** Mean (SD): Antagonist: 37.2 (4.1)	**Definition(s) of outcome(s):**	1) Ongoing pregnancy: Ongoing Ongoin	**Comments:** None

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
al., 2006 **#51460**	**Study dates:** July 2002 and Feb 2004 **Size of population (no. of patients):** 133 **Number of cycles analyzed:** 133 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Antagonist: Of the GnRH-ant cetrorelix 0.125 mg/day administered for 2 days, beginning when at least one follicle ≥ 14 mm was present; thereafter, the GnRH-ant 0.25 mg/day until exogenous hCG administration. On the same day of GnRH-ant administration, a daily dose of 150 IU of rec-LH added until the day of hCG. Agonist: Triptorelin 0.1 mg SC, beginning on the same day of the first rec-FSH administration. In addition, a dose of 150 IU/day of rec-LH added when at least one follicle reached 14 mm. When at least one follicle reached 18–20 mm in diameter, hCG 10,000 IU IM) of hCG given to trigger ovulation.	Agonist: 37.3 (3.7) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Age ≥ 37 years or day 2 FSH (basal FSH) serum concentration ≥ 9 IU/L; menstrual cycles ranging from 24–35 days (intraindividual variability ± 3 days), hysteroscopic evidence of a normal uterine cavity, couples undergoing ICSI. **Exclusion criteria:** BMI ≥ 26 kg/m2; biochemical or US evidence of polycystic ovary syndrome, and stage III–IV endometriosis according to the revised American Fertility Society classification (rAFS, 1985); inflammatory, autoimmune, and chromosomal disorders; endocrine and metabolic disease, including hyperprolactinemia; or the presence of only one ovary	Ongoing pregnancy: Not defined Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	Preg + / g Preg - Antagonist: **14** / **53** — 67 Agonist: **17** / **49** — 66 31 / 102 — 133 **Rel risk** 0.81 (Lower 95% CI 0.44, Upper 95 % CI 1.51) 2) Pregnancy: Preg + / Preg - Antagonist: **12** / **55** — 67 Agonist: **16** / **50** — 66 28 / 105 — 133 **Rel risk** 0.74 (Lower 95% CI 0.38, Upper 95 % CI 1.44)	**Quality assessment:** Randomization method: + Blinding: - (not mentioned) Dropout rate < 20%: + Adequacy of randomization concealment: - (not mentioned)

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Demirol, Guven, Baykal, et al., 2006 **#51520**	**Geographical location:** Ankara, Turkey **Study dates:** January 2001-March 2005 **Size of population (no. of patients):** 99 **Number of cycles analyzed:** 99 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** - Surgery: laparoscopic drainage of endometrioma, dissection of pseudocapsule, control of bleeding with bipolor coagulation, with stimulation 3 months later - Control: no surgery, immediate ISCI, endometrioma drained at time of oocyte retrieval	**Age:** Mean (SD): Surgery 35.2 (0.3); control: 34.9 (0.2) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Endometriosis: 100% **Inclusion criteria:** - Single or unilateral multiple endometriomas ≥ 3cm, < 6 cm, dx'ed by transvaginal US - Scheduled for ICSI **Exclusion criteria:** - Bilateral endometriomas - Suture use during laparoscopy	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Clinical pregnancy: Preg + / Preg - / Total Surgery: 17 / 32 / 49 Control: 19 / 31 / 50 36 / 63 / 99 Rel risk: 0.91 (Lower 95% CI 0.54, Upper 95 % CI 1.54)	**Comments:** - Randomization method not reported **Quality assessment:** Randomization method: - (NR) Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment:- (NR)
Devroey, Fauser, Platteau, et al., 2004	**Geographical location:** Brussels and Ghent, Belgium; Rotterdam, the Netherlands	**Age:** Mean (SD): rFSH: 32.1 (4.3) 120 FSH-CTP: 30.4 (3.8) 180 FSH-CTP: 31.5 (3.8)	**Definition(s) of outcome(s):** Pregnancy: Not defined	1) Ongoing pregnancy – daily 150 IU rFSH vs. 120 IU FSH-CTP: Preg+ / Preg - / Total 120 IU: **4** / **21** / 25	**Comments:** None **Quality assessment:** Randomization method: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#13260	**Study dates:** NR **Size of population (no. of patients):** 98 **Number of cycles analyzed:** 98 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** GnRH antagonist + (a) fixed daily dose of 150 IU rFSH, (b) 120 IU FSH-CTP (long-acting), followed 1 week later by fixed daily 150 IU rFSH (c) 180 IU FSH-CTP + 150 IU rFSH 1 week later (d) 240 IU rFSH + 150 IU rFSH 1 week later	240 FSH-CTP: 33.4 (4.1) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 20 (20%) Endometriosis: 3 (3%) Male factor: 40 (41%) Tubal factor: 24 (24%) Other: Combined 5 (5%) **Inclusion criteria:** - Undergoing COH for IVF/ICSI - Age 18-39 - Ovulatory - BMI 18-29 **Exclusion criteria:** NR	Live birth: NR Multiples: NR Complications: OHSS	FSH-CTP rFSH **10** **14** 24 Total 14 35 49 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.38 0.14 1.06 2) Ongoing pregnancy – 150 IU rFSH vs. 180 IU FSH-CTP: Preg+ / Preg - / Total 180 IU FSH-CTP **5** **19** 24 rFSH **10** **14** 24 Total 15 33 48 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.50 0.20 1.25 3) Ongoing pregnancy – 150 IU rFSH vs. 2400 IU FSH-CTP: Preg+ / Preg - / Total 240 IU FSH-CTP **6** **19** 25 rFSH **10** **14** 24 Total 16 33 49 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.58 0.25 1.34 4) OHSS: 2 cases each in rFSH, 120 FSH-CTP, and 240 FSH-CTP	Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +
Dickey, Nichols, Steinkampf, et al., 2003	**Geographical location:** New Orleans & Baton Rouge, LA, Greenville, SC; Birmingham, AL; Plymouth Meeting, PA;	**Age:** Mean (SD): human FSH 32.0 (3.9), follitropijn-β 32.5 (3.7)	**Definition(s) of outcome(s):** Pregnancy: Clinical pregnancy—intrauterine	1) Clinical pregnancy (Intention to treat) Preg + / Preg - HP-hFSH 51 69 120	**Comments:** - Combined results from 2 separate protocols; individual results not provided

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#11410	Valencia, CA; Odessa, TX; Charlotte, NC **Study dates:** NR **Size of population (no. of patients):** 238 **Number of cycles analyzed:** 238 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Randomized after GnRH down regulation to identical doses of (a) highly purified human-derived FSH, or (b) recombinant follitropijn-β 225 IU sc for 5 days, dose adjusted to maximum of 450 IU/day, maximum duration 12 days	**Race/ethnicity (n [%]):** **Diagnoses (n [%]):** Unexplained infertility: 28% Endometriosis: 16% Male factor: 4% Tubal factor: 53% **Inclusion criteria:** - Age 18-39 - Non-smoking - Normal hormones/ultrasound - Normal semen (partner or donor) **Exclusion criteria:** NR	fetal sac with heart beat Live birth: Yes Multiples: NR Complications: NR	follitropijn-β: 45 / 73 / 118 96 / 142 / 238 **Rel risk** 1.11 (Lower 95% CI 0.82; Upper 95 % CI 1.52) 2) Live birth (intention to treat) Preg + / Preg - HP-hFSH: 42 / 78 / 120 follitropijn-β: 38 / 80 / 118 80 / 158 / 238 **Rel risk** 1.09 (Lower 95% CI 0.76; Upper 95 % CI 1.55)	**Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: - (NR)
Dieterle, Ying, Hatzmann, et al., 2006 **#51570**	**Geographical location:** Dortmund, Germany **Study dates:** NR **Size of population (no.**	**Age:** Mean (SD): Acupuncture: 35.1 (3.8); placebo:34.7 (4.0) **Race/ethnicity (n [%]):**	**Definition(s) of outcome(s):** Pregnancy: Gestational sac on TV US 4-6 weeks after transfer	1) Clinical pregnancy: Preg + / Preg - Active acupuncture: 39 / 77 / 116	**Comments:** - Sample size based on clinical pregnancy rate, powered to detect **Quality assessment:** Randomization method: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	of patients): 225 **Number of cycles analyzed:** 225 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** - All underwent COH with GnRH agonist (nafarelin), hMG or rFSH; no more than 3 embryos transferred - Randomized to active or placebo acupuncture for 30 minutes, immediately after embryo transfer, and 3 days later - Active acupuncture: performed on acupuncture points believed to be associated with fertility, along with placing of Chinese herbal medicine (seed of Caryophyllaceae) to ear - Placebo—acupuncture applied to points not associated with fertility	NR **Diagnoses (n [%]):** Unexplained infertility: Endometriosis: 18% acupuncture, 11% control Male factor: 58% acupuncture, 60% control Tubal factor: 35% acupuncture, 38% control Other – not specified: acupuncture 13%, control 11% **Inclusion criteria:** NR **Exclusion criteria:** NR	Live birth: NR Multiples: NR Complications: NR	Control 17 92 109 56 169 225 Lower 95% CI / Upper 95 % CI **Rel risk** 2.16 1.30 3.58 2) Ongoing pregnancy: Preg + / Preg - Study drug 33 83 116 Control 15 94 109 48 177 225 Lower 95% CI / Upper 95 % CI **Rel risk** 2.07 1.19 3.59	Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +
Dor, Bider, Shulman, et al., 2000 **#7810**	**Geographical location:** Tel Hashomer, Israel **Study dates:** NR **Size of population:**	**Age:** Grp 1 Mean (SEM):27.9 (0.7) Grp 2: Mean (SEM): 30.2 (0.9)	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: Yes	1) Pregnancy rate Grp 1 vs 2: Preg + / Preg - Buserlin **6** **18** 24 hMG only **5** **21** 26	**Comments:** - Pregnancy was not the primary outcome and the study is not powered for such **Quality assessment:**

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Grp 1: 26 Grp 2: 24 Grp 3: 24 **Number of cycles analyzed:** 74 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Grp 1: HMG administration only Grp 2: Downregulation with intranasal Buserelin followed by HMG Grp 3: Downregulation with IM Triptorelin followed by HMG. All women underwent IVF	Grp 3: Mean (SEM): 29.5 (0.6) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Tubal or unexplained infertility **Exclusion criteria:** NR	Multiples: NR Complications: NR	11 39 50 Lower 95% CI / Upper 95 % CI **Rel risk** 1.30 0.46 3.71 2) Preg rate Grp 1 vs 3: Preg + / Preg - Triptorelin **7** **17** 24 hMG only **5** **21** 26 12 38 50 Lower 95% CI / Upper 95 % CI **Rel risk** 1.52 0.56 4.14 3) Preg rate Grp 2 vs 3: Preg + / Preg - / Total Buserelin /HMG **6** **18** 24 Triptorelin/HMG **7** **17** 24 Total 13 35 48 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.86 0.34 2.18 4) Delivery rate also shows no sig difference among the grps	Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -
Drakakis, Loutradis, Kallianidis, et al., 2005 **#41650**	**Geographical location:** Multicenter, Greece **Study dates:** NR **Size of population:** 46	**Age:** Mean (SD): rFSH: 33.0 (3.7) rFSH+hMG 32.4 (3.1) **Race/ethnicity (n [%]):**	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR	1) Clinical pregnancy rate: Preg + / Preg - / Total rFSH + hMG **5** **19** 24 rFSH **6** **16** 22	**Comments:** There are many factors that might effect embryo quality/pregnancy outcome that the paper did not state: 1) Percentage of pts with male

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		NR	Multiples: NR	Total 11 35 46	infertility in each grp.
	Number of cycles analyzed: 46	**Diagnoses (n [%]):** Paper did not state the percentage of the diagnosis in each grp. The paper just said the the diagnosis for each pt is either tubal or male factor**.**	Complications: NR	Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.76 0.27 2.15	2) Other diagnosis that pts might have (PCOS, endometriosis) 3) Paper also did not state the work up for infertility in the population in this study.
	Number of cycles per patient: 1.00			2) There are statistically significant more mature oocytes and no. of transferable embryos in rFSH+hMG group when compared to the control.	
	Study type: RCT				**Quality assessment:**
	Interventions:	**Inclusion criteria:**			Randomization method: +
	Objective: to examine whether exogenous LH (given on the first 4 days of the cycle) administration has a beneficial effect on the quality of oocytes, fertilization potential and pregnancy rate in IVF cycle.	First IVF Cycle Either tubal or male factor			Blinding: + Dropout rate < 20%: - Adequacy of randomization concealment: +
		Exclusion criteria: NR			
	This is a GnRH agonist long protocol.				
	Randomization: Compare the use of 1 amp of hMG (75 IU FSH+75 IU LH)+ r-FSH 150 IU with 200 IU of r-FSH in the first 4 days of stimulation cycle. Both grps received 200 of FSH afterward.				
Driscoll, Tyler, Hangan, et al., 2000 **#58120**	**Geographical location:** Westmead, Australia, and Auckland, New Zealand **Study dates:** NR	**Age:** Mean (SD): Overall: 32.4 (4) Range: 21-38 **Race/ethnicity (n [%]):** NR	**Definition(s) of outcome(s):** Pregnancy: Sac on ultrasound at 42 days Live birth: NR	1) Clinical pregnancy: Preg + / Preg - / Total uhCG **6** **38** 44 rhCG **7** **33** 40 Total 13 71 84	**Comments:** None **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%:+

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Size of population (no. of patients): 84 **Number of cycles analyzed:** 84 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** GnRH down regulation, rFSH hyperstimulation, with either (a) 5000 IU uhCG + placebo or (b) 5000 IU rhCG + placebo for ovarian maturation	**Diagnoses (n [%]):** NR in detail; male factor only in 53% rhCG, 45% uhCG **Inclusion criteria:** - Candidate for IVF/ICSI - Regular cycles **Exclusion criteria:** - Systemic disease - BMI > 30 - PCOS - History of OHSS - History of poor response to COH - >3 previous attempts - Any treatment in past 2 months	Multiples: NR Complications: NR	**Rel risk** Value 0.78; Lower 95% CI 0.29; Upper 95% CI 2.12	Adequacy of randomization concealment: +
Duvan, Ozmen, Satiroglu, et al., 2006 **#51650**	**Geographical location:** Ankara, Turkey **Study dates:** 2001-2002 **Size of population (no. of patients):** 187 **Number of cycles analyzed:** 187 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** - Randomized on day of embryo transfer to 1 of 4 interventions: A: 100 mg/day aspirin B. 10 mg/day prednisolone C. 100 mg/day aspirin +	**Age:** Mean (SD): 31.8 (6.0) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Endometriosis: 3 (1.6%) Male factor: 90 (48.1%) Tubal factor: 27 (14.4%) PCOS: 6 (3.2%) **Inclusion criteria:** - 1st ICSI cycle **Exclusion criteria:** - Contraindication to aspirin or steroid	**Definition(s) of outcome(s):** Pregnancy: + hCG with doubling Clinical pregnancy: gestational sac Live birth: NR Multiples: NR Complications: NR	1) Clinical pregnancy: aspirin vs control: Preg +: Study drug 11, Control 14, 25 Preg -: Study drug 30, Control 26, 56 Study drug total 41, Control total 40, 81 **Rel risk** 0.77; Lower 95% CI 0.40; Upper 95 % CI 1.48 2) Clinical pregnancy: prednisolone vs control: Preg +: Study drug 22, Control 14, 36 Preg -: Study drug 28, Control 26, 54 Study drug total 50, Control total 40, 90 **Rel risk** 1.26; Lower 95% CI 0.74; Upper 95 % CI 2.13	**Comments:** - Abstract states placebo, but not described in methods - No adjustment to sample size or analysis for multiple comparisons **Quality assessment:** Randomization method: + Blinding: ? (unclear from paper) Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	10 mg/day prednisolone D. No treatment (unclear if placebo used—not stated in methods)			3) Clinical pregnancy: prednisolone + aspirin vs control: Preg + / Preg - Study drug: 19 / 37 = 56 Control: 14 / 26 = 40 33 / 63 = 96 Rel risk 0.97 (Lower 95% CI 0.55, Upper 95 % CI 1.69)	
El-Toukhy, Taylor, Khalaf, et al., 2004 **#13690**	**Geographical location:** London, UK **Study dates:** Jan 1998 and July 2001 **Size of population (no. of patients):** 234 **Number of cycles analyzed:** 234 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Pituitary suppression prior to steroid hormone administration: Buserelin nasal spray starting in the mid-luteal phase (day 21) of the menstrual cycle. On day 1 of subsequent menstruation, estrogen stimulation was initiated using oral estradiol	**Age:** Mean (SD): 33 (4) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Tubal factor: 35% **Inclusion criteria:** Previous IVF with or without ICSI with embryo cryopreservation, had regular menstrual cycles **Exclusion criteria:** Patients using cryo-thawed embryos created from donated oocytes were not included	**Definition(s) of outcome(s):** Pregnancy: Observation on US scanning of a gestational sac with fetal heart beat between 4 and 5 weeks after the positive pregnancy test Live birth: Yes Multiples: NR Complications: NR	1) Pregnancy: Preg + / Preg - / Total GnRH: **44** / **73** = 117 No GnRH: **28** / **89** = 117 Total: 72 / 162 = 234 Value 1.57 (Lower 95% CI 1.05, Upper 95% CI 2.34) 2) Live birth: Live birth + / Live birth - / Total GnRH: **23** / **94** = 117 No GnRH: **10** / **107** = 117 Total: 33 / 201 = 234 Value 2.30 (Lower 95% CI 1.15, Upper 95% CI 4.62)	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	valerate 6 mg daily in two divided doses. Steroid supplementation without prior pituitary desensitization: Estrogen 6mg/day stimulation on day 1 of menstruation.				
Emiliani, Fasano, Vandamme, et al., 2005 **#51750**	**Geographical location:** Brussels, Belgium **Study dates:** NR **Size of population (no. of patients):** 187 **Number of cycles analyzed:** 196 **Number of cycles per patient:** 1.06 **Study type:** RCT **Interventions:** - Undergoing single embryo transfer - Randomized on day of retrieval to (a) early cleavage assessed 25 hours after insemination; if positive, used as criterion in addition to day 2 embyro score described below; vs (b) scoring only: 4: 2-cell embryo with regular blastomeres and no anucleate fragments. 3: 2-cell embryo with uneven blastomeres, or fragments <l/3 of the	**Age:** Mean (SD): Early cleavage: 30.3 (3.3); score only: 30.1 (3.3) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Age < 36 - Undergoing 1st IVF or ICSI cycle **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Gestational sac 28 days after retrieval Live birth: Yes Multiples: NR Complications: NR	1) Live birth: Live birth + / Live birth - Early cleavage: **26** / **64** (90) Score only: **24** / **70** (94) 50 / 134 (184) Rel risk 1.13 (Lower 95% CI 0.70; Upper 95 % CI 1.82)	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%:+ Adequacy of randomization concealment:-

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	embryonic surface 2, 1: 2-cell embryo with uneven blastomeres				
Engmann, DiLuigi, Schmidt, et al., 2008 **#70940**	**Geographical location:** Farmington, Conn **Study dates:** Aug 2004-March 2006 **Size of population (no. of patients):** 65 **Number of cycles analyzed:** 65 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** All pretreated with OCPs and GnRH agonist; then rFSH + GnRH antagonist (Ganirelix). Randomized to hCG or leuprolide as ovulation trigger when 2-3 follicles ≥ 18 mm.	**Age:** Mean (SD): hCG: 33.1 ± 3.6; Leuprolide: 32.0 ± 3.7 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 2 (3.1%) Endometriosis: 2 (3.1%) Male factor: 15 (23.1%) Tubal factor: 18 (27.7%) PCOS: 28 (43,1%) **Inclusion criteria:** - Age 20–39 years at the time of screening - Normal early follicular phase serum FSH concentration (%10.0 IU/L) - Undergoing first cycle of IVF with either PCOS or PCOM or undergoing a subsequent cycle with a history of high response in a previous IVF cycle **Exclusion criteria:** Hypogonadotropic hypogonadism	**Definition(s) of outcome(s):** Pregnancy: Gestational sac + heart rate on ultrasound at 7 weeks; ongoing pregnancy: continuing after 12 weeks Live birth: NR Multiples: NR Complications: OHSS (Golan criteria)	1) All OHSS: OHSS + / OHSS - / Total GnRH agonist: **0** / **33** / 33 hCG: **10** / **22** / 32 Total: 10 / 55 / 65 Value / Lower 95% CI / Upper 95% CI **Rel risk**: 0.05 / 0.00 / 0.76 2) Moderate-severe OHSS: OHSS + / OHSS - / Total GnRH agonist: **0** / **33** / 33 hCG: **5** / **27** / 32 Total: 5 / 60 / 65 Value / Lower 95% CI / Upper 95% CI **Rel risk**: 0.09 / 0.01 / 1.53 3) Clinical pregnancy: Preg + / Preg - / Total GnRH agonist: **17** / **16** / 33 hCG: **15** / **17** / 32 Total: 32 / 33 / 65 Value / Lower 95% CI / Upper 95% CI **Rel risk**: 1.10 / 0.67 / 1.80 4) Ongoing pregnancy: Preg + / Preg - / Total GnRH: **16** / **17** / 33	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				agonist / hCG **14** **18** 32; Total 30 35 65 Rel risk 1.11 (0.65, 1.88)	
Escudero, Bosch, Crespo, et al., 2004 **#13600**	**Geographical location:** Valencia, Spain **Study dates:** Oct 2001 and June 2002 **Size of population (no. of patients):** 109 **Number of cycles analyzed:** 109 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** Follicle > 14: GnRH-antagonist when the leading follicle reached a mean diameter of 14 mm. Day 6: GnRH-antagonist on stimulation day 6	**Age:** Mean (SD): 32.1 (3.0) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Male factor: 93 (85.3%) Tubal factor: 16 (14.7%) **Inclusion criteria:** Age ≤ 35 years; regular menstrual cycles ranging from 24–32 days; normal basal serum FSH (≤ 10 IU/L) LH (≤ 10 IU/L), and E2 (≤ 60 pg/mL) levels; body mass index (BMI) ≥ 30 kg/m2; no uterine (adenomyosis, müllerian malformations) or ovarian (polycystic ovarian syndrome [PCOS], endometriosis) abnormalities assessed by vaginal ultrasound **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Presence of a gestational sac with positive heartbeat Live birth: NR Multiples: NR Complications: NR	1) Pregnancy: Preg + / Preg - Day 6 Follicle >14 mm **26** **25** 51 **20** **25** 45 46 50 96 Rel risk 1.15 (0.75, 1.75)	**Comments:** None **Quality assessment:** Randomization method: Blinding: Dropout rate < 20%: Adequacy of randomization concealment:
European and Israeli Study Group on Highly	**Geographical location:** 22 centers from 6 countries: Germany, Denmark, Israel, Netherlands, Switzerland	**Age:** Mean (SD): Menopur: 30.82 (4.21) FSH: 30.81 (4.16)	**Definition(s) of outcome(s):** Biochemical pregnancy: hCG positive test	1) Clinical pregnancy: (includes all randomized patients who began treatment): Preg + / Preg - HP-hMG 98 275 373	**Comments:** Powered to detect 10% absolute difference in clinical pregnancy rate **Quality assessment:**

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Purified Menotropin versus Recom-binant Follicle-Stimulating Hormone, 2002 **#1070**	United Kingdom **Study dates:** May 1966 – Nov 2000 **Size of population:** 727 **Number of cycles analyzed:** 727 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Compare the efficacy of highly purified menotropin (Menopur) and rFSH in IVF/ICSI cycle	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: - Menopur 11.0 - rFSH 13.6 Endometriosis: - Menopur 2.3 - rFSH 2.4 Male factor: - Menopur 67.3 - rFSH 65.8 Unilateral tubal factor: - Menopur 3.8 - rFSH 2.7 Bilateral tubal factor: - Menopur 13.4 - rFSH 14.1 **Inclusion criteria:** - Infertility > 1 yr (except those with bilateral tubal occlusion and/or male factor infertility) - Eligible for IVF/ICSI - Minimum of 1 menstrual cycle w/o treatment with fertility modifiers prior to prestudy exam - Age 18-38 - Regular menstrual cycle 24d-35d - No evidence of ovarian anomalies on u/s - Normal uterus - Normal baseline parameters for hematology/blood chemistry, and urinalysis within the last 12 mos - Baseline endocrine values all within the last 12 mos **Exclusion criteria:**	Clinical pregnancy: + fetal cardiac activity 4 wks after egg retrieval Ongoing pregnancy rate: Confirm clinical pregnancy at 10 wks after egg retrieval Live birth: NR Multiples: Yes Complications: OHSS	rFSH 78 276 354 176 551 727 Lower 95% CI / Upper 95 % CI **Rel risk** 1.19 0.92 1.55 2) Ongoing pregnancy rate: Preg + / Preg - HP-hMG 87 286 373 rFSH 73 281 354 160 567 727 Lower 95% CI / Upper 95 % CI **Rel risk** 1.13 0.86 1.49 3) Multiple gestation: Multiple / Single HP-hMG 30 65 95 rFSH 27 49 76 57 114 171 Lower 95% CI / Upper 95 % CI **Rel risk** 0.89 0.58 1.36 4) OHSS rates similar (1.9% HP-HPG, 1.2% rFSH)	Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		- Presence of a clinically relevant systemic disease, endocrinologic disorder, or ovarian cysts prior to IVF/ICSI procedures - Contraindication to gonadotropins or GnRH antagonist - More than 3 previously unsuccessful IVF/ICSI cycles - BMI <18 or >29 - Smoking: 10 cigarettes per day - History of alcohol abuse and/or other drugs - Currently breast feeding, pregnant, or contraindication to pregnancy - Diagnosis as a poor responder in gonadotropin-stimulated procedures - History of OHSS type III during previous ART treatment - Participation in any study within the last 30d			
European and Middle East Orgalutran Study Group, 2001 **#5570**	**Geographical location:** Multicenter; countries include Austria, Egypt, France, Germany, Israel, Jordan, Spain, Switzerland, The Netherlands **Study dates:** NR	**Age:** Mean (SD): 29.9 Ganirelix 29.8 (4.3) Triptorelin 30.2 (4.2) Range: 18-39 **Race/ethnicity (n [%]):** Caucasian 97.9 **Diagnoses (n [%]):**	**Definition(s) of outcome(s):** Ongoing pregnancy: Pregnancy confirm by u/s at 12-16 wks after embryo transfer Live birth: NR	1) Ongoing pregnancy rate: Preg + / Preg - Ganirelix: **70** / **156** — 226 Triptorelin: **37** / **74** — 111 107 / 230 — 337 Lower 95% CI; Upper 95 % CI	**Comments:** None **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results				Comments/Quality Scoring
	Size of population: 355 **Number of cycles analyzed:** 355 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Compared the clinical outcome between using GnRH antagonist ganirelix and GnRH agonist long protocol	Male factor: - Ganirelix: 60.2 - Triptorelin: 63.1 Tubal factor: - Ganirelix: 17.7 - Triptorelin: 16.2 **Inclusion criteria:** - Female - Age > 18 and < 39 - BMI 18-29 - Regular cycle - Willing to give written consent **Exclusion criteria:** NR	Multiples: NR Complications: NR	**Rel risk**	0.93	0.67	1.29	
European rhCG Study Group, 2000 **#58150**	**Geographical location:** Multicenter in France, Germany, Israel, Italy, the Netherlands, Sweden, UK **Study dates:** Feb 1995-Oct 1996 **Size of population (no. of patients):** 190 **Number of cycles analyzed:** 190 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** GnRH down regulation, rFSH hyperstimulation, with either (a) 5000 IU uhCG + placebo or (b) 5000 IU rhCG + placebo for ovarian maturation	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 54 (28%) Endometriosis: 15 (8%) Male factor: 62 (33%) Tubal factor: 79 (42%) **Inclusion criteria:** - Candidate for IVF/ICSI - Regular cycles - Normal semen analysis **Exclusion criteria:** - Systemic disease - PCOS - History of OHSS - History of poor response to COH - > 3 previous attempts - Any treatment in past 2 months	**Definition(s) of outcome(s):** Pregnancy: Clinical pregnancy not defined Live birth: NR Multiples: NR Complications: Injection site AEs	1) Clinical pregnancy: Preg + / Preg - / Total rhCG: **32** / **65** / 97 uhCG: **23** / **70** / 93 Total: 55 / 135 / 190 Value / Lower 95% CI / Upper 95% CI **Rel risk**: 1.33 / 0.85 / 2.10 2) Live birth: Birth + / BIrtht - / Total rhCG: **26** / **71** / 97 uhCG: **21** / **72** / 93 Total: 47 / 143 / 190 Value / Lower 95% CI / Upper 95% CI **Rel risk**: 1.19 / 0.72 / 1.96 3) Injection site AEs significantly less common with rhCG (0.24; 95% CI 0.11, 0.52)			**Comments:** None **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
European rLH Study Group, 2001 **#5030**	**Geographical location:** 22 centers in 9 European countries **Study dates:** NR **Size of population (no. of patients):** 250 **Number of cycles analyzed:** NR **Number of cycles per patient:** Could not calculate **Study type:** RCT **Interventions:** rhLH: 5,000, 15,000, 30,000, or 15,000 + 10,000 IU (second injection administered 3 days after the first injection u-hCG: 5,000 IU	**Age:** Mean (SD): 31.8 (3.6) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 39 [15.6%] Male factor: 45 [18.0%] Tubal factor: 152 [60.8%] **Inclusion criteria:** Premenopausal women between 18 and 39 yr old; BMI ≤ 32; menstrual cycle lasting between 21 and 35 days; FSH ≤12 IU/L, PRL ≤1040 mIU/L, TSH 0.3–4.1 mIU/L; normal results in pretreatment hematology, clinical chemistry, or urinalysis parameters. Causes of infertility could include at least one of the following: tubal factor, mild endometriosis (American Fertility Society classification stage I or II), unexplained (with a history of at least 3 yr of infertility, and a postcoital test showing at least one forward progressive sperm per high power field), male factor (based on the investigator's judgment, but only if an oocyte fertilization rate of more than 50% had been observed during a previous IVF attempt after regular insemination, or if	**Definition(s) of outcome(s):** Pregnancy: Pregnancy and clinical pregnancy, but not specifically defined. Live birth: Yes Complications: Minor, major AEs; OHSS, defined as at least one of the following clinical symptoms—abdominal distension, abdominal pain, nausea, vomiting, diarrhea or dyspnea lasting for at least 3 days after rhLH or u-hCG injection; diameter of the ovaries (maximum of the left and right ovaries) on days rhLH or u-hCG 6 and 7 greater than 5 cm; and ascites on days rhLH or u-hCG 6 and 7. In addition, the E2 level measured on the day of rhLH or u-hCG injection was used as a predictive factor: in each treatment group, patients were classified based on an E2 cut-off value of 3000 pg/mL as well as on the number of follicles observed just before administration of rhLH or u-hCG, with a cut-off value of 20 follicles.	1) Pregnancy: Preg + / Preg - / Total rhLH: **24** / **105** / 129 u-hCG: **31** / **90** / 121 Total: 55 / 195 / 250 Value (Lower 95% CI, Upper 95% CI) **Rel risk** 0.73 (0.45, 1.16) 2) Clinical pregnancy: Clin preg + / Clin preg - / Total rhLH: **18** / **111** / 129 u-hCG: **23** / **98** / 121 Total: 41 / 209 / 250 Value (Lower 95% CI, Upper 95% CI) **Rel risk** 0.73 (0.42, 1.29) 3) Live birth: Live birth + / Live birth - / Total rhLH: **14** / **115** / 129 u-hCG: **16** / **105** / 121 Total: 30 / 220 / 250 Value (Lower 95% CI, Upper 95% CI) **Rel risk** 0.82 (0.42, 1.61) 4) Adverse events Non-serious: no statistically significant differences Serious: "A total of 12 serious adverse events (3.6%) were recorded after rhLH or u-hCG administration in 10 patients (4.0%). Four of these serious adverse events occurred in the u-hCG treatment group: one patient was	**Comments:** None **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		donor sperm was used), severe male factor (based on the investigator's judgment, but only if intracytoplasmic sperm injection was performed). Patients had to have both ovaries and have undergone no more than three previous assisted reproductive technology cycles, and have had no treatment with clomiphene citrate or gonadotropins for at least 1 month before screening, and a normal uterine cavity confirmed by hysteroscopy, or hysterosalpingography or a US scan performed within the past 5 yr. **Exclusion criteria:** NR		hospitalized for back pain, one for abdominal distension (OHSS), one to evacuate the remaining products of a missed abortion 6 weeks after u-hCG administration, and one for ectopic pregnancy. Six patients treated with rhLH experienced serious adverse events: one experienced retention of the fetal placenta (5,000 IU rhLH), one had abdominal pain (30,000 IU rhLH), one had abdominal pain and suspected ovarian torsion (15,000 1 10,000 IU rhLH), two patients were hospitalized for diarrhea (15,000 + 10,000 IU rhLH), and one patient had preeclampsia (15,000 + 10,000 IU rhLH). The most frequent nonserious adverse events reported after rhLH or u-hCG injection were abdominal enlargement (29 cases), abdominal pain (19 cases), injection site pain (14 cases), diarrhea (10 cases) and nausea (7 cases)." OHSS: "The proportion of patients presenting with moderate OHSS, independent of the number of follicles or E2 level was highly statistically related to treatment received (exact P = 0.0004, Cohchran-Armitage trend test), with the higher incidence in patients treated with 15,000 + 10,000 IU rhLH (12.0%) or 5,000 IU u-hCG (12.4%). In addition, the proportion of patients who did not present any of the three criteria for moderate OHSS was higher for the lower doses of rhLH than for the 15,000110,000 IU rhLH or 5,000 IU u-hCG treatments (48.7%, 28.2%, 23.1%, 20.0%, and 17.4%, respectively, for rhLH 5,000 IU, 15,000 IU, 30,000 IU, or 15,000110,000 IU rhLH and 5,000 IU u-hCG; exact p = 0.0003, Cochran-Armitage trend test)." Note: OHSS by treatment group not reported.	
Fabregues, Creus, Penarrubia, et al., 2006 **#58160**	**Geographical location:** Barcelona, Spain **Study dates:** Nov 2003-Sep 2004 **Size of population (no.**	**Age:** Mean (SD): rFSH + rLH: 38.4 (1.4) rFSH: 38.2 (1.5) **Race/ethnicity (n [%]):** NR	**Definition(s) of outcome(s):** Pregnancy: Gestational sac on ultrasound Live birth: NR	1) Clinical pregnancy: Preg + / Preg - / Total rFSH + rLH: **24** / **36** / 60 rFSH: **25** / **35** / 60	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	of patients): 120 **Number of cycles analyzed:** 120 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Long protocol GnRH agonist, randomized to rFSH alone vs. rFSH + rLH beginning on day 6 of FSH	**Diagnoses (n [%]):** Unexplained infertility: 23 (19%) Endometriosis: 15 (12%) Male factor: 53 (45%) Tubal factor: 29 (24%) **Inclusion criteria:** - 1st cycle IVF/ICSI - Age ≥ 35 - BMI 19-29 - Regular cycles - Day 2-3 FSH < 12 - Hormonal therapy in previous 6 months **Exclusion criteria:** NR	Multiples: NR Complications: NR	Total 49 71 120 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.96 0.62 1.48	Adequacy of randomization concealment: +
Fabregues, Penarrubia, Creus, et al., 2005 **#10170**	**Geographical location:** Barcelona, Spain **Study dates:** Sep 2002 - June 2003 **Size of population (no. of patients):** 150 **Number of cycles analyzed:** 150 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** Group 1 (n = 75) pituitary desensitization was achieved by SC administration of triptorelin acetate (Decapeptyl 0.1 mg; Ipsen Pharma, Barcelona, Spain) (0.1	**Age:** Mean (SEM): Reduced dose: 35.0 (0.3) Constant dose: 34.7 (0.5) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 19 (14%) Endometriosis: 26 (19%) Male factor: 57 (42%) Tubal factor: 35 (26%) **Inclusion criteria:** Regularly menstruating (menstrual cycles of 26–33 days) premenopausal, aged 26–40 years, body mass index (BMI) of 19.5–28.0 kg/m2, normal ovaries, no previous ovarian surgery, and no occult ovarian failure on the basis of their cycle day	**Definition(s) of outcome(s):** Pregnancy: Increasing serum concentrations of β-hCG after embryo transfer, and the subsequent demonstration of an intrauterine gestational sac by ultrasonography. Live birth: NR Multiples: Yes (twins) Complications: Miscarriage	1) Pregnancy: Preg + / Preg - Reduced dose: **28** / **41** — 69 Constant dose: **27** / **41** — 68 55 82 137 Lower 95% CI / Upper 95 % CI **Rel risk** 1.02 0.68 1.54 2) Twins: Twins + / Twins - Reduced dose: **2** / **67** — 69 Constant dose: **3** / **65** — 68 5 132 137 Lower 95% CI / Upper 95 % CI **Rel risk** 0.66 0.11 3.81	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	mg/d) started in the midluteal phase of the previous cycle and continued until the administration of hCG. Group 2 (n = 75 patients) the standard daily dose of triptorelin acetate was reduced to 0.05 mg once the ovarian arrest was confirmed and stimulation with recombinant FSH was commenced	2–3 FSH concentration of <12 IU/L (range 3.8–11 IU/L) (standard International Reference Preparation [IRP] 78/549) measured in the cycle preceding IVF/ICSI. No hormone therapy for at least 6 months preceding the study. **Exclusion criteria:** NR		3) Miscarriage: SAb + / SAb - Reduced dose: **2** / **67** (69) Constant dose: **3** / **65** (68) 5 / 132 (137) Rel risk 0.66 (Lower 95% CI 0.11; Upper 95 % CI 3.81)	
Fatemi, Kolibianakis, Camus, et al., 2006 **#51850**	**Geographical location:** Brussels, Belgium **Study dates:** Oct 2004-Oct 2005 **Size of population (no. of patients):** 201 **Number of cycles analyzed:** 201 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** GnRH antagonist/rFSH COH, randomized to (a) 600 mg vaginal progesterone only, beginning 1 day after oocyte retrieval, until 7 weeks, vs (b) 600 mg progesterone + 4 mg/day E2 valerate over same time	**Age:** Mean (SD): P only: 32.1 (3.7); P + E2: 32.0 (3.6) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 13% Endometriosis: 4% Male factor: 62% Tubal factor: 20% **Inclusion criteria:** - ≤39 years - BMI between 18 and 29 kg/m2 - presence of both ovaries - basal levels of E2 (≤80 pg/ml), progesterone (≤1.6 ng/ml), FSH levels <10 IU/l at initiation of stimulation - fewer than three prior cycles (agonist or antagonist cycles)	**Definition(s) of outcome(s):** Pregnancy: Pregnancy beyond 12 weeks Live birth: NR Multiples: NR Complications: Early pregnancy loss - + hCG without development to 12 weeks	1) Clinical pregnancy: Preg + / Preg - P + E2: **30** / **71** (101) Prog only: **26** / **74** (100) 56 / 145 (201) Rel risk 1.14 (Lower 95% CI 0.73; Upper 95 % CI 1.79) 2) Early pregnancy loss: Loss + / Loss - P + E2: **9** / **30** (39) Prog only: **8** / **26** (34) 17 / 56 (73) Rel risk 0.98 (Lower 95% CI 0.43; Upper 95 % CI 2.26)	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		Exclusion criteria: - PCOS - >Stage 2 endometriosis - need for testicular sperm extraction - PGD			
Fluker, Grifo, Leader, et al., 2001 **#65000**	**Geographical location:** Multicenter in New York, Georgia, New Jersey, Illinois, USA; British Columbia and Ontario, Canada **Study dates:** NR **Size of population (no. of patients):** 313 **Number of cycles analyzed:** 313 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** GnRH agonist (leuprolide) vs GnRH antagonist (cetrorelix)	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 51 (17%) Endometriosis: 42 (13%) Male factor: 42 (13%) Tubal factor: 84 (27%) Combined/other: 78 (25%) **Inclusion criteria:** - Age 18-39 - Regular menses 24-35 days - BMI ≥ 18 and ≤ 29 kg/m^2 - For patients who had IVF without ICSI, partner or donor had to have normal semen characteristics according to WHO criteria (≥ 20 million/mL, > 50% motile, and ≥ 30% with normal morphology) or Kruger's criteria (> 4% with normal morphology) **Exclusion criteria:** Any clinically relevant hormone values outside the reference range during the early follicular phase (menstrual cycle day 2-7); specifically, FSH levels ≥ 10 IU/L or LH levels ≥ 10	**Definition(s) of outcome(s):** Pregnancy: Ultrasound at 6 weeks (clinical) and 12 weeks (ongoing) Live birth: NR Multiples: NR Complications: OHSS	1) Clinical pregnancy (all randomized): Preg + / Preg - / Total Antag: **70** / **138** / 208 Agonist: **38** / **67** / 105 Total: 108 / 205 / 313 Value (Lower 95% CI, Upper 95% CI) **Rel risk** 0.93 (0.68, 1.28) 2) Ongoing pregnancy (all randomized): Preg + / Preg - / Total Antag: **61** / **147** / 208 Agonist: **36** / **69** / 105 Total: 97 / 216 / 313 Value (Lower 95% CI, Upper 95% CI) **Rel risk** 0.86 (0.61, 1.20) 3) OHSS (all treated): Preg + / Preg - / Total Antag: **12** / **187** / 199 Agonist: **2** / **97** / 99 Total: 14 / 284 / 298 Value (Lower 95% CI, Upper 95% CI) **Rel risk** 2.98 (0.68, 13.08) 4) Lower FSH requirement with antagonist	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		IU/L			
Foong, Fleetham, O'Keane, et al., 2006 **#51940**	**Geographical location:** Toronto and Calgary, Canada **Study dates:** 1997-2001 **Size of population (no. of patients):** 60 **Number of cycles analyzed:** 60 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** IVF vs ICSI	**Age:** Mean (SD): IVF: 33.0 (3.6); ICSI: 33.7 (2.1) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 100% **Inclusion criteria:** - Unexplained infertility -female age 18–40 years, regular ovulatory menstrual cycles, - day #3 E2<200 pmol/L, - FSH<15 IU/L - LH < 8 IU/L, normal thyroid stimulating hormone, ≥3 previous intrauterine insemination (IUI) cycles with clomiphene citrate or gonadotropins, normal uterine cavity, fallopian tubes and presence of both ovaries, normal ultrasound (US), and previous laparoscopy excluding stage III or IV endometriosis. All male partners had a normal semen analysis by WHO criteria **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: + FHR on ultrasound at 7 weeks Live birth: Yes Multiples: NR Complications: NR	1) Clinical pregnancy: Preg + / Preg - / Total ICSI: 15 / 15 / 30 IVF: 15 / 15 / 30 30 / 30 / 60 Rel risk: 1.00 (Lower 95% CI 0.60; Upper 95 % CI 1.66) 2) Live birth: Preg + / Preg - / Total ICSI: **15** / **15** / 30 IVF: **14** / **16** / 30 29 / 31 / 60 Rel risk: 1.07 (Lower 95% CI 0.63; Upper 95 % CI 1.81)	**Comments:** None **Quality assessment:** Randomization method: - Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -
Friedler, Schachter,	**Geographical location:** Tel Aviv, Israel	**Age:** Mean (SD):	**Definition(s) of outcome(s):**	1) Clinical pregnancy:	**Comments:** Study stopped after unplanned

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Strass-burger, et al., 2007 **#71050**	**Study dates:** June 2004-Nov 2006 **Size of population (no. of patients):** 101 **Number of cycles analyzed:** 101 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** All undergoing ICSI; embryo transfer with either hyaluronic acid enriched medium (EmbryoGlue®) or [human tubal fluid (HTF) medium with gentamicyn enriched with 20% serum substitute supplement, with no hyaluronic acid	Standard media: 31.7 (5.6) EmbryoGlue: 33.1 (5.1) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Age < 43 years - Failed to achieve an ongoing pregnancy after > 4 previous embryo transfers, during which 2-4 embryos were transferred each time, including at least one embryo with optimal cleavage rate and morphology (four cells on day 2 or eight cells on day 3, equal-sized blastomeres and 50% fragmentation) **Exclusion criteria:** - Any systemic disease - Body mass > 29 kg/m^2 - Uterine malformation - Evidence of low ovarian response in previous treatment cycles with < 4 oocytes retrieved - Elevated baseline (day 3) FSH (> 12 IU/l) - Ultrasonographic evidence of hydrosalpinx - Participation in any other clinical study	Pregnancy: Gestational sac on ultrasound Live birth: NR Multiples: NR Complications: NR	Preg + / Preg - / Total Hyaluronic acid: **18** / **33** / 51 No HA: **5** / **45** / 50 Total: 23 / 78 / 101 Value / Lower 95% CI / Upper 95% CI **Rel risk**: 3.53 / 1.42 / 8.78 2) Ongoing pregnancy: Preg + / Preg - / Total Hyaluronic acid: **16** / **25** / 41 No HA: **2** / **48** / 50 Total: 18 / 73 / 91 Value / Lower 95% CI / Upper 95% CI **Rel risk**: 9.76 / 2.38 / 39.99	interim analysis – original sample size = 224 **Quality assessment:** Randomization method:+ Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -
Frydman, Howles, and Truong, 2000	**Geographical location:** France **Study dates:** Dec 1995 – Dec 1996	**Age:** Grp 1 Mean (SD): 31.4 (3.5) Grp 2: Mean (SD): 31.2 (4.0)	**Definition(s) of outcome(s):** Pregnancy: Ongoing	1) Ongoing pregnancy rate: Preg + / Preg - / Total u-HFSH: **25** / **114** / 139	**Comments:** - 3 subjects included that had exclusion criteria: 1 age 39, 1 with > 3 previous attempts, and 1 with BMI > 30

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#8600	**Size of population:** Grp 1: 139 Grp 2: 139 **Number of cycles analyzed:** 278 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Grp 1: recombinant FSH for IVF/ICSI Grp 2: urinary FSH for IVF/ICSI	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Grp 1: Unexplained infertility: 12 (8.6) Endometriosis: 2 (1.4) Male factor: 52 (37.4) Tubal factor: 60 (43.2) Grp 2: Unexplained infertility: 10 (7.2) Endometriosis: 2 (1.4) Male factor: 70 (50.4) Tubal factor: 39 (28.1) **Inclusion criteria:** - Age 18-38 - Regular cycles 25-35 d - Normal FSH, LH, PRL, T, and < 10 follicles per ovary - 2 ovaries - Normal uterus - No more than 3 previous ART attempts - No treatment with fertility drugs in last month **Exclusion criteria:** - Clinically significant systemic disease - BMI > 30 - History of severe OHSS - History of poor response to gonadotropins - Male with azoospermia or leukospermia	Live birth: Yes Multiples: Yes Complications: OHSS, SAB Primary endpoint: # of oocytes per treatment	r-FSH: **25** / **114** / 139 Total: 50 / 228 / 278 Rel risk (Value / Lower 95% CI / Upper 95% CI): 1.00 / 0.61 / 1.65 2) Liveborn: Live birth + / Live birth - / Total u-hFSH-HP: 35 / **104** / 139 r-hFSH: **36** / **103** / 139 Total: 71 / 207 / 278 Rel risk (Value / Lower 95% CI / Upper 95% CI): 0.97 / 0.65 / 1.45 4) Incidence of OHSS: Grp 1: 7 (5%) Grp 2: 3 (2.2%) 5) SAB rate: Grp 1: 8 (5.7%) Grp 2: 11 (7.9%)	- Underpowered to detect differences in adverse events **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +
Frydman, Madoux, Hesters, et al., 2006	**Geographical location:** Clarmart, France **Study dates:** NR	**Age:** Mean (SD): Control: 38.5; assisted hatching 39.0	**Definition(s) of outcome(s):** Pregnancy: Not defined	1) Clinical pregnancy: Preg + / Preg - Assisted: **17** / **32** / 49	**Comments:** None **Quality assessment:**

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		Range: 37.0-42.3		hatching Control Rel risk 2) Live birth: Assisted hatching Control Rel risk	Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +
#52000	**Size of population (no. of patients):** 103 **Number of cycles analyzed:** 103 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Randomized to (a) no extra treatment of (b) assisted hatching with laser immediately prior to transfer	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 9% Endometriosis: 17% Male factor: 43% Tubal factor: 31% **Inclusion criteria:** (i) ≥37 years of age; (ii) < 3 previous IVF-embryo transfer attempts and (iii) having reached embryo transfer process **Exclusion criteria:** NR	Live birth: Yes Multiples: NR Complications: NR	Pregnancy rate: Preg + / Preg - Prog + hCG: **21** / **33** / 54 Prog: 38 / 65 / 103 Lower 95% CI / Upper 95 % CI Rel risk: 0.89 / 0.54 / 1.48 Birth + / Birth - Assisted hatching: **11** / **38** / 49 Control: **16** / **38** / 54 27 / 76 / 103 Lower 95% CI / Upper 95 % CI Rel risk: 0.76 / 0.39 / 1.47	
Fujimoto, Osuga, Fujiwara, et al., 2002 **#230**	**Geographical location:** Tokyo and Saitama, Japan **Study dates:** 1/1998 - 12/2000 **Size of population:** 114 **Number of cycles analyzed:** 114 **Number of cycles per patient:** 1.00 **Study type:** RCT	**Age:** Mean (SD): P4: 35.2 (0.5) P4+hCG: 35.3 (0.5) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** h/o failed IVF and had luteal phase E2 less than 100 pg/ml **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: + gestational sac on U/S 21d after ET Live birth: NR Multiples: NR Complications: OHSS	1) Pregnancy rate: Preg + / Preg - Prog + hCG: 20 / 43 / 63 Prog: 7 / 44 / 51 27 / 87 / 114 Lower 95% CI / Upper 95 % CI Rel risk: 2.31 / 1.06 / 5.03 2) 2 pts in P4+ hCG grp have OHHS	**Comments:** Randomization method not stated **Quality assessment:** Randomization method:- Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Interventions: Pts who failed 1st cycle of IVF and had luteal phase E2 less than 100 pg/ml were randomized to the study. Luteal support with 25 mg of IM progesterone vs. 20 mg of IM progesterone and 3000 IU of hCG on day 1, 4, 7 after ET				

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Garcia-Velasco, Isaza, Requena, et al., 2000 **#6630**	**Geographical location:** Madrid, Spain **Study dates:** Nov 1, 1998 to Feb 28, 2000 **Size of population (no. of patients):** 70 **Number of cycles analyzed:** 70 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** Non-stop protocol: Long GnRHa suppression with high doses of gonadotrophins. On days 1 and 2 of ovarian stimulation, three ampoules of HMG were administered together with five ampoules of FSH. On days 3, 4 and 5 of ovarian stimulation, two ampoules of HMG and three ampoules of FSH were administered. From day 6 onward, gonadotrophin dosage was estimated according to serum estradiol concentrations and transvaginal ovarian ultrasound scans. Stop protocol: GnRHa administration is stopped with the onset of menses, while gonadotrophin doses remained similar	**Age:** Mean (SD): 34.2 (0.6) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 15 (21.4%) Male factor: 26 (37.1%) Tubal factor: 8 (11.4%) Other – combination male and female factors: 21 (30%) **Inclusion criteria:** At least one previous cancelled IVF attempt I which fewer than three follicles ≥ 18mm in diameter were obtained and basal FSH concentrations were < 12 IU/ml. **Exclusion criteria:** None	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Pregnancy: Preg + / Preg - Stop with menses: **5** / **31** — 36 Constant dose: **6** / **28** — 34 11 / 59 — 70 Rel risk 0.79 (Lower 95% CI 0.26; Upper 95 % CI 2.34)	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	to the non-stop protocol				
Gardner, Surrey, Minjarez, et al., 2004 **#13610**	**Geographical location:** Englewood, CO **Study dates:** NR; 24-mo period **Size of population:** Grp 1: 23 Grp 2: 25 **Number of cycles analyzed:** 48 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Grp 1: transfer of 1 blastocyst during IVF/ICSI Grp 2: transfer of 2 blastocyst during IVF/ICSI	**Age:** Grp 1: Mean (SEM): 33.5 (0.9) Range: 26-43 Grp 2: Mean (SEM): 34.2 (0.7) Range: 29-41 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Day 3 FSH < 10 - Day 3 estradiol < 80 - At least 10 follicles > 12 mm on day of hCG **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Cardiac activity on USD at least 4.5 wks after ET Live birth: NR Multiples: Yes Complications: NR	1) Pregnancy rate: Preg + / Preg - / Total 1 blasto-cyst: 14 / **9** / 23 2 blasto-cysts: **19** / **6** / 25 Total: 33 / 15 / 48 Rel risk: Value 0.80; Lower 95% CI 0.54; Upper 95% CI 1.19 2) Multiples: 0 in single blastocyst, 9/19 in double	**Comments:** - No information on diagnoses or previous IVF attempts - Two blastocyst group had greater number of oocytes retrieved, fewer **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: - (NR)
Geber, Moreira, de Paula, et al., 2007 **#52040**	**Geographical location:** Belo Horizonte, Brazil **Study dates:** Jan-Dec 2001 **Size of population (no. of patients):** 244 **Number of cycles analyzed:** 244 **Number of cycles per patient:** 1.0	**Age:** Mean (SD): Capsules: 34.8 (5.6) Gel: 34.5 (5.1) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 90 (40.6%) Male factor: 106 (43.4%) Tubal factor: 39 (16.0%) **Inclusion criteria:**	**Definition(s) of outcome(s):** Pregnancy: + FHR 4 weeks after transfer Ongoing pregnancy: 20 weeks Live birth: NR Multiples: NR Complications: Early pregnancy loss	1) Pregnancy: Preg + / Preg - Gel: **54** / **68** / 122 Capsule: **44** / **78** / 122 98 / 146 / 244 Rel risk: 1.23; Lower 95% CI 0.90; Upper 95 % CI 1.67 2) Early pregnancy loss: Loss + / Loss -	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Study type: RCT **Interventions:** Randomized to vaginal progesterone after fertilization confirmed, continued for 13 days or 12 weeks gestation(a) 200 mg micronized P capsules 3x/day, or (b) micronized P in gel once daily	Day 3 FSH < 15 IU/L **Exclusion criteria:** NR		Gel 8 46 54 Capsule 7 37 44 15 83 98 Rel risk 0.93 (Lower 95% CI 0.37, Upper 95 % CI 2.37) 3) Ongoing pregnancy: Preg + / Preg - Gel **46** **76** 122 Capsule **37** **85** 122 83 161 244 Rel risk 1.24 (Lower 95% CI 0.87, Upper 95 % CI 1.77)	
Gokmen, Ugur, Ekin, et al., 2001 **#5190**	**Geographical location:** Ankara, Turkey **Study dates:** 1/1998 - 8/1998 **Size of population:** 250 (168 analyzed) **Number of cycles analyzed:** 168 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** The study compared the prophylaxis usage of Intravenous albumin vs. hydroxyethyl starch for the prevention of OHHS	**Age:** Mean (SD): Albumin: 29.6 (2.8) HES: 31.2 (3.7) Control: 32.3 (2.9) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** estradiol > 300 pg/ml or >20 follicles (>14 mm) on the day of hCG administration **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: OHHS (diagnosed using Schenker and Weinstein criteria)	1) Pregnancy rate, HES vs. control: Out + / Out - / Total HES **12** **73** 85 Control **10** **73** 83 Total 22 146 168 Value (Lower 95% CI, Upper 95% CI) Rel risk 1.17 (0.54, 2.56) 2) Pregnancy rate, HES vs. albumin: Out + / Out - / Total HES **12** **73** 85 Albumin **11** **72** 82 Total 23 145 168 Value (Lower 95% CI, Upper 95% CI) Rel risk 1.07 (0.50, 2.28) 3) Pregnancy rate, albumin vs. control:	**Comments:** Sample size/analysis not corrected for multiple comparisons **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

The pt received either albumin, hydroxyethyl starch (HES), or did not receive anything (served as control) on the oocyte retrieval date.

	Out +	Out -	Total
Albumin	**11**	**72**	82
Control	**10**	**73**	83
Total	21	145	166

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.10	0.49	2.45

4) Moderate OHHS, albumin vs. control:

	Preg +	Preg -	
Albumin	4	81	85
Control	12	71	83
	16	152	168

		Lower 95% CI	Upper 95 % CI
Rel risk	0.33	0.11	0.97

5) Moderate OHHS, HES vs. control:

	Out +	Out -	Total
HES	**5**	**78**	85
Control	**12**	**71**	83
Total	17	149	166

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.42	0.15	1.13

6) Moderate OHHS, HES vs. albumin:

	Out +	Out -	Total
HES	**5**	**78**	85
albumin	**4**	**78**	82
Total	9	156	165

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.23	0.34	4.44

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

7) Severe OHHS, HES vs. albumin:

	Out +	Out -	Total
HES	**0.5**	**85**	85
Albumin	**0.5**	**82**	82
Total	1	167	168

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.96	0.02	48.07

8) Severe OHHS, HES vs. control:

	Out +	Out -	Total
HES	**0.5**	**78**	85
Control	**4**	**79**	83
Total	4.5	157	161.5

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.13	0.01	2.46

9) Severe OHHS, albumin vs. control:

	Out +	Out -	Total
Albumin	**0.5**	**82**	82
Control	**4**	**79**	83
Total	4.5	161	165.5

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.13	0.01	2.34

10) Overall OHHS rate, HES vs. albumin:

	Out +	Out -	Total
HES	**5**	**78**	85
Albumin	**4**	**78**	82
Total	9	156	165

	Value	Lower 95% CI	Upper 95%

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

			CI
Rel risk	1.23	0.34	4.44

11) Overall OHHS rate, HES vs. control:

	Out +	Out -	Total
HES	**5**	**85**	85
Control	**16**	**67**	83
Total	21	152	173

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.29	0.11	0.75

12) Overall OHHS rate, albumin vs. control:

	Out +	Out -	Total
Albumin	**4**	**78**	82
Control	**16**	**67**	83
Total	20	145	165

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.25	0.09	0.72

Gomez-Palomares, Acevedo-Martin, Andres, et al., 2005

#39220

Geographical location: Madrid, Spain

Study dates: NR

Size of population:
Grp 1: HMG 58
Grp 2: rLH 36

Number of cycles analyzed: 94

Number of cycles per patient: 1.00

Age:
Mean (SD):
Grp 1: 39 [0.7]
Grp 2: 38.8 [1.5]

Race/ethnicity (n [%]):
NR

Diagnoses (n [%]):
Grp 1
Unexplained infertility: NR
Endometriosis: 4 [6.9]
Male factor: 23 [39.7]
Tubal factor: 15 [25.9]
PCOS: 0
Insemination failure: 16

Definition(s) of outcome(s):

Pregnancy: clinical – positive fetal heart beat

Live birth: NR

Multiples: NR

Complications: SAB rate

1) Clinical pg rate grp 1 vs 2:

	pg pos	Pg neg	Total
HMG	**12**	**46**	58
rLH	**16**	**20**	36
Total	28	66	94

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.47	0.25	0.87

2) SAB rate:

	SAB	No SAB	Total
Grp 1	**2**	**12**	14
Grp 2	**2**	**14**	16

Comments:
- Secondary change in enrollment led to differences in numbers in 2 grps
- Randomization not clearly described-inequality between groups quite large

Quality assessment:
Randomization method: +
Blinding: no
Dropout rate < 20%: NR
Adequacy of randomization concealment: no

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Study type: RCT **Interventions:** Compare the usage of rFSH+hMG vs. rFSH+LH for the first 5 days of controlled ovarian stimulation in women older than 38 yo. Both grps received only rFSH after 5 days of combined therapy Treatment detailed Control: rFSH 225 IU + 150 IU of hMH (equal to 75 IU of FSH and 75 IU of LH) Study grp: rFSH 300 IU + 75 IU of rLH This is a GnRH agonist long protocol.	[27.6] Grp 2 Unexplained infertility: NR Endometriosis: 3 [8.3] Male factor: 14 [38.9] Tubal factor: 11 [30.6] PCOS: 0 Insemination failure: 8 [22.2] **Inclusion criteria:** Age 38-40 Nl basal FSH, LH, E2. Regular cycle 25-32 d. BMI 19-25 **Exclusion criteria:** NR		Total 4 26 30 Value / Lower 95% CI / Upper 95% CI **Rel risk** 1.14 0.18 7.08	
Gordon, Harrison, Fawzy, et al., 2001 **#58250**	**Geographical location:** Dublin, Ireland **Study dates:** NR **Size of population (no. of patients):** 128 **Number of cycles analyzed:** 128 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** 4 different gonadotropin regimens with varying levels of LH:	**Age:** Mean: 32.5 Range: 31-36 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 65 (51%) Endometriosis: 21 (16%) Tubal factor: 36 (28%) Other: Anovulation: 6 (5%) **Inclusion criteria:** - Age 20-39 - Weight 80-130% ideal body weight - Normal cycles	**Definition(s) of outcome(s):** Pregnancy: Gestational sac on ultrasound at 7 weeks Live birth: Yes Multiples: NR Complications: NR	1) Pregnancy, rFSH alone vs. uFSH: Preg + / Preg - / Total uFSH **4** **26** 30 rFSH **11** **28** 39 Total 15 54 69 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.47 0.17 1.34 2) Pregnancy, rFSH alone vs. FSH + 25 IU LH: Preg + / Preg - / Total rFSH + 25 IU LH **8** **22** 30 rFSH **11** **28** 39 Total 19 50 69	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

a) rFSH alone
b) uFSH (< 1 IU LH)
c) hMG with 25 IU LH
d) hMG with 75 IU LH

All FSH doses 75 IU

- 2 year history of infertility
- 1st IVF cycle

Exclusion criteria:
- PCOS
- Male factor

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.95	0.43	2.06

3) Pregnancy, rFSH alone vs. FSH + 75 IU LH:

	Preg +	Preg -	Total
rFSH + 75 IU LH	**11**	**18**	29
rFSH	**11**	**28**	39
Total	22	46	68

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.34	0.68	2.66

4) Live birth, rFSH alone vs. uFSH:

	Preg +	Preg -	Total
uFSH	**2**	**28**	30
rFSH	**9**	**30**	39
Total	11	58	69

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.29	0.07	1.24

5) Live birth, rFSH alone vs. FSH + 25 IU LH:

	Preg +	Preg -	Total
rFSH + 25 IU LH	**6**	**24**	30
rFSH	**9**	**30**	39
Total	15	54	69

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.87	0.35	2.17

6) Live birth, rFSH alone vs. FSH + 75 IU LH:

	Preg +	Preg -	Total
rFSH + 75 IU LH	**9**	**21**	30
rFSH	**9**	**30**	39

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Total 18 51 69 Value / Lower 95% CI / Upper 95% CI **Rel risk** 1.30 0.59 2.87	
Goswami, Das, Chatto-padhyay, et al., 2004 **#11140**	**Geographical location:** West Bengal, India **Study dates:** July 2002-Aug 2003 **Size of population:** 48 recruited with 10 excluded Grp 1: 13 Grp 2: 25 **Number of cycles analyzed:** 38 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Grp 1: 2.5 mg Letrozole plus 75IU rFSH on days 3 and 8 Grp 2: Luteal phase down-regulation with Lupron followed by rFSH At doses of 300-450IU	**Age:** Mean (SD): Grp 1: 38.5 (1.7) Grp 2: 39.1 (1.1) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Age > 35 - Failed 1-3 IVF attempts due to "poor ovarian response" - 1-3 no treatment cycles between last IVF and study cycle **Exclusion criteria:** - Severe endometriosis (n = 4) - History of pelvic surgery (n = 3) - FSH > 12 (n = 1) - Refusal to participate (n = 2)	**Definition(s) of outcome(s):** Pregnancy: +FCM Live birth: NR Multiples: NR Complications: NR	1) Clinical pregnancy: Preg + / Preg - / Total rFSH + letrozole: 3 / **10** / 13 rFSH: **6** / **19** / 25 Total: 9 / 29 / 38 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.96 0.29 3.23	**Comments:** - Low power - No embryo status reported **Quality assessment:** Randomization method: + Blinding: single to investigator Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Goverde, McDonnell, Vermeiden, et al., 2000 **#58260**	**Geographical location:** Amsterdam, The Netherlands **Study dates:** NR **Size of population (no. of patients):** 258 **Number of cycles analyzed:** 943 **Number of cycles per patient:** 3.6 **Study type:** RCT **Interventions:** (a) IUI alone (spontaneous cycle, timed by urinary LH) (b) IUI with mild stimulation (gonadotropin dosed to reach 2-3 dominant follicles, hCG final maturation) (c) IVF	**Age:** Mean (SD): IUI alone: 31.6 (3.7) IUI + stimulation: 31.7 (3.9) IVF: 32.1 (4.2) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 181 (70%) Male factor: 77 (30%) **Inclusion criteria:** Idiopathic infertility for 3 years, or male infertility for 1 year **Exclusion criteria:** - Cycle disorders - Untreated endometriosis (American Fertility Society criteria grade 2–4) - Bilateral occluded tubes - Semen sample yielding < 1 million progressively motile spermatozoa after processing by Percoll 40/80 gradient centrifugation - > 20% of spermatozoa carrying antibodies as tested with an immunobead test after Percoll processing - > 50% of spermatozoa with no acrosome	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: Yes Complications: NR	1) Cumulative pregnancy, IUI vs. IUI with mild stimulation: Preg + / Preg - / Total IUI + stim: **31** / **54** / 85 IUI: **25** / **61** / 86 Total: 56 / 115 / 171 Value (Lower 95% CI, Upper 95% CI) **Rel risk** 1.25 (0.81, 1.93) 2) Cumulative pregnancy, IUI vs. IVF: Preg + / Preg - / Total IVF: **33** / **54** / 87 IUI: **25** / **61** / 86 Total: 58 / 115 / 173 Value (Lower 95% CI, Upper 95% CI) **Rel risk** 1.30 (0.85, 2.00) 3) Per cycle rate higher with IVF, but greater dropout rate in those who failed to conceive. Multiples higher in IUI with stimulation and IVF compared to IUI alone.	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +
Greco,	**Geographical location:**	**Age:**	**Definition(s) of**	1) Pg rate grp 1 vs 2:	**Comments:**

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Polonio-Balbi, Ferrero, et al., 2005 **#39210**	Rome, Italy; Granada, Spain **Study dates:** May 2000-Feb 2003 **Size of population:** Grp 1 used drug injector - 148 Grp 2 used syringe – 152 **Number of cycles analyzed:** 300 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Women undergoing IVF/ICSI randomized to administer rFSH by automated injector vs syringe	Mean (SD): Grp 1: 30.5 [3.9] Grp 2: 30.9 [3.6] **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Grp 1 Unexplained infertility: 22 [15] Endometriosis: 0 Male factor: 100 [68] Tubal factor: 19 [13] PCOS: 0 Other: 6 [4] Grp 2 Unexplained infertility: 21 [14] Endometriosis: 0 Male factor: 106 [70]] Tubal factor: 17 [11] PCOS: 0 Other: 8 [5] **Inclusion criteria:** Age < 36 BMI 18-29 2 ovaries basal FSH <12 Absence of PCOS or endometriosis by USD **Exclusion criteria:** NR	**outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	pg pos / pg neg / Total Injector: **66** / **82** / 148 Syringe: **58** / **94** / 152 Total: 124 / 176 / 300 Value / Lower 95% CI / Upper 95% CI **Rel risk**: 1.17 / 0.89 / 1.53	None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: NR
Griesinger, Schultze-	**Geographical location:** Luebeck, Germany	**Age:** Mean (SD):	**Definition(s) of outcome(s):**	1) Clinical pregnancy rate:	**Comments:** None

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Mosgau, Dafopoulos, et al., 2005 **#42140**	**Study dates:** 6/03 - 12/03 **Size of population:** 127 **Number of cycles analyzed:** 127 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** The study compared the usage of rFSH alone vs rFSH+rLH for ovulation induction in GnRH antagonist cycle. Both grps started the gonadotropins (either rFSH alone or rFSH and rLH) on cycle day 2. This is an IVF cycle!!	rFSH: 30.5 (4.2) rFSH+rLH: 30.3 (4.7) Median: NR Range: 20-39 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: See other Endometriosis: See other Male factor only: rFSH: 32 (49.2) rFSH+rLH: 34 (54.8) Tubal factor only: rFSH: 7 (10.8) rFSH+rLH: 9 (14.5) PCOS: 0 Other (specify): Idiopathic/endometriosis: rFSH: 9 (13.8) rFSH+rLH: 5 (8.0) Male factor and endometriosis: rFSH: 2 (3.0) rFSH+rLH: 2 (3.2) **Inclusion criteria:** Inclusion criteria: - Age 20-39 - BMI 18-35 - Regular menstrual cycle (ranging 24d-35d) - Intra-individual cycle variability of ≤3d - Use of fresh as well as frozen thawed sperm retrieved by testicular biopsy.	Pregnancy: Biochemical pregnancy: hCG ≥ 10 mIU/ml 14d after embryo transfer Clinical pregnancy: An ongoing pregnancy at 12 wks of gestation Live birth: NR Multiples: NR Complications: NR	Preg + / Preg - / Lower 95% CI / Upper 95 % CI Study drug: **8** / **54** / 62 Control: **12** / **53** / 65 20 / 107 / 127 **Rel risk** 0.70 (0.31 – 1.59)	**Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		Exclusion criteria: - > 3 failed ART - Previous poor response to gonadotropin stimulation defined as< 3 preovulatory follicles. - History of ovarian hyperstimulation syndrome grade II-III - PCOS - Other endocrine disorder - No natural luteal phase prior to treatment cycle - Abnormal uterine cavity as evaluated by u/s. - Presence of a clinically significant systemic disease			
Hassan, Azab, Rahman, et al., 2001 **#3810**	**Geographical location:** Alexandria, Egypt **Study dates:** NR **Size of population (no. of patients):** 88 **Number of cycles analyzed:** 88 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** ICSI, agonist down regulation, immature oocytes retrieved (in vitro maturation), randomized to no extra treatment or hGH 4 IU daily during stimulation	**Age:** Mean (SD): GH: 32.4 (0.4) No GH: 31.7 (0.6) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Male factor: 88 (100%) **Inclusion criteria:** Undergoing ICSI for male infertility **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Pregnancy (based on reported percentages): Preg + / Preg - / Total hGH: **14** / **30** / 44 No GH: **11** / **33** / 44 Total: 25 / 63 / 88 Value (Lower 95% CI – Upper 95% CI) **Rel risk** 1.27 (0.65 – 2.49)	**Comments:** Randomization method not specified **Quality assessment:** Randomization method: - Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Heijnen Eijkemans, De Klerk, et al., 2007 **#52530**	**Geographical location:** Rotterdam and Utrecht, Netherlands **Study dates:** Feb 2002 to Mar 2004 **Size of population (no. of patients):** 404 **Number of cycles analyzed:** 769 **Number of cycles per patient:** 1.9 **Study type:** RCT **Interventions:** Mild: mild ovarian stimulation with gonadotropin-releasing hormone [GnRH] antagonist cotreatment combined with single embryo transfer Standard: Stimulation with a GnRH agonist long protocol and transfer of two embryos.	**Age:** Mean (SD): 32.8 (3.1) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 91 (22%) Endometriosis: 0 (0%) Male factor: 221 (55%) Tubal factor: 67 (17%) PCOS: 0 (0%) Other (specify): 26 (7%) **Inclusion criteria:** No previous IVF treatment or had borne a healthy child after previous IVF treatment, were aged younger than 38 years, and had a menstrual cycle length of 25–35 days and a body-mass index of 18–28 kg/m² **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Continuing pregnancy: Positive heartbeat on ultrasound at 10 weeks after embryo transfer Live birth: Yes Multiples: Yes Complications: NR	1) Continuing pregnancy: |	Clinical pregnancy	No clinical pregnancy	Total
---	---	---	---
Mild	**96**	**109**	205
Standard	**102**	**97**	199
Total	198	206	404 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Rel risk	0.91	0.75	1.11 | 2) Live birth: |	Live birth	No live birth	Total
---	---	---	---
Mild	**70**	**135**	205
Standard	**78**	**121**	199
Total	148	256	404 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Rel risk	0.87	0.67	1.13	 3) Multiple births: Mild 0.5% (CI 0 to 2.7%) Standard 13.1% (CI 8.7 to 18.6%)	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -
Heijnen, Klinkert, Schmout-ziguer, et al., 2006	**Geographical location:** Utrecht and Arnhem, Netherlands **Study dates:** Oct 2001	**Age:** Mean (SD): 41 (2.1) **Race/ethnicity (n [%]):** NR	**Definition(s) of outcome(s):** Pregnancy: Clinical pregnancy	1) Clinical pregnancy: |	Clinical preg +	Clinical preg -	Total
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Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	to Dec 2003			DET **18** **5** 23 TET **11** **11** 22 Total 29 16 45	Blinding: - Dropout rate < 20%: +
#52550		**Diagnoses (n [%]):**	Live birth:		Adequacy of randomization concealment: -
	Size of population (no. of patients): 45	Unexplained infertility: (41%) Male factor: 31%	Term: >37 weeks Multiples: Yes		
	Number of cycles analyzed: 112	Tubal factor: 22% Other: 4.4%	Complications: NR	Value / Lower 95% CI / Upper 95% CI **Rel risk** 1.57 0.98 2.50	
	Number of cycles per patient: 2.5	**Inclusion criteria:** 38 years and older and an indication for an IVF or IVF/ICSI treatment either for the first time or after a previous IVF or IVF/ICSI childbirth		2) Live term birth: Live term birth / No live term birth / Total DET **10** **13** 23 TET **8** **14** 22 Total 18 27 45	
	Study type: RCT				
	Interventions: DET: double embryo transfer over a maximum of 4 cycles	**Exclusion criteria:** NR			
	TET: triple embryo transfer over a maximum of 3 cycles			Value / Lower 95% CI / Upper 95% CI **Rel risk** 1.20 0.58 2.46	
				3) Multiple pregnancy: Multiple + / Multiple - / Total DET **0** **10** 10 TET **3** **5** 8 Total 3 15 18	
				Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.12 0.01 1.98	

Hohmann, Macklon, and Fauser, 2003	**Geographical location:** Rotterdam, Netherlands **Study dates:** Nov 1999-	**Age:** Median: 33 for all 3 groups	**Definition(s) of outcome(s):** Pregnancy: Ongoing	1) Ongoing pregnancy, GnRH antagonist day 2 start vs GnRH agonist long protocol: Preg + Preg -	**Comments:** - Power based on differences in E2 levels - No adjustment for multiple

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#17550	May 2003 **Size of population (no. of patients):** 169—13 did not start IVF, 14 excluded for violation of inclusion criteria or protocol—4 pregnancies in this group 142 analyzed Allocation of subjects excluded from analysis not described **Number of cycles analyzed:** 142 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** a) Long protocol GnRH agonist (triptorelin) down-regulation for COH for IVF/ICSI, with fixed daily dose of 150 IU rFSH only b) rFSH + 0.25 microgram/day GnRH antagonist cetrorelix, beginning on day 2 c) rFSH + 0.25 microgram/day GnRH antagonist cetrorelix, beginning on day 5 All continued through day of hCG administration	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** 1) age between 20–38 yr; 2) body mass index (body weight divided by the square of body height) between 19–29 kg/m2; 3) history of regular menstrual cycles, ranging from 25–35 d; 4) no relevant systemic disease, severe endometriosis, or uterine and ovarian abnormalities; 5) no more than three previous IVF cycles; and 6) no previous IVF cycle with a poor response or ovarian hyperstimulation syndrome **Exclusion criteria:** NR	pregnancy: fetal heart rate at 12 weeks Live birth: NR Multiples: NR Complications: NR	Day 2 GnRH agonist: **10** / **38** / 48; **10** / **35** / 45; 20 / 73 / 93 **Rel risk** 0.94 (Lower 95% CI 0.43, Upper 95 % CI 2.04) 2) Ongoing pregnancy, GnRH antagonist day5 start vs GnRH agonist long protocol: Preg + / Preg - Day 5: **10** / **39** / 49 Control: **10** / **35** / 45 20 / 74 / 94 **Rel risk** 0.92 (Lower 95% CI 0.42, Upper 95 % CI 2.00) 3) Ongoing pregnancy, GnRH antagonist day5 start vs GnRH antagonist day 2 start: Preg + / Preg - Day 5: **10** / **39** / 49 Day 2: **10** / **38** / 48 20 / 77 / 97 **Rel risk** 0.98 (Lower 95% CI 0.45, Upper 95 % CI 2.14)	comparisons - Unable to calculate intention-to-treat rates from presented data **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: - (~15%, but allocation of dropouts/exclusions not included Adequacy of randomization concealment: +
Hoomans, Mulder, and Asian Purgeon Study	**Geographical location:** Multiple sites in Hong Kong, Thailand, Singapore, and India	**Age:** Mean (SD): 100 IU: 31.6 (3.6); 200 IU 32.1 (3.8) **Race/ethnicity (n [%]):**	**Definition(s) of outcome(s):** Pregnancy: Not defined	1) Clinical pregnancy: Preg + / Preg - 100 IU: 33 / 130 / 163	**Comments:** None **Quality assessment:** Randomization method: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Group, 2002 **#610** ***and*** **Ng, Yeung, and Ho, 2000** **#6200**	**Study dates:** Dec 1997-July 1999 **Size of population (no. of patients):** 230 **Number of cycles analyzed:** 230 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** **-** GnRH agonist down regulation - Randomized to 1 of 2 starting doses of rFSH (100 IU vs 200 IU)	100% Asian **Diagnoses (n [%]):** Unexplained infertility: 31% Endometriosis: 24% Male factor: 58% Tubal factor: 68% **Inclusion criteria:** - Age 18-39 - BMI 18-29 - Candidate for IVF/ICSI - Regular menses **Exclusion criteria:** - Infertility caused by endocrine abnormalities such as hyperprolactinemia, polycystic ovarian syndrome and absence of ovarian function - previous assisted reproduction in which fewer than three oocytes were retrieved. - previous hospitalization due to severe ovarian hyperstimulation syndrome, -chronic cardiovascular, hepatic, renal, or pulmonary disease -history of (within 12 months) or currently indulged in abuse of alcohol or drugs -used investigational drugs within 3 months before screening.	Live birth: NR Multiples: NR Complications: NR	200IU: 30 / 136 / 166 63 / 266 / 329 **Rel risk** 1.12 (Lower 95% CI 0.72, Upper 95 % CI 1.75) 2) Ongoing pregnancy: Preg + / Preg - 100 IU: 27 / 136 / 163 200 IU: 25 / 141 / 166 52 / 277 / 329 **Rel risk** 1.10 (Lower 95% CI 0.67, Upper 95 % CI 1.81) 3) More oocytes retrieved in 200 IU group:	Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Hreinsson, Rosenlund, Friden, et al., 2003 **#15400**	**Geographical location:** Stockholm, Sweden **Study dates:** NR **Size of population (no. of patients):** 73 **Number of cycles analyzed:** 73 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** In vitro oocyte maturation with (a) recombinant hCG or (b) recombinant LH	**Age:** Mean (SD): hCG: 31.3 (3.8) LH: 31.9 (3.6) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 24 (33%) Male factor: 25 (34%) Tubal factor: 6 (8%) Other: Anovulation 18 (25%) **Inclusion criteria:** - Age 20-40 - Indication for IVF/ICSI **Exclusion criteria:** Male factor requiring testicular sperm extraction	**Definition(s) of outcome(s):** Pregnancy: Gestational sac on ultrasound at 6 weeks Live birth: NR Multiples: NR Complications: NR	1) Pregnancy (not ITT – only data on completed cycles reported): Preg + / Preg - / Total rLH: **1** / **36** / 37 rhCG: **3** / **33** / 36 Total: 4 / 69 / 73 Value / Lower 95% CI / Upper 95% CI **Rel risk**: 0.32 / 0.04 / 2.97	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: - Adequacy of randomization concealment: +
Hreinsson, Rosenlund, Fridstrom, et al., 2004 **#10540**	**Geographical location:** Stockholm, Sweden **Study dates:** NR **Size of population (no. of patients):** 144 **Number of cycles analyzed:** 144 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Embryo transfer on (a) day 2-3 vs (b) day 3-5 1-2 embryos transferred	**Age:** Mean (SD): Day 2-3: 33.1; Day 5-6:32.1 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 30 (20.8%) Endometriosis: 16 (11.1%) Male factor: 45 (31.3%) Tubal factor: 29 (20.1%) PCOS: 12 (8.0%) Combined: 20 (13.9%) **Inclusion criteria:** ≥ 6 follicles **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: Yes (twins) Complications: NR	1) Clinical pregnancy: Preg + / Preg - / Total Day 5-6: **22** / **42** / 64 Day 2-3: **25** / **55** / 80 47 / 97 / 144 Lower 95% CI / Upper 95 % CI **Rel risk**: 1.10 / 0.69 / 1.76 2) Ongoing pregnancy: Preg + / Preg - / Total Day 5-6: **18** / **46** / 64 Day 2-3: **23** / **57** / 80 41 / 103 / 144 Lower 95% CI / Upper 95 % CI	**Comments:** - Study stopped due to change in national policy - Relatively large imbalance between arms - Greater proportion tubal factor in Day 2-3 group (26% vs 13%) **Quality assessment:** Randomization method: Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Rel risk 0.98 (0.58 – 1.65) 3) Twins: Preg + / Preg - Day 5-6: **2** / **20** (22) Day 2-3: **4** / **21** (25) 6 / 41 (47) **Rel risk** 0.57 (Lower 95% CI 0.11 – Upper 95 % CI 2.81)	
Hsieh, Tsai, and Chang, 2000 **#6580**	**Geographical location:** Taichung, Taiwan **Study dates:** July 1998-June 1999 **Size of population (no. of patients):** 359 **Number of cycles analyzed:** 359 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Randomized to transfer day 2 or day 5	**Age:** Mean (SD): Day 2: 32.9 (3.1); Day 5: 32.5 (3.6) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR for entire group **Inclusion criteria:** NR **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Clinical pregnancy: Preg + / Preg - Day 5: **84** / **117** (201) Day 2: **59** / **99** (158) 143 / 216 (359) **Rel risk** 1.12 (Lower 95% CI 0.86 – Upper 95 % CI 1.45) 2) Ongoing pregnancy: Preg + / Preg - Study drug: **65** / **136** (201) Control: **47** / **111** (158) 112 / 247 (359) **Rel risk** 1.09 (Lower 95% CI 0.80 – Upper 95 % CI 1.49)	**Comments:** - Randomization method not described - Large discrepancy in arms not explained - Significantly more embryos/ transfer in day 2 group (3.7 vs 2.1) **Quality assessment:** Randomization method: - Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -
Hughes, Beecroft, Wilkie, et al., 2004 **#12420**	**Geographical location:** Hamilton, London, Toronto, Ottawa, and Vancouver, Canada **Study dates:** May 2000-	**Age:** Mean (SD): IVF: 32.9 (3.2); no treatment 33.1(3.7) **Race/ethnicity (n [%]):**	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: Delivery of	1) Clinical pregnancy: Preg + / Preg - IVF: **21** / **47** (68) No Rx: **3** / **68** (71) 24 / 115 (139)	**Comments:** None **Quality assessment:** Randomization method: + Blinding: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	April 2002 **Size of population (no. of patients):** 139 **Number of cycles analyzed:** 139 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Observation for 90 days vs IVF/ICSI within 90 days of randomization	NR **Diagnoses (n [%]):** Unexplained infertility: 42 (30.2%) Endometriosis: 11 (7.9%) Male factor: 51 (36.7%) Tubal factor: 9 (6.5%) PCOS: 19 (13.7%) **Inclusion criteria:** - duration of subfertility >2 years, defined as no live birth during that time; - no previous IVF treatment; female age 18±39 years; - willingness to commence either IVF within 6 weeks of allocation or a 3 month period of observation without intervention; day 3 serum FSH level of >15 IU/l or the standard level for inclusion in an individual centre's IVF programme, whichever level was lower; semen analysis available within the last 6 months showing an adequate number of sperm to perform ICSI; and evidence of Fallopian tube patency, based on a hysterosalpingogram (HSG) or laparoscopy. - All had “exhausted” other options **Exclusion criteria:** - women with bilateral Fallopian tube occlusion confirmed by HSG or	fetus with heart beat after 24 weeks, or neonate that survives at least 10 minutes Multiples: NR Complications: NR	 **Rel risk** 7.31 (Lower 95% CI 2.28; Upper 95 % CI 23.39) 2) Live birth: Preg + / Preg - IVF: **20** / **48** (68) No Rx: **1** / **70** (71) 21 / 118 (139) **Rel risk** 20.88 (Lower 95% CI 2.88; Upper 95 % CI 151.35)	Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		laparoscopy; - the use of donor sperm; - need for sperm recovery procedures; and - concurrent serious medical illnesses			
Hugues, Barlow, Rosenwaks, et al., 2003 **#17010**	**Geographical location:** Bondy, France; Oxford, UK; Geneva, Switzerland **Study dates:** NR **Size of population (no. of patients):** 131 **Number of cycles analyzed:** 131 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** **-** Down regulation with GnRH agonist **-** Randomized to rFSH prepared either by bioassay (ampules with 75 IU rFSH) or mass equivalent (5.5 micrograms) - 5 day starting dose of 150 IU day	**Age:** Mean (SD): Mass assay 30.8 (4.0); bioassay 31.4 (3.5) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** **-** 18-38 years - Normal menses, endocrine profile, semenanalysis - BMI <30 - No more than 3 previous attempts **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Clinical pregnancy: Preg + / Preg - / Total Mass assay: 20 / 46 / 66 Bioassay: 17 / 48 / 65 37 / 94 / 131 Rel risk: 1.16 (Lower 95% CI 0.67, Upper 95 % CI 2.01)	**Comments:** Primary outcome = follicle # **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +
Huirne, van Loenen, Donnez, et al., 2006 **#52680**	**Geographical location:** Amsterdam, The Netherlands and Brussels, Belgium **Study dates:** NR **Size of population (no.**	**Age:** Mean (SD): 32.3 (3.9) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 15	**Definition(s) of outcome(s):** Pregnancy: Biochemical: positive pregnancy test (HCG> 10 IU/l) Clinical: > 1 intrauterine	1) Biochemical pregnancy: Biochem preg + / Biochem preg - / Total OC: **8** / **23** / 31 No OC: **13** / **19** / 32 Total: 21 / 42 / 63	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	of patients): 63 **Number of cycles analyzed:** 63 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** On cycle day 2 or 3 patients were randomized to receive either OC pretreatment (OC group) or not (control group)**.** The control group started with recombinant human FSH (r-FSH) (Gonal-f™ Serono, Geneva. Switzerland) on day 2 or 3 of a natural cycle. In the OC group, patients started witb daily OC pills (Microgynon 30*; Schering, Madrid. Spain, containing 30 *µg* ethinyl oestradiol and 150 *µg* levenorgestrel) on cycle day 2-3 for a variable period of 14-28 days. The date of the last OC intake was to be decided by the investigator on administrative criteria to schedule the initiation of stimulation. Instead of taking a fixed number of days of OC pretreatment, it was decided to vary this duration allowing analyses of its effect on IVF outcome. Gonal-f administration was started 2 or 3 days after OC withdrawal,	(24%) Endometriosis: 3 (4.7%) Male factor: 35 (55%) Tubal factor: PCOS: Other (specify): 1 (2%) **Inclusion criteria:** Patients needed to have a regular IVF or ICSI indication (i.e. idiopathic infertility after six unsuccessful intrauterine inseminations, infertility based on male or tubal factor), a spontaneous regular ovulatory menstrual cycle, two ovaries and a normal uterine cavity, age between 18 and 38. **Exclusion criteria:** FSH >12 IU/1 on cycle day 2-4, BMI > 30 kg/m, abnormal gynecological bleeding, an extrauterine pregnancy within the last 3 months, any previous assisted reproductive technique cycles with fewer than three oocytes or severe OHSS or patients with any contraindication to receive gonadotrophins or oral contraceptives, or presence of polycystic ovarian syndrome (defined as patients with oligomenorrhoea and at least two of the following criteria: elevated LH concentrations, signs of hyperandrogenism, or polycystic ovaries by	fetal sac on ultrasound at gestational age of 6 weeks. Ongoing: intrauterine heart activity at a gestational age of 12 weeks. Live birth: NR Multiples: NR Complications: Side effects or local skin reactions were recorded daily on a personal diary card	 Value (Lower 95% CI, Upper 95% CI) **Rel risk** 0.64 (0.31, 1.32) 2) Clinical pregnancy: Clin preg + / Clin preg - / Total OC **4** / **27** / 31 No OC **12** / **20** / 32 Total 16 / 47 / 63 Value (Lower 95% CI, Upper 95% CI) **Rel risk** 0.34 (0.12, 0.95) 3) Ongoing pregnancy: Ongoing preg + / Ongoing preg - / Total OC **4** / **27** / 31 No OC **8** / **24** / 32 Total 12 / 51 / 63 Value (Lower 95% CI, Upper 95% CI) **Rel risk** 0.52 (0.17, 1.54) 4) The treatment was well tolerated. In total, 117 new adverse events were reported in 51 patients. The majority of the adverse events (98%) were reported as mild, five were moderate, and one was severe (tubal infection after oocyte retrieval). The most frequently reported adverse events were injection site reactions (20.5%), headache (22.2%), abdominal pain (12.8%), gastrointestinal discomfort such as nausea (12.0%), fatigue (9.4%), ovarian cyst *(5.1%)* and mood changes (3.4%). Ovarian hyperstimulation was observed twice, only in the OC group: both cases were considered to be mild, and neither treatment nor admission was required; one of these patients	concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	independent of their bleeding pattern. In both groups, r-FSH was administered daily up to the day of r-HCG administration. The starting dose of r-FSH (150-300 IU) was maintained for 5 days, after which it could be adjusted according to the ovarian response (increase if fewer than 3 oocytes were >11 mm and decrease if a patient was at risk for OHSS) up to a maximal dose of 450 IU/day. From stimulation day 6 up to and including r-HCG day, a GnRH antagonist (antide/Serono) (0.5 mg/ml per day) was given.	ultrasound).		turned out to be pregnant. The number and type of reported adverse events per patient were similar in both groups	
Humaidan, Bredkjaer, Bungum, et al., 2005 **#42080**	**Geographical location:** Multicenters in Denmark **Study dates:** 8/03 - 2/04 **Size of population:** 122 **Number of cycles analyzed:** 122	**Age:** Range: 25-40 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** -FSH and LH < 12IU	**Definition(s) of outcome(s):** Pregnancy: Biochemical pregnancy: a plasma βhCG of >10IU/l on 12d after embryo transfer (reported per ET) Chemical pregnancy: an	1) Clinical pregnancy rate: Out + / Out - / Total Buserelin: **3** / **52** / 55 hCG: **24** / **43** / 67 Total: 27 / 95 / 122 Lower Upper	**Comments:** None **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Number of cycles per patient: 1.00 **Study type:** RCT **Interventions:** Using GnRH agonist (busereline) vs. 10,000 IU hCG for ovulation induction in GnRH antagonist IVF/ICSI cycles protocol	-Menstrual cycle between 25d - 34d -BMI 18-30 -Both ovaries present -No uterine abnormalities **Exclusion criteria:** NR	intrauterine gestational sac with a heartbeat 3 wks after a positive hCG test Live birth: NR Multiples: NR Complications: Early pregnancy loss	Value 95% CI 95% CI **Rel risk** 0.15 0.05 0.48 2) No difference in the positive hCG rate (per ET): 29% in Buserelin grp and 44% in hCG grp 3) More early pregnancy loss in Buserelin grp compared to hCG grp: 79% vs. 4%	
Humaidan, Brock, Bungum, et al., 2006 **#52690**	**Geographical location:** Skive, Sweden **Study dates:** August 2004 to May 2005 **Size of population (no. of patients):** 152 **Number of cycles analyzed:** 152 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** Mixed frequency electro-acupuncture (MFA) Fixed frequency acupuncture (FFA)	**Age:** Mean (SD): 31.7 (4.0) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 51 (34%) Endometriosis: 6 (4%) Male factor: 46 (30%) Tubal factor: 29 (19%) Other (specify): 20 (13%) **Inclusion criteria:** NR **Exclusion criteria:** Chronic pelvic pain	**Definition(s) of outcome(s):** Pregnancy: A positive pregnancy test: plasma β-HCG concentration > 10 IU/l. 12 days after embryo transfer. Ongoing clinical pregnancy rate: an intrauterine pregnancy with a heartbeat 8 weeks after a positive β-HCG test (i.e. 10 weeks of pregnancy). Live birth: NR Multiples: NR Complications: Pain assessed using visual analog scale (VAS)	1) Positive pregnancy test: Pos preg test + / Pos preg test - / Total MFA **27** **49** 76 FFA **29** **47** 76 Total 56 96 152 Value Lower 95% CI Upper 95% CI **Rel risk** 0.93 0.61 1.41 2) Ongoing clinical pregnancy: Clincal preg + / Clinical preg - / Total MFA **29** **47** 76 FFA **32** **44** 76 Total 61 91 152 Value Lower 95% CI Upper 95% CI **Rel risk** 0.91 0.61 1.34 3) Similar analgesic effect	**Comments:** None **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +
Humaidan, Bungum, Bungum, et al., 2004	**Geographical location:** Copenhagen, Denmark **Study dates:** Nov 2001-	**Age:** Grp 1: Mean (SD): 30.8 (3.9) Range: 23-40	**Definition(s) of outcome(s):** Pregnancy: + FCM	1) Clinical pregnancy: Preg + / Preg - / Total rFSH + 42 **74** 116	**Comments:** - Embryo quality and transfer day NR - *A priori* sample size based on

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#13150	Oct 2002 **Size of population:** Grp 1: 116 Grp 2: 115 **Number of cycles analyzed:** 231 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Grp 1: Received rLH during IVF stimulation starting on day 8 of stimulation Grp 2: Control All received luteal downregulation with GnRHa and stimulation with rFSH.	Grp 2: Mean (SD): 30.5 (4) Range: 22-39 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Grp 1: Unexplained infertility: 20 [17] Endometriosis: 5 [4] Male factor: 42 [36] Tubal factor: 33 [29] PCOS: 16 [14] Grp 2: Unexplained infertility: 23 [20] Endometriosis: 1 [1] Male factor: 46 [40] Tubal factor: 36 [31] PCOS: 9 [8] **Inclusion criteria:** - Age < 40 - Baseline FSH < 10 - Cycles 25d-34d **Exclusion criteria:** NR	Live birth: NR Multiples: NR Complications: NR	rLH rFSH **35** **80** 115 Total 77 154 231 Value; Lower 95% CI; Upper 95% CI **Rel risk** 1.19 0.82 1.72 2) Clinical pregnancy, women 35 and older: Preg +; Preg - Study group 7 14 21 Control 4 14 18 11 28 39 Lower 95% CI; Upper 95 % CI **Rel risk** 1.50 0.52 4.31 Rates identical in women < 35 years	absolute difference of 10% **Quality assessment:** Randomization method: + Blinding: single Dropout rate < 20%: + Adequacy of randomization concealment: +
Humaidan, Bungum, Bungum, et al., 2006 **#52700**	**Geographical location:** Copenhagen, Denmark **Study dates:** Dec 2004-May 2005 **Size of population (no. of patients):** 45 **Number of cycles analyzed:** 45	**Age:** NR **Race/ethnicity (n [%]):** White: 45 (100%) **Diagnoses (n [%]):** NR **Inclusion criteria:** (i) female age >25 and <40 years; (ii) baseline FSH and LH	**Definition(s) of outcome(s):** Pregnancy: Gestational sac with + FHR 3 weeks after + serum hCG Live birth: NR Multiples: NR	1) Clinical pregnancy, 10,000 IU hCG vs GnRH agonist + 1500 IU hCG 12 hours later: Preg +; Preg - GnRHa + hCG 12 hours 2 15 17 hCG 8 7 15 10 22 32	**Comments:** None **Quality assessment:** Randomization method: Blinding: Dropout rate < 20%: Adequacy of randomization concealment:

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Number of cycles per patient: 1.0 **Study type:** RCT **Interventions:** GnRH antagonist/FSH COH; randomized to ovulation triggering with (a) 10,000 IU hcg, (b) buserelin 0.5 mg + 1500 IU hCG 12 hours later, (c) buserelin 0.5 mg + 1500 IU hCG 35 hours later (immediately after oocyte retrieval)	<12 IU/1; (iii) menstrual cycles between 25 and 34 days; (iv) body mass index (BMI) >18 and <30; (v) both ovaries present; (vi) absence of uterine abnormalities. **Exclusion criteria:** NR	Complications: NR	Lower Upper 95% CI 95 % CI **Rel risk** 0.22 0.06 0.88 2) Clinical pregnancy, 10,000 IU hCG vs GnRH agonist + 1500 IU hCG 35 hours later: Preg + Preg - GnRHa + hCG 35 hours: 6 7 13 hCG: 8 7 15 14 14 28 Lower Upper 95% CI 95 % CI **Rel risk** 0.87 0.41 1.84 3) Clinical pregnancy, 10,000 IU hCG vs GnRH agonist + 1500 IU hCG 35 hours later: Preg + Preg - GnRHa + hCG 35 hours: 6 7 13 GnRHa + hCG 12 hours: 2 15 17 8 22 30 Lower Upper 95% CI 95 % CI **Rel risk** 3.92 0.94 16.36	
Humaidan and Stener-Victorin, 2004 **#58270**	**Geographical location:** Skive, Denmark **Study dates:** Apr 2002-Dec 2002 **Size of population (no. of patients):** 200	**Age:** Mean (SD): Acupuncture: 30.5 Conventional: 31.5 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):**	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR	1) Pregnancy: Preg + Preg - Total Electro-acupuncture: **46** **54** 100 Conventional: **50** **50** 100 Total: 96 104 200 Lower Upper	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%:+ Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Number of cycles analyzed: 200 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Oocyte retrieval with paracervical block and (a) electroacupuncture or (b) benzodiazepine/ alfentanil (conventional)	Unexplained infertility: 56 (28%) Endometriosis: 8 (4%) Male factor: 57 (29%) Tubal factor: 48 (24%) PCOS: 15 (7%) Other or combined: 26 (13%) **Inclusion criteria:** Scheduled for embryo transfer for IVF **Exclusion criteria:** None	Complications: Pain on VAS scale	<table><tr><th></th><th>Value</th><th>95% CI</th><th>95% CI</th></tr><tr><td>**Rel risk**</td><td>0.92</td><td>0.69</td><td>1.23</td></tr></table> 2) No difference in pain on VAS scale	
Hwang, Seow, Lin, et al., 2004 **#11100**	**Geographical location:** Taipei, Taiwan **Study dates:** Jan – Dec 2003 **Size of population:** Grp 1: 27 Grp 2: 29 **Number of cycles analyzed:** 56 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Grp 1: ICSI with Diane OCP pretreatment followed by a Cetrorelix Antagonist + hMG Grp 2: ICSI with long GnRHa downregulation followed by hMG	**Age:** Grp 1: Mean (SD): 31.4 (3.5) Grp 2: Mean (SD): 31.7 (3.7) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** PCOS: 100 **Inclusion criteria:** - PCOS defined by oligo or amenorrhea, anovulation by BBT or serum P4, USD of ovary showing > 10 peripheral follicles, and 1 of 2 hormonal abnormalities, including increased LH:FSH ratio or T > 0.8 ng/mL **Exclusion criteria:** - Age > 38 - Diagnoses of CAH, Cushing's, androgen producing tumor	**Definition(s) of outcome(s):** Pregnancy: +FCM Live birth: NR Multiples: NR Complications: OHSS, SAB	1) Clinical pregnancy: <table><tr><th></th><th>Preg +</th><th>Preg -</th><th>Total</th></tr><tr><td>Grp 1</td><td>**10**</td><td>**17**</td><td>27</td></tr><tr><td>Grp 2</td><td>**10**</td><td>**19**</td><td>29</td></tr><tr><td>Total</td><td>20</td><td>36</td><td>56</td></tr></table> <table><tr><th></th><th>Value</th><th>Lower 95% CI</th><th>Upper 95% CI</th></tr><tr><td>**Rel risk**</td><td>1.07</td><td>0.53</td><td>2.17</td></tr></table> 2) SAB: Grp 1: 10% Grp 2: 20% p = NS 3) OHSS: Grp 1: 8% Grp 2: 8.3% p = NS	**Comments:** - Low power - Dropout rate of 7.4% in Grp 1 and 17.2% in Grp 2 **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: - Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		hyperprolactinemia, or thyroid dysfunction			
Ingerslev, Hojgaard, Hindkjaer, et al., 2001 **#5510**	**Geographical location:** Aarhus, Denmark **Study dates:** Aug 1997-Dec 1997 **Size of population (no. of patients):** 132 **Number of cycles analyzed:** 225 **Number of cycles per patient:** 1.7 **Study type:** RCT **Interventions:** Randomized to (a) clomiphene citrate 100 mg/day cycles day 3-7, or (b) no treatment - No other stimulation - hCG given based on ultrasound monitoring	**Age:** Mean (SD): Clomiphene 30.2 (2.9), control 30.7 (2.5) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 52 (21.5%) Male factor: 74 (30.6%) Tubal factor: 115 (47.5%) **Inclusion criteria:** - <35 years - Unexplained, tubal, or severe male factor - Regular menses - No previous IVF - 2 ovaries **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Clinical Pregnancy: Intrauterine pregnancy with FHR 5 weeks after transfer Live birth: NR Multiples: NR Complications: NR	1) Clinical pregnancy Preg + / Preg - / Total Clomiphene: 20 / 48 / 68 Control: 4 / 60 / 64 24 / 108 / 132 Rel risk 4.71 (Lower 95% CI 1.70, Upper 95 % CI 13.02)	**Comments:** - High prevalence of smoking - Allocated treatment continued for subsequent cycles, after washout **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +
Isik, Vicdan, Kaba, et al., 2000 **#7460**	**Geographical location:** Ankara, Turkey **Study dates:** 4-1-98 to 10-31-98 **Size of population:** Grp 1: 22 Grp 2: 24 **Number of cycles analyzed:** 46	**Age:** Grp 1: Mean (SD): 29.1 (3.6) Median: NR Range: NR Grp 2: Mean (SD): 30.5 (5.2) Median: NR Range: NR **Race/ethnicity (n [%]):** NR	**Definition(s) of outcome(s):** Pregnancy: Clinical - presence of fetal pole with or w/o heart beat Ongoing - > 12 wks EGA Live birth: NR Multiples: Yes (twins)	1) Pregnancy rate: Preg + / Preg - / Total Zona free: **15** / **9** / 24 Zona intact: **10** / **12** / 22 25 / 21 / 46	**Comments:** Low power **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

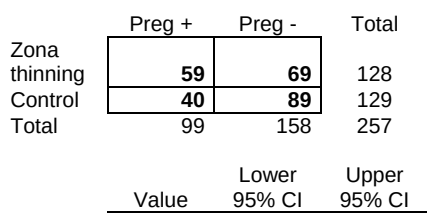
Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
			Complications: NR	**Rel risk** 1.38 (0.79, 2.39)	
	Number of cycles per patient: 1.0 **Study type:** RCT **Interventions:** Grp 1: Zona intact blastocyst transfer Grp 2: Zona free blastocyst transfer	**Diagnoses (n [%]):** NR **Inclusion criteria:** More than 5 day 3 cleaved embryos **Exclusion criteria:** NR		2) Ongoing pregnancy: Preg + / Preg - Study drug: **11** / **13** (24) Control: **6** / **16** (22) 17 / 29 (46) **Rel risk** 1.68 (Lower 95% CI 0.75, Upper 95% CI 3.77)	
				3) Twins: Singleton / Twin / Total Zona intact: **8** / **2** (10) Zona free: **13** / **2** (15) Total: 21 / 4 (25) **Rel risk** Value 0.92 (Lower 95% CI 0.64, Upper 95% CI 1.33)	
Isikoglu, Ozgur, and Oehninger, 2007 **#71450**	**Geographical location:** Antalya, Turkey **Study dates:** NR **Size of population (no. of patients):** 181 **Number of cycles analyzed:** 181	**Age:** Mean (SD): Luteal GnRH: 30. 1 (4.9) Control: 30.1 (4.3) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Fetal cardiac activity 4 weeks after transfer Live birth: Yes Multiples: NR	1) Clinical pregnancy: Preg + / Preg - / Total Luteal GnRH: **44** / **46** (90) Control: **45** / **46** (91) Total: 89 / 92 (181) **Rel risk** Value 0.99 (Lower 95% CI 0.74, Upper 95% CI 1.33)	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
			Complications: NR		
	Number of cycles per patient: 1.0 **Study type:** RCT **Interventions:** Long protocol GnRH agonist suppression, randomized to (a) continued agonist through day 12 after embryo transfer, vs. (b) day of hCG administration. ICSI for fertilization	**Exclusion criteria:** NR		2) Live birth: Out + / Out - / Total Exp +: **34** / **56** / 90 Exp -: **32** / **59** / 91 Total: 66 / 115 / 181 Rel risk: Value 1.07, Lower 95% CI 0.73, Upper 95% CI 1.58	
Jaroudi, Al-Hassan, Sieck, et al., 2004 **#13750**	**Geographical location:** Riyadh, Saudi Arabia **Study dates:** Dec 2001-Oct 2002 **Size of population (no. of patients):** 302 (7 dropouts, 41 no transfers) **Number of cycles analyzed:** 156 in paper, 302 included here in intent-to-treat **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Randomized to transfer of 2 embryos on (a) day 1 or (b) day 3	**Age:** Mean (SD): Day 1: 31.1, Day 3: 31.5 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 26 (8.6) Endometriosis: Male factor: 171 (56.6%) Tubal factor: 36 (11.9%) Other (unspecified): 21 (7.0%) **Inclusion criteria:** NR **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: + hCG, ultrasound 5 weeks after transfer Live birth: NR Multiples: NR Complications: NR	1) Pregnancy (intent-to-treat): Preg + / Preg - / Day 1: **34** / **117** / 151 Day 3: **55** / **96** / 151 89 / 213 / 302 Rel risk: 0.62, Lower 95% CI 0.43, Upper 95 % CI 0.89 2) Ongoing pregnancy (intent-to-treat): Preg + / Preg - / Day 1: **27** / **124** / 151 Day 3: **42** / **109** / 151 69 / 233 / 302 Rel risk: 0.64, Lower 95% CI 0.42, Upper 95 % CI 0.99 3) Results similar when only cycles where ET occurred analyzed	**Comments:** Sample size powered to detect 15% absolute difference **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +
Jelinkova,	**Geographical location:**	**Age:**	**Definition(s) of**	1) Pregnancy:	**Comments:**

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Pavelkova, Strehler, et al., 2003 **#70000**	Ulm, Germany **Study dates:** NR **Size of population (no. of patients):** 257 **Number of cycles analyzed:** 257 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Day 5 transfers randomized to (a) chemical zona removal vs (b) no thinning	Mean (SD): Zona thinning: 32.3 (4.2) No thinning: 32.1 (3.2) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - At least 2 previous implantation failures - 2-3 embryos reaching morula or blastocyst stage after 5 days of in vitro culture - Homogenous morphology of transferred embryos as optimal, poor, or delayed, according to investigators' classification system **Exclusion criteria:** NR	**outcome(s):** Pregnancy: FHR on ultrasound 10 weeks after retrieval Live birth: NR Multiples: NR Complications: NR	 	Randomization method not described **Quality assessment:** Randomization method: - Blinding: - Dropout rate < 20%: - Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Karaki, Samarraie, Younis, et al., 2002 **#2960**	**Geographical location:** Amman, Jordan **Study dates:** June 1999-June 2000 **Size of population:** Grp 1: 82 Grp 2: 80 **Number of cycles analyzed:** 162 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Grp 1: Day 3 ET after IVF/ICSI Grp 2: Blastocyst transfer after IVF/ICSI	**Age:** Mean (SD): Grp 1: 29.2 (5) Grp 2: 30 (4.5) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Grp 1: Unexplained infertility:4 [5] Endometriosis: 6 [7] Male factor: 42 [51] Tubal factor: 8 [10] PCOS: 7 [9] Combined male and female: 15 [18] Grp 2: Unexplained infertility:6 [7] Endometriosis: 4 [5] Male factor: 42 [52] Tubal factor: 6 [8] PCOS: 9 [11] Combined male and female: 13 [17] **Inclusion criteria:** At least 5 2PN embryos on day after TVOR **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: +FCM Live birth: NR Multiples: Yes Complications: NR	1) Clinical pregnancy rate: Preg + / Preg - / Total Blastocyst: **23** / **57** / 80 Day 3: **21** / **61** / 82 44 / 118 / 162 Rel risk: 1.12 (Lower 95% CI 0.68, Upper 95 % CI 1.86) 2) Multiples: Mult + / Mult - / Total Blastocyst: 9 / 14 / 23 Day 3: 10 / 11 / 21 19 / 25 / 44 Rel risk: 0.82 (Lower 95% CI 0.42, Upper 95 % CI 1.62) 3) Multiples greater than 2: Grp 1: 19% Grp 2: 4% $p < 0.05$	**Comments:** Bias to higher pregnancy rate in Grp 1due to statistically significantly greater number of embryos transferred, 3.5 vs. 2.0. **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: 11% of Grp 2 did not get transfer but were included in analysis Adequacy of randomization concealment: - (NR)

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Kattera and Chen, 2003 **#15170**	**Geographical location:** Singapore **Study dates:** NR **Size of population (no. of patients):** 259 **Number of cycles analyzed:** 259 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Randomized to co-incubation of ooycte and sperm for (a) 2 hours vs. (b) 20 hours	**Age:** Mean (SD): Short: 35.4 (4.1); Long: 35.1 (3.9) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 30 (11.6%) Endometriosis: 89 (34.3%) Tubal factor: 31 (12.9%) PCOS: 109 (42.1%) **Inclusion criteria:** NR **Exclusion criteria:** - Very poor responders (those who produced fewer than three follicles) - men with severe oligoasthenoteratozoospermia (density ≤ 5 m/mL, motility ≤ 30% and morphology ≤ 5% as per strict criteria)	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Ongoing pregnancy: Preg + / Preg - / Lower 95% CI / Upper 95 % CI 2 hours: **63** / **67** = 130 20 hours: **37** / **92** = 129 100 / 159 = 259 **Rel risk** 1.69 (1.22 – 2.34)	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -
Keay, Lenton, Cooke, et al., 2001 **#4330**	**Geographical location:** Sheffield and Bristol, UK **Study dates:** NR **Size of population (no. of patients):** 290 **Number of cycles analyzed:** 290 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:**	**Age:** Mean (SD): Dexamethasone: 32.5 (3.8) Placebo: 32.2 (3.7) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 57 (20%) Endometriosis: 21 (7%) Male factor: 88 (30%) Tubal factor: 125 (43%) PCOS: 11 (4%)	**Definition(s) of outcome(s):** Pregnancy: Ultrasound confirmation of gestational sac with FHR Live birth: NR Multiples: NR Complications: NR	1) Clinical pregnancy: Preg + / Preg - / Lower 95% CI / Upper 95 % CI Dex: **39** / **106** = 145 Placebo: **25** / **120** = 145 64 / 226 = 290 **Rel risk** 1.56 (1.00 – 2.44) 2) Overall cancellation rate: Preg + / Preg - Study drug: **10** / **135** = 145	**Comments:** - A priori sample size based on reduction in cancellation rate **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment:+

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	- Norethisterone prior to beginning pituitary suppression with buserelin - stimulation with rFSH - nightly dose of either 1 mg dexamethasone or placebo from beginning of gonadotropins until night before oocyte retrieval	**Inclusion criteria:** - Scheduled for IVF/ICSI **Exclusion criteria:** - ≥ 40 years - Concurrent use of steroids - History of IDDM or peptic ulcer		Control **21** **124** 145 31 259 290 Lower 95% CI / Upper 95 % CI **Rel risk** 0.48 0.23 0.98 Greatest benefit for cancellation for poor response (2.8% vs 12.4%); small numbers of cancellations for over-response, but more common in dexamethasone group (4% vs 2%)	
Kilani, Dakkak, Ghunaim, et al., 2003 **#16640**	**Geographical location:** Bologna, Italy **Study dates:** NR **Size of population (no. of patients):** 100 **Number of cycles analyzed:** 100 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** - GnRH agonist suppression - Randomized to stimulation with either 150 IU rFSH or 150 IU HP-hMG daily - Dose maintained until 3 follicles ≥ 18 mm and E2 >600 pg/ml, or 14 days. - Dose adjusted after 14 days	**Age** Mean (SD): rFSH 25.9 (5); HP-hMG 27.0 (0.4) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Normal menstrual cycles - BMI 18-27 - 3 or fewer previous I VF/ICSI cycles - PCOS/endometrosis **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: Yes Multiples: NR Complications: OHSS	1) Pregnancy: Preg + / Preg - / rFSH 14 36 50 HP-hMG 15 35 50 29 71 100 Lower 95% CI / Upper 95 % CI **Rel risk** 0.93 0.51 1.72 2) Live birth: Preg + / Preg - / rFSH 11 39 50 HP-hMG 12 38 50 23 77 100 Lower 95% CI / Upper 95 % CI **Rel risk** 0.92 0.45 1.88 3) Moderate OHSS—1 in rFSH, 3 in HP-hMG	**Comments:** Powered on duration and amount of gonadotropin **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +
Kjotrod, von	**Geographical location:**	**Age:**	**Definition(s) of**	1) Clinical pregnancy rate overall—intent-to-	**Comments:**

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
During, and Carlsen, 2004 **#12090**	Trondheim, Norway **Study dates:** Jan 2001-June 2002 **Size of population:** Grp 1: 37 with final analysis of 31 Grp 2: 36 with final analysis of 32 **Number of cycles analyzed:** 73 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** IVF/ICSI cycles with long luteal downregulation with GnRHa and stimulation with rFSH Grp 1: Metformin 1000 mg BID for at least 16 wks stopping on day of hCG Grp 2: Control – no metformin	Grp 1: Mean (SD): 28.9 CI 27.6-30.2 Grp 2: Mean (SD): 30.2 CI 29 - 31.5 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Grp 1: Endometriosis: 3 [7] Male factor: 22 [31] Tubal factor: 12 [29] PCOS: 100 Above diagnoses in addition to PCOS, not all pts evaluated for each diagnosis **Inclusion criteria:** - PCOS by use of > 10 follicles/ovary, oligo/amenorrhea - At least 1 of 5 abnormal labs including T > 2.0, SHBG < 30, LH/FSH ratio > 2, fastin C-peptide >1.0 and hirsutism **Exclusion criteria:** - DM, renal or liver disease - Oral steroids - Abnormal prolactin, TSH, CAH - Androgen tumor	**outcome(s):** Pregnancy: Gestational sac only Live birth: Yes Multiples: NR Complications: OHSS	treat: Preg + / Preg - / Total Meformin: 19 / 18 / 37 Placebo: 16 / 20 / 36 35 / 38 / 73 Rel risk 1.16 (Lower 95% CI 0.71, Upper 95 % CI 1.87) 2) Live birth rate (intent-to-treat): Preg + / Preg - / Total Meformin: 12 / 25 / 37 Placebo: 11 / 25 / 36 23 / 50 / 73 Rel risk 1.06 (Lower 95% CI 0.54, Upper 95 % CI 2.09) 3) OHSS: Grp 1: 3.2% Grp 2: 12.5% P = 0.3 4) Outcomes stratified by BMI of < or > 28 showed no difference in clinical pregnancy or live birth but did show statistically significantly higher positive pregnancy test rate in metformin 1 of the < 28 BMI compared to placebo	- Dropouts: Grp 1 16.2%; Grp 2 11.1% - 6 spontaneous pregnancies in normal weight women **Quality assessment:** Randomization method: + Blinding: + - Dropout rate < 20%: + Adequacy of randomization concealment: +
Kleinstein and Luteal	**Geographical location:** Magdeburg, Germany	**Age:** Grp 1:	**Definition(s) of outcome(s):**	1) Pregnancy rate grp 1 vs 2:	**Comments:** None

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Phase Study Group, 2005 **#40060**	**Study dates:** 7/99 - 9/2001 **Size of population:** Grp 1: Utrogest-218 Grp 2: Crinone-212 **Number of cycles analyzed:** 430 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Women undergoing 1st attempt at IVF/ICSI randomized to receive vaginal progesterone in oil 200 mg TID (Utrogest) or Crinone 8% progesterone gel vaginally BID	Mean (SD): 30.7 [2.9] Grp 2: Mean (SD): 30.1 [3.0] **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Grp 1 Unexplained infertility: NR Endometriosis: 12 [5.5] Male factor: 104 [47.7] Tubal factor: 66 [30.3] PCOS: 0 Other: 36 [16.5] Grp 2 Unexplained infertility: NR Endometriosis: 16 [7.6] Male factor: 117 [55.2] Tubal factor: 48 [22.6] PCOS: 0 Other: 31 [14.6] **Inclusion criteria:** - First attempt - Age ≥18 and ≤35. - Normal PAP **Exclusion criteria:** Contraindication to P treatment	Pregnancy: ongoing at end of 12th wk Live birth: NR Multiples: NR Complications: SAB	pg pos / pg neg / Total Utrogest: **55** / **163** / 218 Crinone: **47** / **165** / 212 Total: 102 / 328 / 430 Value (Lower 95% CI, Upper 95% CI) **Rel risk** 1.14 (0.81, 1.60) 2) SAB rate: SAB / No SAB / Total Utrogest: **10** / **45** / 55 Crinone: **9** / **38** / 47 Total: 19 / 83 / 102 Value (Lower 95% CI, Upper 95% CI) **Rel risk** 0.95 (0.42, 2.14)	**Quality assessment:** Randomization method: + Blinding: no Dropout rate < 20%: + Adequacy of randomization concealment: +
Klinkert, Broekmans, Looman, et	**Geographical location:** Rotterdam, Netherlands	**Age:** Grp 1: Mean (SD): 40.4	**Definition(s) of outcome(s):**	1) Clinical pregnancy: Preg + / Preg -	**Comments:** Low power

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
al., 2005 **#9240**	**Study dates:** May 2001 – Nov 2002 **Size of population:** Grp 1: 26 Grp 2: 26 **Number of cycles analyzed:** 52 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Grp 1: std dose of 150 IU rFSH Grp 2: double dose of 300 IU rFSH First IVF/ICSI cycle in pts with low antral follicle count (AFC)	Range: 36.6-44.5 Grp 2: Mean (SD): 42.2 Range: 33.7-44.6 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Grp 1: Unexplained infertility: 9 [34.6] Male factor: 12 [46.2] Tubal factor: 5 [19.2] Grp 2: Unexplained infertility: 7 [26.9] Male factor: 10 [38.5] Tubal factor: 9 [34.6]] **Inclusion criteria:** - Less than 5 antral follicles 2-5 mm - Regular cycles of 25-35 days - Presence of both ovaries **Exclusion criteria:** Ovarian cyst > 3 cm	Pregnancy: Clinical, not defined Ongoing pregnancy: +FCM at 12 wks EGA Live birth: NR Multiples: Reported, but none occurred Complications: NR	300 IU **1** **25** 26 150 IU **3** **23** 26 4 48 52 Lower 95% CI; Upper 95 % CI **Rel risk** 0.33 0.04 3.00 2) Ongoing pregnancy: Preg +; Preg - Study drug **1** **25** 26 Control **2** **24** 26 3 49 52 Lower 95% CI; Upper 95 % CI **Rel risk** 0.50 0.05 5.18 3) No difference in total # of follicles, # oocytes, # embryos between grps.	**Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +
Koicihi, Yukiko, Shima, et al., 2006	**Geographical location:** Miyagi, Japan **Study dates:** Jan-Sep	**Age:** Mean (SD): GnRH agonist: 32.3 (2.8); GnRH antagonist 32.6 (2.9);	**Definition(s) of outcome(s):** Pregnancy: Clinical	1) Clinical pregnancy (intention-to-treat), FSH + GnRH antagonist vs GnRH agonist long protocol:	**Comments:** No adjustment for multiple comparisons

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#53120	2004 **Size of population (no. of patients):** 192 **Number of cycles analyzed:** 192 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** - 3 weeks OCPs - Randomized to (a) Long protocol GnRH agonist (buserelin 900 microgram/day), with urinary human FSH daily. (b) uhFSH until follicle diameter of 14 mm, then increased dose of uFSH to 300 IU/day and addition of GnRH antagonist (Citrorelix) (c) uhFSH until follicle diameter of 14 mm, dose decreased to 75 IU/day, Cetrorelix begun with 200 IU/day hCG. - 10,000 IU hCG when 3 follicles 18mm - maximum 2 embryos transferred	antagonist + hCG: 33.3 (3.1) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 21 (10.9%) Endometriosis: 8 (4.2%) Male factor: 91 (47.3%) Tubal factor: 58 (30.2) PCOS: Other (specify): **Inclusion criteria:** - IVF/ICSI - Age <40 - BMI < 27 **Exclusion criteria:** NR	pregnancy—gestational sac with FHR at 6 weeks Live birth: NR Multiples: NR Complications: Miscarriage	Preg + / Preg - / Lower 95% CI / Upper 95 % CI GnRH antagonist: 21 / 42 / 63 GnRH agonist: 33 / 33 / 66 54 / 75 / 129 **Rel risk** 0.67 (0.44 – 1.02) 2) Clinical pregnancy (intention-to-treat), FSH + GnRH antagonist + hCG vs GnRH agonist long protocol: Antagonist + HCG: 23 / 40 / 63 GnRH agonist: 33 / 33 / 66 56 / 73 / 129 **Rel risk** 0.73 (0.49 – 1.10) 3) Clinical pregnancy (intention-to-treat),FSH + GnRH antagonist + FSH vs GnRH antagonist + hCG: Antag + hCG: 23 / 40 / 63 Antag only: 21 / 42 / 63 44 / 82 / 126 **Rel risk** 1.10 (0.68 – 1.77) 4) Miscarriage rate higher in agonist long protocol (16.2%) vs 10.5 and 9.1%	**Quality assessment:** Randomization method: Blinding: Dropout rate < 20%: Adequacy of randomization concealment:

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Kolibianakis, Albano, Camus, et al., 2003 **#14560**	**Geographical location:** Brussels, Belgium **Study dates:** May 2002 to January 2003 **Size of population (no. of patients):** 60 **Number of cycles analyzed:** 60 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** GnRH antagonist starting either from day 1 or from day 6 of stimulation	**Age:** Mean (SD): 32 (0.7) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Male factor: 65% Tubal factor: 18% Other: 17% **Inclusion criteria:** Age < 39 y, no more than three previous ART attempts, body-mass index between 18–29 kg/m2, regular menstrual cycles, no polycystic ovaries, no endometriosis or previous poor response to ovarian stimulation, and basal hormonal levels at initiation of stimulation (FSH < 10 IU/liter, LH < 10 IU/liter, E2 < 80 pg/ml, and progesterone (P) < 1.6 ng/ml) **Exclusion criteria:** None	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Ongoing pregnancy: Preg + / Preg - / Total Day 6: **15** / **15** / 30 Day 1: **14** / **16** / 30 29 / 31 / 60 Rel risk: 1.07 (Lower 95% CI 0.63, Upper 95% CI 1.81)	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: - (not clearly reported) Adequacy of randomization concealment: -
Kolibianakis, Albano, Camus, et al., 2004	**Geographical location:** Brussels, Belgium **Study dates:** May 2002 to April 2003	**Age:** Mean (SD): 32.5 (.03)* *not reported if this is SD or SEM; likely the latter.	**Definition(s) of outcome(s):** Pregnancy: Ongoing: pregnancy	1) Ongoing pregnancy: Ongoing preg + / Ongoing preg - / Total Early: **69** / **139** / 208	**Comments:** None **Quality assessment:**

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#12870	**Size of population (no. of patients):** 413 **Number of cycles analyzed:** 413 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** Early-hCG: 10,000 IU of hCG either as soon as ≥3 follicles ≥17 mm were present on ultrasound Late-hCG: 2 days after this criterion was met	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Endometriosis: [2%] Male factor: [62%] Tubal factor: [16%] PCOS: [4%] Other: [15%] Only %s reported **Inclusion criteria:** Age <39 years, presence of both ovaries, and basal levels of E2 (<80 pg/mL) and P (<1.6 ng/mL) at initiation of stimulation. **Exclusion criteria:** NR	progressing beyond the 12th week of gestation Multiples: Multiple ongoing pregnancy reported, not live birth Live birth: NR Multiples: Yes Complications: NR	Late **49** **156** 205 Total 118 295 413 Value / Lower 95% CI / Upper 95% CI **Rel risk** 1.39 1.02 1.89 2) Multiples: Sixteen twin pregnancies and one triplet pregnancy occurred in the early hCG group (multiple pregnancy rate, 24.6%) while 89 twin pregnancies occurred in the late-hCG group (multiple pregnancy rate, 18.4%).	Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +
Kolibianakis, Papanikolaou, Camus, et al., 2006 **#53150**	**Geographical location:** Brussels, Belgium **Study dates:** May 2002 to December 2004 **Size of population (no. of patients):** 504 **Number of cycles analyzed:** 504 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** OCP pretreatment: Low-dose monophasic combined OCP (150 µg desogestrel and 30 µg ethinylestradiol	**Age:** Mean (SD): 31.2 ± 0.3 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Endometriosis: 3% Male factor: 62% Tubal factor: 16% Other – idiopathic 19% **Inclusion criteria:** Age < 39 years; ≤ 3 previous assisted reproduction (ART) attempts; body mass index (BMI) of 18–29 kg/m2; regular menstrual cycles; basal hormonal levels of FSH (<10 IU/l) and LH (<10 IU/l) at initiation of stimulation for the non-	**Definition(s) of outcome(s):** Pregnancy: Ongoing pregnancy was defined as pregnancy developing beyond 12 weeks. Live birth: NR Multiples: Yes (twins) Complications: Admission for hyperstimulation syndrome	1) Ongoing pregnancy: Ongoing preg + / Ongoing preg - / Total OCP **51** **199** 250 Non-OCP **60** **194** 254 Total 111 393 504 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.86 0.62 1.20 2) Multiple births: Ongoing twin pregnancy rate of 17.8%, no difference between OCP (16.3%) and non-OCP (19%). 3) Complications: 4 patients in OCP and 1 in non-OCP group were admitted due to ovarian hyperstimulation syndrome.	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	(Marvelon®; Organon), for 2 weeks starting on day 1 of the cycle. Non-OCP pretreatment: [Recombinant FSH was started on day 2 of the menstrual cycle in the non-OCP group or 5 days after discontinuation of the OCP in the OCP group at 200 IU per day.]	OCP group and at initiation of OCP in the OCP group. **Exclusion criteria:** Polycystic ovaries; endometriosis > stage II; previous poor response to ovarian stimulation.			
Kolibi-anakis, Schultze-Mosgau, Schroer, et al., 2005 **#39570**	**Geographical location:** Brussels, Belgium Lubeck, Germany **Study dates:** 12/03 - 10/04 **Size of population:** Grp 1: Surge with GnRH agonist-52 Grp 2: Surge with hCG-54 **Number of cycles analyzed: 106** **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Women undergoing IVF with a GnRH antagonist protocol were randomized to receive either GnRH agonist or hCG for final oocyte maturation.	**Age:** Mean (SD): Grp 1: 32.4 (0.6) Grp 2: 32.3 (0.5) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Grp 1: Unexplained infertility: 5 [9.6] Endometriosis: 0 Male factor: 36 [69.2] Tubal factor: 4 [7.7] PCOS: 0 Other: 7 [13.5] Grp 2 Unexplained infertility: 3 [5.6] Endometriosis: 0 Male factor: 40 [74.1] Tubal factor: 6 [11.1] PCOS: 0 Other: 5 [9.3] **Inclusion criteria:** ≥ 39, nl day 3 FSH, ≤ 3 previous ART cycles, BMI 18-29, regular cycles, no PCOS or hx of poor	**Definition(s) of outcome(s):** Pregnancy: Ongoing past 12 wks Live birth: NR Multiples: NR Complications: SAB	1) Ongoing pg rate grp 1 vs 2: preg + / preg neg / Total GnRH: **2** / **50** / 52 hCG: **15** / **39** / 54 Total: 17 / 89 / 106 Value (Lower 95% CI, Upper 95% CI) **Rel risk** 0.14 (0.03, 0.58) 2) SAB: SAB / No SAB / Total Grp 1: **7** / **2** / 9 Grp 2: **2** / **15** / 17 Total: 9 / 17 / 26 Value (Lower 95% CI, Upper 95% CI) **Rel risk** 6.61 (1.72, 25.45)	**Comments:** Powered to detect 30% absolute difference in pregnancy rates **Quality assessment:** Randomization method: + Blinding: no Dropout rate < 20%: + Adequacy of randomization concealment: no

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		response, 2 ovaries, fresh sperm and no embryo biopsy **Exclusion criteria:** NR			
Kolibi-anakis, Zikopoulos, Verpoest, et al., 2004 **#10880**	**Geographical location:** Brussels, Belgium **Study dates:** Jan 2001-Dec 2003 **Size of population (no. of patients):** 460 **Number of cycles analyzed:** 460 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Randomized to day 3 or day 5 transfer at time of initial evaluation 1-2 embryos/transferred	**Age:** Mean (SD): Day 3: 31.3 (0.3); Day 5: 31.5 (0.2) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 16% Endometriosis: 5% Male factor: 65% Tubal factor: 10% PCOS: 3.5% **Inclusion criteria:** - Age < 43 years - Indication for IVF **Exclusion criteria:** - PGD - Azoospermia	**Definition(s) of outcome(s):** Pregnancy: Pregnancy beyond 12 weeks Live birth: NR Multiples: Yes (twins) Complications: NR	1) Ongoing pregnancy: Preg + / Preg - / Total Day 5: **75** / **151** / 226 Day 3: **75** / **159** / 234 150 / 310 / 460 Rel risk: 1.04 (Lower 95% CI 0.80; Upper 95 % CI 1.35) 2) Multiples (twins): Preg + / Preg - / Total Day 5: **20** / **55** / 75 Day 3: **15** / **60** / 75 35 / 115 / 150 Rel risk: 1.33 (Lower 95% CI 0.74; Upper 95 % CI 2.40)	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -
Konto-ravdis, Makrakis, Pantos, et al., 2006	**Geographical location:** Athens, Greece **Study dates:** 2000-June 2005	**Age:** Mean (SD): Salpingectomy: 31 (4.5); occlusion: 29.8 (3.4); control: error in table (reads "3.4)	**Definition(s) of outcome(s):** Clinical pregnancy: Gestational sac 4 weeks after transfer	1) Ongoing pregnancy: any surgery vs control, intention-to-treat: Preg + / Preg - / Total Surgery: 40 / 60 / 100 Control: 1 / 14 / 15	**Comments:** - No adjustment for multiple comparisons - Rationale for sample size for control group not clear

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#53180	**Size of population (no. of patients):** 115 **Number of cycles analyzed:** 115 (9 randomized subjects not included in analysis) **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** - A: unilateral or bilateral laparoscopic salpingectomy - B: proximal laparoscopic tubal occlusion (bilateral or unilateral) - C: No surgery - All underwent long protocol COH with GnRH agonist, rFSH - Groups A and B began 2 menstrual cycles after surgery	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Tubal factor: 100% **Inclusion criteria:** - Presence of unilateral or bilateral hydrosalpinges confirmed by hysterosalpingography; - age of ≤41 years - suitability for IVF–intracytoplasmic sperm injection treatment, with FSH levels on females' cycle day 2–3 of ≤12 mIU/mL and available spermatozoa in semen - no contraindication for laparoscopic surgery; no history of IVF attempts before recruitment - absence of any other obvious pelvic pathology in females **Exclusion criteria:** NR	Ongoing pregnancy: Beyond first trimester Live birth: NR Multiples: NR Complications: NR	41 74 115 Lower 95% CI / Upper 95 % CI **Rel risk** 6.00 0.89 40.47 2) Ongoing pregnancy, salpingectomy vs control, intention-to-treat: Preg + / Preg - Salpingectomy 17 / 33 = 50 Control 1 / 14 = 15 18 / 47 = 65 Lower 95% CI / Upper 95 % CI **Rel risk** 5.10 0.74 35.23 3) Ongoing pregnancy, occlusion vs control, intention-to-treat: Preg + / Preg - Occlusion 23 / 27 = 50 Control 1 / 14 = 15 24 / 41 = 65 Lower 95% CI / Upper 95 % CI **Rel risk** 6.90 1.01 46.93 4) Ongoing pregnancy, salpingectomy vs occlusion, intention-to-treat: Preg + / Preg - Salping-ectomy 17 / 33 = 50 Occlusion 23 / 27 = 50 40 / 60 = 100 Lower 95% CI / Upper 95 % CI **Rel risk** 0.74 0.45 1.21	**Quality assessment:** Randomization method: + Blinding: Dropout rate < 20%: Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Korosec, Virant-Klun, Tomazevic, et al., 2007 **#71680**	**Geographical location:** Ljubljana, Slovenia **Study dates:** Apr 2004-June 2006 **Size of population (no. of patients):** 279 **Number of cycles analyzed:** 279 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Randomized to embryo transfer with hyaluronic acid containing media (EmbryoGlue®) vs. standard non-HA containing media All single blastocyst transfers	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 15% Endometriosis: 18% Male factor: 39% Tubal factor:43% Other: "Endocrine" **Inclusion criteria:** - Age < 37 - 1st 3 attempts **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Pregnancy, fresh cycles: Preg+ / Preg - / Total HA: **12** / **16** / 28 No HA: **11** / **26** / 37 Total: 23 / 42 / 65 Value / Lower 95% CI / Upper 95% CI **Rel risk**: 1.44 / 0.75 / 2.77 2) Pregnancy, frozen-thawed transfers: Out + / Out - / Total HA: **17** / **85** / 102 No HA: **17** / **95** / 112 Total: 34 / 180 / 214 Value / Lower 95% CI / Upper 95% CI **Rel risk**: 1.10 / 0.59 / 2.03	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +
Kosmas, Janssens, De Munck, et al., 2007 **#71690**	**Geographical location:** Brussels, Belgium **Study dates:** Aug 2005-Feb 2006 **Size of population (no.**	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 35	**Definition(s) of outcome(s):** Pregnancy: Rising hCG Clinical pregnancy—confirmed on ultrasound	1) Clinical pregnancy: Preg+ / Preg - / Total Ultra-sound: **63** / **87** / 150 Clinical: **63** / **87** / 150	**Comments:** 3 interim analyses, with no stated a priori stopping rules – described procedure not standard for stopping trial (original N = 700) **Quality assessment:**

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	of patients): 300 **Number of cycles analyzed:** 300 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Single operator, ultrasound guided transfer vs. clinical touch	(11.7%) Endometriosis: 19 (6.3%) Male factor: 179 (59.7%) Tubal factor: 35 (11.7%) PCOS: 12(4.0%) Other: 36 (12.0%) **Inclusion criteria:** - Age 40 or less - BMI 20-30 - Fresh transfer **Exclusion criteria:** Treatment of CIN	Live birth: NR Multiples: NR Complications: NR	Total 126 174 300 Value / Lower 95% CI / Upper 95% CI **Rel risk** 1.00 0.77 1.30	Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -
Latin-American Puregon IVF Study Group, 2001 **#3580**	**Geographical location:** 15 sites in Argentina, Brazil, Chile, Colombia, Mexico, and Venezuela **Study dates:** June 1998-Sept 1999 **Size of population (no. of patients):** 404 **Number of cycles analyzed:** 404 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** **-** Down-regulation with leuprolide Randomized to 150 or 250 IU rFSH, fixed dosage; maximum duration of treatment 3 weeks rFSH started when E2 < 200 pg/ml, continued	**Age:** Mean (SD): 150 IU 35.1 (3.1); 250 IU 35.3 (2.9) **Race/ethnicity (n [%]):** **Diagnoses (n [%]):** Unexplained infertility: 47 (11.6%) Endometriosis: 17 (4.2%) Male factor: 177 (43.8%) Tubal factor: 97 (24.0%) PCOS: 0 Other (specify): Multiple: 66 (16.3%) **Inclusion criteria:** - Ages 30-39 - Candidates for IVF/ICSI - Normal menstrual cycles -BMI 18-29 **Exclusion criteria:** Endocrine abnormality (PCOS, etc) ; 1 ovary or history of ovarian resection; severe endometriosis (grade III and IV); previous COH cycles in which less than	**Definition(s) of outcome(s):** Pregnancy: Gestational sac with fetal heart rate Live birth: NR Multiples: NR Complications: OHSS	1) Clinical pregnancy: Preg + / Preg - / (total) 250 IU 34 169 203 150 IU 34 167 201 68 336 404 Lower 95% CI / Upper 95 % CI **Rel risk** 0.99 0.64 1.53 2) 2 cases of hospitalized OHSS in 250 IU group, 0 in 150 IU group; overall OHSS 8 in 150 IU group, 5 in 250 IU group	**Comments:** Sample size based on # of cumulus-oocyte complexes, total dose rFSH **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	until at least 2 follicles ≥20 mm	three oocytes were retrieved; previous hospitalization due to the ovarian hyperstimulation syndrome (OHSS); chronic cardiovascular, hepatic, renal, or pulmonary disease; a history of (within 12 months) or current abuse of alcohol or drugs; administration of nonregistered investigational drugs within 3 months before screening.			
Laverge, De Sutter, Van der Elst, et al., 2001 **#5740**	**Geographical location:** Ghent, Belgium **Study dates:** NR **Size of population (no. of patients):** 746 **Number of cycles analyzed:** 746 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Randomized after fertilization to (a) Day 2 transfer or (b) day 3 transfer 2 embryos transferred in patients <38 years; 3 if 2 failed cycles, age >38 years, or no good quality embryos	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Scheduled for IVF or ICSI ≥7 fertilized oocytes **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Clinical pregnancy: + hCG with gestational sac 4 weeks after transfer Live birth: NR Multiples: NR Complications: NR	1) Clinical pregnancy: Preg + / Preg - Day 2: **166** / **208** — 374 Day 3: **164** / **208** — 372 330 / 416 — 746 **Rel risk** 1.01 (Lower 95% CI 0.86; Upper 95 % CI 1.18)	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Lee, Wu, Chen, et al., 2005 **#40040**	**Geographical location:** Taipei, Taiwan **Study dates:** NR **Size of population:** Grp 1: 20 MD Grp 2: 20 SD Grp 3: 20 LP **Number of cycles analyzed:** 60 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** MD: IVF with multiple doses of GnRH antagonist (cetrorelix) starting on day 5 SD: IVF with single dose of GnRH antagonist (cetrorelix) on day 7 LP: luteal phase GnRH agonist using nasal buserelin	**Age:** Grp 1: Mean (SD): 31.7 [3.8] Grp 2: Mean (SD): 32.9 [3.2] Grp 3 Mean (SD): 32.8 [4.4] **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Grp 1: Unexplained infertility: 1 [5] Endometriosis: 2 [10] Male factor: 7 [35] Tubal factor: 13 [65] PCOS: 0 Grp 2: Unexplained infertility: 2 [10] Endometriosis: 2 [10] Male factor: 11 [55] Tubal factor: 7 [35]] PCOS: 0 Grp 3: Unexplained infertility: 2 [10] Endometriosis: 2 [10] Male factor: 13 [65] Tubal factor: 6 [30] PCOS: 0 **Inclusion criteria:** ≤ 39, reg cycle 26-33 d, BMI 18-29, no hx of poor ovarian response, baseline FSH ≤ 10, nl liver and renal fx, 2 ovaries, no hormone tx within 3 mo	**Definition(s) of outcome(s):** Pregnancy: + FCM Live birth: NR Multiples: NR Complications: NR	1) Pg rate grp 1 vs 2: pg pos / pg neg / Total MD antagonist: **10** / **10** / 20 SD antagonist: **5** / **15** / 20 Total: 15 / 25 / 40 Value / Lower 95% CI / Upper 95% CI **Rel risk**: 2.00 / 0.83 / 4.81 2) Pg rate grp 1 vs 3: pg pos / pg neg / Total MD antagonist: **10** / **10** / 20 GnRH agonist: **9** / **11** / 20 Total: 19 / 21 / 40 Value / Lower 95% CI / Upper 95% CI **Rel risk**: 1.11 / 0.58 / 2.14 3) P rate grp 2 vs 3: pg pos / pg neg / Total SD antagonist: **5** / **15** / 20 GnRH agonist: **9** / **11** / 20 Total: 14 / 26 / 40 Value / Lower 95% CI / Upper 95% CI **Rel risk**: 0.56 / 0.23 / 1.37	**Comments:** Low numbers No adjustment for multiple comparisons **Quality assessment:** Randomization method: NR Blinding: no Dropout rate < 20%: + Adequacy of randomization concealment: no

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		Exclusion criteria: Women with ovarian factor, uterine factor infertility or presence of ovarian cysts			
Lenton, Soltan, Hewitt, et al., 2000 **#7970**	**Geographical location:** Multicenters in UK **Study dates:** Jan 1997 - Feb 1998 **Size of population:** 168 **Number of cycles analyzed:** 155 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** The study compares the usage of rFSH (follitropin alpha) vs. uFSH (urofollitropin HP) for ovulation induction for IVF or ICSI.	**Age:** Mean (SD): - rFSH: 32.1 (2.9) - uFSH: 31.9 (3.5) Median: NR Range: 18-38 **Race/ethnicity (n [%]):** NR **Diagnoses (%):** Unexplained infertility: - rFSH: 25.0 - uFSH: 22.7 Endometriosis: - rFSH: 2.5 - uFSH: 2.7 Male factor: - rFSH: 35 - uFSG: 47.7 Tubal factor: - rFSH: 37.5 - uFSH: 45.3 **Inclusion criteria:** - Tubal factor - Gr I or II endometriosis - 1st cycle of ART - Regular ovulatory menstrual cycle of 25d-35d - BMI ≥ 18 but ≤ 26 kg/m^2 - Presence of both ovaries - Normal uterine cavity - No gonadotropins in the month prior to the study **Exclusion criteria:** - Previous poor or hyper-response to gonadotropins	**Definition(s) of outcome(s):** Clinical Pregnancy: + gestational sac on u/s 28d after egg collection Live birth: Yes Multiples: NR Complications: Adverse events were recorded on the basis of the pt's or physician's observation An adverse event was classified as serious if it was fatal or life-threatening, was permanently disabling, required inpatient or prolonged hospitalization or was a congenital anomaly, cancer or overdose	1) Positive pregnancy test: Preg + / Preg - / Total rFSH: **31** / **49** / 80 uFSH: **27** / **48** / 75 58 / 97 / 155 Value (Lower 95% CI, Upper 95% CI) **Rel risk** 1.08 (0.72, 1.62) 2) Clinical pregnancy rate: Preg + / Preg - / Total rFSH: **27** / **53** / 80 uFSH: **24** / **51** / 75 51 / 104 / 155 Value (Lower 95% CI, Upper 95% CI) **Rel risk** 1.05 (0.67, 1.66) 3) Live birth rate: LB + / LB - / Total rFSH: **27** / **53** / 80 uFSH: **20** / **55** / 75 47 / 108 / 155 Value (Lower 95% CI, Upper 95% CI) **Rel risk** 1.27 (0.78, 2.06) 4) Safety outcomes: Most adverse events were mild in nature. Of 50 pts, 25(30.9%) in rFSH and 26 (34.2%) in uFSh grp reported at lease one adverse event. Five pts had serious adverse events:	**Comments:** Powered to detect difference in mean # of oocytes retreived **Quality assessment:** Randomization method:+ Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment:+

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		- Previous history of severer OHSS - PCOS - Male partner with azoospermia or clinical signs of infection detected in semen analysis within 12 mos		- 2 in rFSH (both OHSS) - 3 in uFSH (2 OHSS, one with iliac fossa pain) 13 pts had OHSS (7 from rFSH and 6 from uFSH Local tolerance: > 70% of pts reported either none or mild pain, tenderness, redness, itching, and bruising around the injection site 5) Pregnancy rate: No statistically significant differences between the 2 grps. Data reported on per- cycle and per-embryo-transfer basis. 6) Embryological characteristics of the two grps: No statistically significant differences between the 2 grps.	
Levi-Setti, Cavagna, and Bulletti, 2006 **#53590**	**Geographical location:** Milan, Italy **Study dates:** NR **Size of population (no. of patients):** 40 **Number of cycles analyzed:** 40 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** **-** Pretreated with OCPs - On day 2, begin 225 IU/day rFSH; Cetrorelix 0.25 mg sc added when mean follicular diameter 14 mm	**Age:** Mean (SD): rFSH: 32.3 (2.3); rFSH + rLH: **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Male factor: 100% **Inclusion criteria:** - COH for ISCI for male factor - normal cycles - fresh ejaculated semen only - Age < 37 - BMI < - no previous pelvic surgery - no evidence of endometriosis on U/S	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Pregnancy: Preg + / Preg - rFSH + rLH: 7 / 13 (20) rFSH only: 6 / 14 (20) 13 / 27 (40) Rel risk 1.17 (Lower 95% CI 0.48; Upper 95 % CI 2.86)	**Comments :** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	- Randomized to (a) no additional treatment (225 IU rFSH alone) (b) 150 IU rFSH + 75 IU rLH	**Exclusion criteria:** NR			
Levitas, Lunenfeld, Har-Vardi, et al., 2004 **#13590**	**Geographical location:** Beer-Sheva, Israel **Study dates:** NR **Size of population:** Grp 1: 31 Grp 2: 23 **Number of cycles analyzed:** 54 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Women undergoing IVF/ICSI with history of 3 or more failed previous attempts Grp 1: Day 2-3 ET Grp 2: Blastocyst transfer	**Age:** Grp 1 Mean (SD): 31.2 (3.4) Grp 2: Mean (SD): 29.1 (3.1)) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Grp 1: Male factor: 19 [62.5] Tubal factor: 10 [33] Grp 2: Male factor: 18 [78.9]] Tubal factor: 5 [21.1] **Inclusion criteria:** - Failure to conceive in at least 3 previous IVF cycles with acceptable ovarian response and fertilization - Age < 37 - Normal uterine cavity **Exclusion criteria:** - Peak estradiol < 500 or retrieval of < 3 oocytes during previous IVF cycle	**Definition(s) of outcome(s):** Pregnancy: +FCM Live birth: NR Multiples: Yes Complications: NR	1) Clinical pregnancy rate: Preg + / Preg - / Total Blastocyst: 5 / 18 / 23 Day 2-3: 4 / 31 / 35 9 / 49 / 58 Rel risk: 1.90 (Lower 95% CI 0.57, Upper 95 % CI 6.35) 2) Multiple pregnancy: Preg + / Preg - / Total Study drug: **2** / **3** / 5 Control: **3** / **1** / 4 5 / 4 / 9 Rel risk: 0.53 (Lower 95% CI 0.16, Upper 95 % CI 1.79)	**Comments:** Biases favoring pregnancy in Day 2-3 group include greater # of embryos transferred per cycle and greater # of pts receiving embryo transfer **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +
Li, Lu, Hao, et al., 2005 **#9590**	**Geographical location:** Peking, China **Study dates:** June 2001-June 2003	**Age (mean [SD]):** U/S: 32.2 (3.9) Control: 32.5 (3.2) **Race/ethnicity (n [%]):**	**Definition(s) of outcome(s):** Pregnancy: Ultrasound at 6-7 weeks (requirement	1) Clinical pregnancy: Preg + / Preg - / Total U/S: 66 / 112 / 178	**Comments:** Relatively large discrepancy in group size **Quality assessment:**

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		NR, assume 100% Asian	for FHR not stated)	Control: 38 / 114 / 152 104 / 226 / 330 Rel risk: 1.48 (Lower 95% CI 1.06, Upper 95 % CI 2.07)	Randomization method: - (NR) Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +
	Size of population (no. of patients): 330 **Number of cycles analyzed:** 330 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** - Embryo transfers 2-3 days after oocyte retrieval - U/S group: transabdominal U/S using Wallace catheter; embryos transferred when catheter tip within 1.5-2.0 cm of fundus - Controls: clinician judgment	**Diagnoses (n [%]):** Unexplained infertility: 24 (7.3%) Endometriosis: 42 (12.7%) Male factor: 125 (37.8%) Tubal factor: 123 (37.3%) Multiple diagnoses: 16 (4.8%) **Inclusion criteria:** Age 28-41, undergoing IVF or ICSI **Exclusion criteria:** NR	Live birth: NR Multiples: NR Complications: NR		
Lok, Chan, Chan, et al., 2002 **#58340**	**Geographical location:** Hong Kong, China **Study dates:** Mar 2001-Aug 2001 **Size of population (no. of patients):** 106 **Number of cycles analyzed:** 106	**Age:** Mean (SD): PCA: 32.9 (4.1) Physician controlled: 34.9 (3.3) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 20 (18%)	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: Pain	1) Pregnancy: Patient: **8** / **43** / 51 Physician: **13** / **42** / 55 Total: 21 / 85 / 106 Rel risk: 0.66 (Lower 95% CI 0.30, Upper 95% CI 1.47)	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Number of cycles per patient: 1.0 **Study type:** RCT **Interventions:** Patient-controlled sedation (PCS) vs. physician administered IV sedation	Endometriosis: 7 (5%) Male factor: 10 (9%) Tubal factor: 61 (55%) PCOS: 7 (5%) Other: 1 (<1%) **Inclusion criteria:** Scheduled for oocyte retrieval **Exclusion criteria:** - < 3 dominant follicles - Contraindication to drugs used		2) Pain scores higher with patient control, but overall satisfaction similar	
Loutradis, Stefanidis, Drakakis, et al., 2004 **#58350**	**Geographical location:** Chelmsford, MA **Study dates:** NR **Size of population (no. of patients):** 116 **Number of cycles analyzed:** 116 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Long-protocol GnRH agonist down-regulation (triptoreline) vs. GnRH antagonist (cetrorelix)	**Age:** Mean (SD): Agonist: 34.9 (4.7) Antagonist: 35.8 (4.9) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Age 20-38 - No low response in a previous treatment cycle - No uterine or ovarian anomalies - History of regular menstrual cycles ranging from 25 to 35 days **Exclusion criteria:** Poor responder	**Definition(s) of outcome(s):** Pregnancy: Gestational sac at 4 weeks Live birth: NR Multiples: NR Complications: NR	1) Pregnancy: Preg + / Preg - / Total Antagonist: **11** / **47** / 58 Agonist: **14** / **44** / 58 Total: 25 / 91 / 116 Value / Lower 95% CI / Upper 95% CI **Rel risk**: 0.79 / 0.39 / 1.58	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: - Adequacy of randomization concealment: +
Ludwig, Felberbaum, Devroey, et al., 2000 **#6990**	**Geographical location:** Brussels, Belgium; Lubeck and Frankfurt, Germany **Study dates:** NR	**Age:** Mean (SD): Cetrorelix: 31.9 (3.7) Buserelin: 31.6 (3.8) **Race/ethnicity (n [%]):**	**Definition(s) of outcome(s):** Clinical Pregnancy: u/s showed gestational sac and fetus with cardiac	1) Clinical pregnancy rate: Preg + / Preg - Cetrorelix: **42** / **146** / 188 Buserelin: **22** / **66** / 88	**Comments:** None **Quality assessment:** Randomization method: + Blinding: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
(OHSS results only) *and* **Albano, Felberbaum, Smitz, et al., 2000** **#8590**	**Size of population:** 273 **Number of cycles analyzed:** 273 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** Compared the use of GnRH agonist (buserelin) and GnRH antagonist (cetrorelix) in ovarian stimulation with HMG	NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Age ≤ 39 - Regular menstrual cycle ranging 24d-35d - Normal ovarian function (detected by FSH ≤ 10 IU/L) - Normal ovarian morphology - Normal uterus - No more than three previous IVF or ICSI **Exclusion criteria:** NR	activity Live birth: NR Multiples: NR Complications: Miscarriage, ectopic pregnancies, OHSS using WHO criteria: OHSS II: Moderate OHSS III: Severe	64 212 276 Lower 95% CI / Upper 95 % CI **Rel risk** 0.89 0.57 1.40 2) Number of deliveries (patients): Del + / Del - Cetrorelix **34** **154** 188 Busereln **19** **69** 88 53 223 276 Lower 95% CI / Upper 95 % CI **Rel risk** 0.84 0.51 1.38 3) Outcomes of all pregnancies: Cetrorelix / Buserelin / P-value Clinical preg 42 22 NS Miscarriage 7 2 Ectopic preg 1 0 No of deliveries 34 19 NS Singletons 26 17 Twins 8 2 No. children born 42 21 4) OHSS rate: OHSS + / OHSS - / Total Cetrorelix **2** **186** 188 Buserelin **5** **80** 85 Total 7 266 273 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.18 0.04 0.91 5) One pt in Buserelin group had severe OHSS 6) 3 (1.6%) pts in Cetrorelix and 6 (5.9%) in Buserelin grp did not get hCG trigger due to threatened OHSS.	Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Significantly higher E2 on the date of hCG trigger was noted in Buserelin grp.	
Ludwig, Finas, Katalinic, et al., 2001 **#5200**	**Geographical location:** Lubeck, Germany **Study dates:** NR **Size of population (no. of patients):** 413 **Number of cycles analyzed:** 413 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** COH by GnRH agonist long protocol -Randomization stratified by OHSS risk; low risk (<12 oocytes, E2<2500 pg/mL day of retrieval) (a) 5000 IU hCG day of ET, 5000 IU 3 days later,2500 IU 6 days post-transfer (b) 5000 IU hCG day of ET, vaginal progesterone 600mg/day from day prior to ET to menstrual bleeding or + hCG (c) vaginal progesterone 600 mg/day High risk (d) 5000 IU hCG day of ET, vaginal progesterone 600mg/day from day prior to ET to menstrual bleeding or + hCG (e) vaginal progesterone 600 mg/day	**Age:** Mean (SD): 32.2 (4.1) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Age < 40 - IVF/ICSI **Exclusion criteria:** - E2 > 5000 pg/ml - Abdominal discomfort on day of ET	**Definition(s) of outcome(s):** Pregnancy: +FHR on ultrasound Live birth: Live or stillbirth > 500 g or live birth < 500 g Multiples: NR Complications: NR	1) Clinical pregnancy, Progesterone only vs Progesterone + hCG (both high and low risk groups combined): Preg + / Preg - Prog + hCG: **36** / **109** — 145 Prog onlyl: **47** / **144** — 191 83 / 253 — 336 Rel risk 1.01 (Lower 95% CI 0.69, Upper 95 % CI 1.47) 2) Clinical pregnancy, progesterone only vs hCG only (high, low risk groups combined for progesterone only): Preg + / Preg - hCG only: 15 / 62 — 77 Prog only: 47 / 144 — 191 62 / 206 — 268 Rel risk 0.79 (Lower 95% CI 0.47, Upper 95 % CI 1.33) 3) Similar results for ongoing pregnancy	**Comments:** No adjustment for multiple comparisons **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Ludwig, Schwartz, Babahan, et al., 2002 **#1940**	**Geographical location:** Lubeck, Germany **Study dates:** NR **Size of population (no. of patients):** 126 **Number of cycles analyzed:** 126 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Vaginal progesterone (a) 8 % gel once daily or (b) 200 mg capsule 3x/daily, beginning day before ET Long prototol GnRH agonist COH	**Age:** Mean (SD): Gel: 31.4 (5.5) ; capsules: 31.5 (4.3)acoss 5 groups—no significant differences **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** IVF/ICSI **Exclusion criteria:** Estradiol <2000 pg/mL day of retrieval	**Definition(s) of outcome(s):** Pregnancy: Clinical pregnancy: + FHR Ongoing pregnancy: > 12 weeks Live birth: NR Multiples: NR Complications: NR	1) Clinical pregnancy: Preg + / Preg - / Total Gel: **21** / **52** / 73 Capsule: **10** / **43** / 53 31 / 95 / 126 Rel risk: 1.52 (Lower 95% CI 0.78, Upper 95 % CI 2.96) 2) Ongoing pregnancy: Preg + / Preg - / Total Study drug: **18** / **55** / 73 Control: **9** / **44** / 53 27 / 99 / 126 Rel risk: 1.45 (Lower 95% CI 0.71, Upper 95 % CI 2.98)	**Comments:** - Randomization method not described - Relatively large discrepancy between arms **Quality assessment:** Randomization method: - Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -
Lukassen, Braat, Wetzels, et al., 2005 **#9180**	**Geographical location:** Nijmegen, Netherlands **Study dates:** Jan 2001 – Feb 2003 **Size of population:** Grp 1: 54 Grp 2: 53 **Number of cycles analyzed:** 14 **Number of cycles per**	**Age:** Grp 1 Mean (SD): 30.2 (3.2) Range: 20-34 Grp 2: Mean (SD): 31.2)2.9) Range: 25-34 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Grp 1	**Definition(s) of outcome(s):** Pregnancy: + FCM Live birth: Yes Multiples: Yes Complications: NR	1) Clinical pregnancy rate: Preg + / Preg - / Total Grp 1: **30** / **24** / 54 Grp 2: **25** / **28** / 53 Total: 55 / 52 / 107 Value (Lower 95% CI, Upper 95% CI) Rel risk: 1.18 (0.81, 1.71) 2) Live birth:	**Comments:** - 4 pts did not undergo 2nd cycle in Grp 1 - 3 pts received 2 embryos during 2nd cycle of Grp 1 **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	patient: 1.37 **Study type:** RCT **Interventions:** Grp 1: 2 IVF/ICSI cycles with single embryo transfer Grp 2: 1 IVF/ICSI cycle with double embryo transfer IVF/ICSI with luteal phase GnRH downregulation and rFSH stimulation	Unexplained infertility: 5 [9] Male factor: 36 [67] Tubal factor: 5 [9] "Other female": 8 [15] Grp 2 Unexplained infertility:14[[27] Male factor: 26 [49] Tubal factor: 9 [17] "Other female": 4 [8] **Inclusion criteria:** - Age < 35 - Basal FSH < 10 - First IVF/ICSI attempt ever or after successful pregnancy - At least 2 embryos (1 grade 4 and 1 at least grader 3) available for transfer on day 3 **Exclusion criteria:** NR		LB + / LB - / Total Grp 1: **22** / **32** / 54 Grp 2: **19** / **34** / 53 Total: 41 / 66 / 107 Rel risk: Value 1.14, Lower 95% CI 0.70, Upper 95% CI 1.84 3) Multiples: Multi + / Multi - / Total Grp 1: **0** / **22** / 22 Grp 2: **7** / **12** / 19 Total: 7 / 34 / 41 Rel risk: Value 0.06, Lower 95% CI 0.00, Upper 95% CI 0.95 4) Costs per live birth similar (€ 13,438 for SET, €13,680 for DET)	
Lukaszuk, Liss, Lukaszuk, et al., 2005 **#40480**	**Geographical location:** Gdansk, Poland **Study dates:** Mar 2002-Mar 2003 **Size of population (no. of patients):** 166 **Number of cycles analyzed:** 231 **Number of cycles per patient:** 1.39	**Age:** Mean (SD): P only: 32.1 (4.5); P + 2 mg E2: 31.7 (3.9); P + 6 mg E2: 31.1 (3.7) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 19 (11.4%) Endometriosis: 6 (3.6%) Male factor: 66 (39.8%) Tubal factor: 36 (21.7%)	**Definition(s) of outcome(s):** Pregnancy: Gestational sac at 5 weeks 2 days Live birth: NR Multiples: NR Complications: NR	1) Pregnancy per randomized patient, P only vs P + 2 mg E2: Preg + / Preg - / Total P + 2 mg E2: **24** / **23** / 47 P only: **18** / **32** / 50 42 / 55 / 97 Rel risk: 1.42, Lower 95% CI 0.89, Upper 95 % CI 2.26 2) Pregnancy per randomized patient, P only	**Comments:** - Unclear if randomized to same treatment for multiple cycles—Table 1 suggests this was the case, but not explicitly described - Randomization method not described - Relatively large imbalance in patient numbers by group No adjustment for multiple comparisons **Quality assessment:** Randomization method: - Blinding: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Study type: RCT **Interventions:** From day of transfer, randomized to (a) 600 mg vaginal progesterone (capsules) (b) 2 mg estradiol daily (c) 6 mg estradiol daily	PCOS: 20 (12.1%) Other: Mixed: 19 (11.4%) **Inclusion criteria:** - < 40 years - ICSI **Exclusion criteria:** NR		vs P + 6 mg E2: Preg + / Preg - / Total P + 6 mg E2: 40 / 29 / 69 P only: 18 / 32 / 50 58 / 61 / 119 Rel risk: 1.61 (Lower 95% CI 1.06, Upper 95 % CI 2.45) 3) Pregnancy 6 mg E2 vs 2 mg E2: 1.14 (0.80, 1.60); Multiple pregnancies significantly higher with E2 regimens (0% P only, 30.4% 2 mg E2, 25.6% 6 mg E2)	Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Ma, Rowe, and Yuen, 2006 **#53850**	**Geographical location:** Vancouver, Canada **Study dates:** 1999-2003 **Size of population (no. of patients):** 172 **Number of cycles analyzed:** 172 (14 excluded because of few oocytes) **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Randomized to (a) control or (b) assisted hatching with acidic Tyrode's solution day 3 prior to transfer	**Age:** Mean (SD): Control: 35.5 (3.8); assisted hatching 35.4 (4.7) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - semen analysis with fewer than 1 x 10^6 sperm/mL with <50% progressively motile sperm (grade 3) or<5% normal sperm morphology (Kruger's criteria) - ≥ 1 failed IVF cycle with an adequate number of inseminated oocytes or with a fertilization rate of <20%. **Exclusion criteria:** Retrieval of fewer than 4 oocytes and a baseline serum FSH of <12 IU/mL.	**Definition(s) of outcome(s):** Pregnancy: Intrauterine gestational sac at 5 weeks Live birth: Yes Multiples: Yes Complications: NR	1) Clinical pregnancy: Preg + / Preg - / Total Assisted hatching: **29** / **56** / 85 Control: **18** / **65** / 83 47 / 121 / 168 Rel risk: 1.57 (Lower 95% CI 0.95; Upper 95% CI 2.61) 2) Live birth: Birth + / Birth - / Total Assisted hatching: 20 / 65 / 85 Control: 15 / 68 / 83 35 / 133 / 168 Rel risk: 1.30 (Lower 95% CI 0.72; Upper 95% CI 2.37) 3) Multiple pregnancy hatching vs control 1.5 (0.65, 1.47); implantation rate significantly higher with hatching (16% vs 8%)	**Comments:** None **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +
Mahani and Davar, 2007 **#71900**	**Geographical location:** Kerman, Iran **Study dates:** Sep 2003-Jan 2004 **Size of population (no. of patients):** 60 **Number of cycles analyzed:** 60 **Number of cycles per patient:** 1.0	**Age:** Mean (SD): HA: 27.5 (4.3) Albumin: 28.6 (3.7) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Male factor: 35 (58.3%) Tubal factor: 16 (26.7%) PCOS: 9 (15%) **Inclusion criteria:** - Age ≤ 35 years	**Definition(s) of outcome(s):** Pregnancy: Gestational sac on ultrasound Live birth: NR Multiples: NR Complications: NR	1) Pregnancy: Preg + / Preg - / Total HA: **11** / **19** / 30 Albumin: **7** / **23** / 30 Total: 18 / 42 / 60 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.57 (0.71; 3.50) 2) Ongoing pregnancy: Preg + / Preg - / Total	**Comments:** Randomization method not described **Quality assessment:** Randomization method: - Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Study type: RCT **Interventions:** Embryo transfer with media with hyaluronic acid vs. media with albumin	- At least 3 embryos for transfer - No previous IVF **Exclusion criteria:** NR		HA **9** **21** 30 Albumin **5** **25** 30 Total 14 46 60 Value / Lower 95% CI / Upper 95% CI **Rel risk** 1.80 0.68 4.74	
Makrakis, Angeli, Agapitou, et al., 2006 **#53910**	**Geographical location:** Athens, Greece **Study dates:** Sep 2002-April 2005 **Size of population (no. of patients):** 316 **Number of cycles analyzed:** 316 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Randomized to assisted hatching on day 3 with (a) laser or (b) mechanical method	**Age:** Mean (SD): Mechanical: 40.9 (1.5) Laser: 41.0 (1.5) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - advanced age (≥39 years), - primary infertility - no previous application of ART - decision for IVF treatment - embryos available for transfer **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Clinical pregnancy: gestational sac on ultrasound Viable pregnancy: pregnancy beyond 12 weeks Live birth: NR Multiples: NR Complications: NR	1) Clinical pregnancy: Preg + / Preg - Mechanical **33** **125** 158 Laser **43** **115** 158 76 240 316 Lower 95% CI / Upper 95 % CI **Rel risk** 0.77 0.52 1.14 2) Viable pregnancy: Preg + / Preg - Mechanical **31** **127** 158 Laser **37** **121** 158 68 248 316 Lower 95% CI / Upper 95 % CI **Rel risk** 0.84 0.55 1.28	**Comments:** None **Quality assessment:** Randomization method:+ Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment:+

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Malmusi, La Marca, Giulini, et al., 2005 **#40280**	**Geographical location:** Modena, Italy **Study dates:** NR **Size of population:** Grp 1: 30-GnRH a Grp 2: 25- GnRH antagonist **Number of cycles analyzed:** 55 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Women undergoing ICSI with a hx of previous poor response were randomized to use of a GnRH agonist flare vs GnRH antagonist protocol GnRH agonist received 0.1 mg triptorelin on cycle day 1. GnRH antagonist grp received 0.25 mg ganirelix when lead follicle reached 14 mm	**Age:** Grp 1 Mean (SD): 36.6 [0.8] Grp 2 Mean (SD): 36.2 [1.2] **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: NR Endometriosis: NR Male factor: NR Tubal factor: NR PCOS: NR **Inclusion criteria:** Hx of poor response defined as no ovarian response with ≥ 300 IU rFSH for ≥ 15 d or less than 5 oocytes retrieved. FSH < 15. **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: defined as sac on USD Live birth: NR Multiples: NR Complications: NR	1) Pg rate grp 1 vs 2: Preg + / Preg - / Lower 95% CI / Upper 95 % CI Study drug: **3** / **22** / 25 Control: **6** / **24** / 30 9 / 46 / 55 **Rel risk**: 0.60 / 0.17 / 2.16	**Comments:** Low power **Quality assessment:** Randomization method: + Blinding: no Dropout rate < 20%: + Adequacy of randomization concealment: no

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Mamas, 2006 **#53940**	**Geographical location:** Athens, Greece **Study dates:** July 2002 to December 2004 **Size of population (no. of patients):** 276 **Number of cycles analyzed:** 403 **Number of cycles per patient:** 1.45 **Study type:** RCT **Interventions:** FSP: Fallopian tube sperm perfusion IUTPI: Intrauterine tubo-peritoneal insemination	**Age:** Mean (SD): 33 (3.7) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Other (specify): "All couples suffered from unexplained infertility, mild or moderate male infertility, or mild or moderate endometriosis after treatment." **Inclusion criteria:** Women with age < 40 years, regular menstrual cycle of 25–33 days, spontaneous ovulation by vaginal ultrasound and normal serum progesterone concentrations (> 10 ng/mL) in midluteal phase serum, serum FSH <10 U/L on day 3, LH, PRL, T, sex hormone–binding globulin, and thyroid hormone concentrations in the normal range, negative chlamydia detection tests, body mass index between 20 and 29 kg/m2, and male with inseminate motile sperm count (IMC) recovered after gradients > 10^6 **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: Yes Complications: OHSS	1) Pregnancy: Preg + / Preg - / Total IUTPI: **60** / **78** / 138 FSP: **35** / **103** / 138 95 / 181 / 276 Rel risk: 1.71 (Lower 95% CI 1.22, Upper 95 % CI 2.42) 2) Three twin pregnancies in FSP and 5 in IUTPI (plus 1 quintuplets reduced to twins) 3) Three cases of mild ovarian hyperstimulation syndrome (OHSS) in both groups, no severe OHSS.	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -
Manau,	**Geographical location:**	**Age:**	**Definition(s) of**	1) Pregnancy:	**Comments:**

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Fabregues, Arroyo, et al., 2002 **#58370**	Barcelona, Spain **Study dates:** NR **Size of population (no. of patients):** 30 **Number of cycles analyzed:** 30 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Long protocol GnRH agonist, rFSH for COH, randomized to (a) hCG or (b) rLH for follicular maturation	Mean (SD): hCG: 33.2 (0.9) LH: 32.6 (0.8) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 7 (23%) Endometriosis: 1 (3%) Male factor: 17 (57%) Tubal factor: 5 (17%) **Inclusion criteria:** - Age 27-37 - Regular menses - FSH < 12 **Exclusion criteria:** - PCOS - > 2 previous attempts	**outcome(s):** Pregnancy: Gestational sac on ultrasound Live birth: NR Multiples: NR Complications: OHSS		None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +
Marci, Caserta, Dolo, et al., 2005 **#58380**	**Geographical location:** L'Aquila, Italy **Study dates:** Jan 2001-Dec 2002 **Size of population (no. of patients):** 60 **Number of cycles analyzed:** 60 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** GnRH agonist vs. antagonist (Cetrorelix)	**Age:** Mean (SD): Agonist: 39.0 (3.1) Antagonist: 38.8 (2.9) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Age 32-44 - Estradiol concentrations < 600 pg/nil on the day of HCG administration - Poor response (number of oocyte retrieved < 3) after a previous standard long protocol using analogues for down regulation and recombinant	**Definition(s) of outcome(s):** Pregnancy: Gestational sac on ultrasound 28-35 days after transfer Live birth: NR Multiples: NR Complications: NR		**Comments:** Randomization method not described **Quality assessment:** Randomization method: - Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

1) Clinical pregnancy:

	Preg +	Preg -	Total
Antagonist	**5**	**25**	30
Agonist	**2**	**28**	30
Total	7	53	60

	Value	Lower 95% CI	Upper 95% CI
Rel risk	2.50	0.53	11.89

2) Ongoing pregnancy:

	Preg +	Preg -	Total
Antagonist	**4**	**26**	30
Agonist	**0**	**30**	30
Total	4	56	60

	Value	Lower 95% CI	Upper 95% CI
Rel risk	9.00	0.51	160.18

	Preg +	Preg -	Total
rLH	**9**	**6**	15
hCG	**9**	**6**	15
Total	18	12	30

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.00	0.56	1.79

2) OHSS:

	OHSS +	OHSS -	Total
rLH	**0**	**15**	15
hCG	**2**	**13**	15
Total	2	28	30

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.20	0.01	3.85

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		gonadotrophin at a dose of 225 IU for stimulation **Exclusion criteria:** NR			
Marrs, Meldrum, Muasher, et al., 2004 **#13850**	**Geographical location:** ReDondo Beach, CA **Study dates:** NR **Size of population:** Grp 1: 212 Grp 2: 219 **Number of cycles analyzed:** 431 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** ICSI cycles with luteal phase GnRH and rFSH Up to 3 embryos transferred. Grp 1: 150 IU rLH starting stim day 6 + rFSH Grp 2: rFSH only	**Age:** Grp 1 Mean (SD): 32.4 (3.8) Grp 2 Mean (SD): 31.9 (3.7) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Normo-ovulatory - Age 18-40 - FSH < 11.3 - Both ovaries present - Male factor infertility requiring ICSI **Exclusion criteria:** - More than 2 previous ICSI cycles - Smoking > 10/day - LH/FSH > 2 - Systemic disease	**Definition(s) of outcome(s):** Pregnancy: +FCM Live birth: NR Multiples: NR Complications: NR	1) Clinical pregnancy: Preg + / Preg - / Total rFSH+rLH: **90** / **122** / 212 rFSH: **91** / **128** / 219 Total: 181 / 250 / 431 Value / Lower 95% CI / Upper 95% CI **Rel risk**: 1.02 / 0.82 / 1.28 2) Subgroup—women 35 or older Preg + / Preg - / Total Study group: 27 / 38 / 65 Control: 17 / 39 / 56 44 / 77 / 121 Lower 95% CI / Upper 95 % CI **Rel risk**: 1.37 / 0.84 / 2.23	**Comments:** Higher # of embryos transferred in Grp 1: 2.9 vs. 2.8, P = 0.04 **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: - (NR)
Martinez, Coroleu, Parera, et	**Geographical location:** Barcelona, Spain	**Age:** Mean (SD): hCG: 32.9 (3.5)	**Definition(s) of outcome(s):**	1) Pregnancy: Preg + / Preg - / Total	**Comments:** None

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
al., 2000 **#58390**	**Study dates:** Jan 1996-Sep 1996 **Size of population (no. of patients):** 310 **Number of cycles analyzed:** 310 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** GnRH agonist, hMG COH, randomized to (a) 10 mg vaginal micronized progesterone daily for 10 days after transfer, or (b) 2500 IU hCG days 2, 4, 6	Progesterone: 32.9 (3.4) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - BMI 22-25 - FSH < 12 - Normal response to COH - Embryos for transfer **Exclusion criteria:** History of OHSS	Pregnancy: Gestational sac on ultrasound 28 days after transfer Live birth: NR Multiples: NR Complications: NR	hCG **47** **95** 142 Prog **65** **103** 168 Total 112 198 310 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.86 0.63 1.16	**Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: - Adequacy of randomization concealment: -
Martinez, Coroleu, Parriego, et al., 2001 **#5330**	**Geographical location:** Barcelona, Spain **Study dates:** Jun – Oct 1999 **Size of population:** Grp 1: 51 Grp 2: 49 **Number of cycles analyzed:** 100 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Grp 1: Immediate withdraw of catheter after embryo transfer	**Age:** Grp 1 Mean (SD): 34.33 (4.27) Grp 2 Mean (SD): 34.52 (3.92) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Grp 1 Unexplained infertility: 7 [14] Endometriosis: 4 [8] Male factor: 9 [18] Tubal factor: 22 [44] Other (not specified): 8 [16] Grp 2 Unexplained infertility: 6	**Definition(s) of outcome(s):** Pregnancy: sac only Live birth: NR Multiples: NR Complications: NR	1) Pregnancy rate: Preg + / Preg - / Total Immed with-drawal **31** **20** 51 30 s delay **34** **15** 49 Total 65 35 100 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.88 0.66 1.17	**Comments:** - Low power - No power analysis **Quality assessment:** Randomization method: + (randomized sequentially) Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		[12.2] Endometriosis: 4 [8.2] Male factor: 9 [18.4] Tubal factor: 19 [38.8] Other (not specified): 10 [22.4]			
	Grp 2: 30 sec delayed removal of catheter after embryo transfer IVF/ICSI with long GnRH downregulation, FSH stimulation and transfer of 2-3 embryos on days 2-3 or 5-6	**Inclusion criteria**: - IVF/ICSI pt with at least 2 embryos of "good quality" - No difficulty with trial transfer **Exclusion criteria:** NR			
Masten-broek, Twisk, van Echten-Arends, et al., 2007 **#73010**	**Geographical location:** Amsterdam and Groeningen, the Netherlands **Study dates:** May 2003-Jan 2007 **Size of population (no. of patients):** 408 **Number of cycles analyzed:** 836 **Number of cycles per patient:** 2.0 **Study type:** RCT **Interventions:** Pre-implantation genetic diagnosis with transfer of only chromosomally normal embryos (n = 2), vs. no PGD (n = 2) Treatment allocated for duration of therapy (up to 3 cycles)	**Age:** Mean (SD): PGD: 38.0 (1.7) Control: 37.9 (1.6) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 151 (37%) Endometriosis: 19 (4%) Male factor: 156 (38%) Tubal factor: 92 (23%) PCOS: 25 (6%) Other: Cervical: 17 (4%) Ovarian failure (donor eggs): 3 (<1%) **Inclusion criteria:** - Age 35-41 - Eligible for IVF - No previous failed IVF cycles - Did not object to a possible double embryo transfer **Exclusion criteria:**	**Definition(s) of outcome(s):** Pregnancy: Clinical pregnancy: gestational sac at 7 weeks Ongoing pregnancy (primary outcome): Live birth: Yes Multiples: NR Complications: Trisomy, early pregnancy loss	1) Clinical pregnancy: Preg + / Preg = / (row total) PGD: **61** / **145** / 206 No PGD: **88** / **114** / 202 149 / 259 / 408 Rel risk: Value 0.68; Lower 95% CI 0.52; Upper 95% CI 0.88 2) Ongoing pregnancy: Preg + / Preg = / (row total) PGD: **52** / **154** / 206 No PGD: **74** / **128** / 202 126 / 282 / 408 Rel risk: Value 0.69; Lower 95% CI 0.51; Upper 95% CI 0.93 3) Live birth: Preg + / Preg = / (row total) PGD: **49** / **157** / 206 No PGD: **71** / **131** / 202 120 / 288 / 408	**Comments:** None **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		Exclusion criteria for IVF (not described in detail)			

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.68	0.50	0.92

4) 1 trisomy 18 in both groups, 3 ante- or post-partum losses in both groups

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Matorras, Urquijo, Mendoza, et al., 2002

#1660

Geographical location: Baracaldo, Spain

Study dates: NR

Size of population (no. of patients): 515

Number of cycles analyzed: 515

Number of cycles per patient: 1.0

Study type: RCT

Interventions:
- Mock transfer during cycle prior to study cycle
- Frydman catheter
- Embryo transfer 2-3 days after retrieval (86%)
- U/S: transabdominal U/S guidance; embryos released when catheter tip within 1 cm of fundus
- Clinical touch: when clinician judgment of tip within 1 cm, based on mock transfer results

Age (mean [SD]):
U/S: 34.0 (3.1)
Clinical touch: 34.2 (3.0)

Race/ethnicity (n [%]):
NR

Diagnoses (n [%]):
Unexplained infertility: 102 (19.9%)
Endometriosis: 35 (6.8%)
Male factor: 147 (28.7)
Tubal factor: 159 (31.0%)
Failed IUI: 86 (16.8)

Inclusion criteria:
Age < 40, scheduled for IVF (ICSI not done at time of study)

Exclusion criteria:
Cryopreserved embryos, embryos from donated oocytes

Definition(s) of outcome(s):

Pregnancy: Not defined

Live birth: NR

Multiples: NR

Complications: NR

1) Pregnancy rate:

	Preg +	Preg -	
U/S	67	188	255
Control	47	213	260
	114	401	515

		Lower 95% CI	Upper 95 % CI
Rel risk	1.45	1.04	2.02

2) Ongoing pregnancy:

	Preg +	Preg -	
U/S	57	198	255
Control	37	223	260
	94	421	515

		Lower 95% CI	Upper 95 % CI
Rel risk	1.57	1.08	2.29

3) Multiple pregnancy:

	Preg +	Preg -	
Study drug	22	45	67
Control	14	33	47
	36	78	114

		Lower 95% CI	Upper 95 % CI
Rel risk	1.10	0.63	1.92

4) Proportion of transfers judged "easy" significantly higher in U/S group (96.9% vs 80.8% in controls).

Comments:
None

Quality assessment:
Randomization method: +
Blinding: -
Dropout rate < 20%: +
Adequacy of randomization concealment: - (NR)

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
McIlveen, Lok, Pritchard, et al., 2005 **#39890**	**Geographical location:** Sheffield, UK **Study dates:** 9/2002 - 5/2004 **Size of population:** Grp 1: Wallace-75 Grp 2: Cook-75 (cycles—142 subjects) **Number of cycles analyzed:** 150 **Number of cycles per patient:** 1.06 **Study type:** RCT **Interventions:** Women undergoing IVF/ICSI randomized to embryo transfer with either the Wallace or Cook K-Jet catheter	**Age:** Grp 1: Mean (SD): 32.7 Range: 21-39 Grp 2: Mean (SD): 32.3 Range: 21-39 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: NR Endometriosis: NR Male factor: NR Tubal factor: NR PCOS: NR **Inclusion criteria:** NR **Exclusion criteria:** Age < 39, high basal FSH, previous difficult ET, > 6 previous ETs	**Definition(s) of outcome(s):** Pregnancy: +FCM Live birth: NR Multiples: NR Complications: NR	1) Pg rate Grp 1 vs 2: pg pos / pg neg / Total Wallace: **22** / **53** / 75 Cook: **23** / **52** / 75 Total: 45 / 105 / 150 Rel risk: Value 0.96; Lower 95% CI 0.59; Upper 95% CI 1.56	**Comments:** 8 women received more than 1 cycle—unclear if same instrument was used in both cycles **Quality assessment:** Randomization method: + Blinding: pt yes, investigator-no Dropout rate < 20%: + Adequacy of randomization concealment: +
Mikkelsen, Smith, and Lindenberg, 2000 **#6160**	**Geographical location:** Copenhagen, Denmark **Study dates:** NR **Size of population:**	**Age:** Range: 18-37 **Race/ethnicity (n [%]):** NR	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR	1) Pregnancy rate: Preg + / Preg - / Total Grp 1: **3** / **7** / 10 Grp 2: **2** / **8** / 10	**Comments:** - Low power - 2 other separate studies reported in the paper could not be evaluated due to pts having multiple cycles and pg rate not given per pt

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Grp1: 10 Grp 2: 10 **Number of cycles analyzed:** 20 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** ICSI cycle of in vitro maturation of immature oocytes Grp 1: no stimulation Grp 2: 150 IU rFSH for cycle days 3-5	**Diagnoses (n [%]):** NR **Inclusion criteria:** - Male factor or tubal infertility - Normo-ovulatory **Exclusion criteria:** - "Endocrine abnormality," e.g., hyperprolactinemia - Day 3 antral follicle ct < 3 - Day 3 FSH > 15 and/or inhibin B < 45 - More than 3 previous failed IVF attempts - < 20% embryo cleavage rate on previous IVF - Women with PCOS	Multiples: NR Complications: NR	Total 5 15 20 Value / Lower 95% CI / Upper 95% CI **Rel risk** 1.50 0.32 7.14	**Quality assessment:** Randomization method: - (method NR) Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: - (NR)
Mochtar and Dutch Banirelix Study Group, 2004 **#11570**	**Geographical location:** Amsterdam, Netherlands **Study dates:** 4/2001 – 10/2002 **Size of population:** Grp 1: 101 Grp 2: 103 **Number of cycles analyzed:** 204 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Grp 1: GnRH antagonist started when lead follicle 15 mm. Grp 2: GnRH antagonist started on stimulation day 6	**Age:** Grp 1: Mean (SD): 33.1 (3.6) Median: NR Range: NR Grp 2: Mean (SD): 33.0 (3.4) Median: NR Range: NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Grp 1: Unexplained infertility:28 [27.7] Endometriosis: 3 [3] Male factor: 42 [41.6] Tubal factor:18 [17.8] PCOS: 0 Cervical factor: 3 [3] Other (specify): 3 [3]	**Definition(s) of outcome(s):** Pregnancy: Clinical: +FCM Ongoing: +FCM at 8 wks EGA Live birth: NR Multiples: NR Complications: NR	1) Clinical preg rate: Preg + / Preg - Day 6 Follicle size: **34** / **69** = 103 **23** / **78** = 101 57 / 147 = 204 Lower 95% CI / Upper 95 % CI **Rel risk** 1.45 0.92 2.28 2) Ongoing preg rate: Preg + / Preg - Study drug: **32** / **71** = 103 Control: **22** / **79** = 101 54 / 150 = 204 Lower 95% CI / Upper 95 % CI **Rel risk** 1.43 0.89 2.28	**Comments:** Preg not primary outcome of study (powered for difference of total number of retrieved oocytes of 2) **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	All received IVF/ICSI with rFSH	Grp 2 Unexplained infertility:29 [28.2] Endometriosis: 4 [3.9] Male factor: 40 [39.8] Tubal factor:18 [17.5] PCOS: 0 Cervical factor: 0 Other (specify): 5 [5] **Inclusion criteria:** Age 18-39, BMI 18-29, regular cycle of 24d-35d with individual variation of 3d **Exclusion criteria:** Contraindication to GnRH antagonist, PCOS, ovarian cyst, hx oophorectomy, > 3 previous IVF attempts, hx of previous low response			
Mochtar, Van Wely, and Van der Veen, 2006 **#54210**	**Geographical location:** Amsterdam, the Netherlands **Study dates:** Jan 1993-Dec 1997 **Size of population (no. of patients):** 385 randomized; 355 treated **Number of cycles analyzed:** 355 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** GnRH agonist long protocol	**Age:** Mean (SD): HCG: 34.4 (3.9) OR: 33.7 (4.5) ET 33.6 (4.1) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 30% Male factor: 29% Tubal factor: 31% Other: 10% **Inclusion criteria:** 1st IVF cycle **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Clinical: gestational sac on U/S 35th day after retrieval Ongoing pregnancy: + FHR after 10 weeks Live birth: Yes Multiples: NR Complications: NR	1) Clinical pregnancy, day of embryo transfer vs day of hCG: Preg + / Preg - / Total hCG: **33** / **97** / 130 ET: **41** / **86** / 127 74 / 183 / 257 Rel risk: 0.79 (Lower 95% CI 0.53, Upper 95% CI 1.16) 2) Clinical pregnancy, day of embryo transfer vs day of hCG: Preg + / Preg - / Total OR: 39 / 88 / 127 ET: 41 / 86 / 127 80 / 174 / 254	**Comments:** No adjustment for multiple comparisons **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	COH; randomized to 400 mg vaginal progesterone daily, starting (a) at hCG administration for ovulation (hCG) (b) evening after oocyte retrieval (OR) (c) evening after embryo transfer (ET)			<table><tr><th></th><th></th><th>Lower 95% CI</th><th>Upper 95 % CI</th></tr><tr><td>**Rel risk**</td><td>0.95</td><td>0.66</td><td>1.37</td></tr></table> 3) OR vs hCG: 1.21 (0.82, 1.79) 4) Live birth, hCG vs ET: 0.98 (0.6, 1.59); OR vs ET: 1.03 (0.64, 1.66); OR vs hCG: 1.05 (0.65, 1.7)	
Mohamed, Sbracia, Pacchia-rotti, et al., 2006 **#54220**	**Geographical location:** Rome, Italy **Study dates:** NR **Size of population (no. of patients):** 257 (analysis done for 241) **Number of cycles analyzed:** 257 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** **-** Long protocol GnRH agonist (buserelin) downregulation **-** Randomized to (a) 300 IU rFSH or (b) 300 IU/day uFSH Gonadotropins started day 2 of menses, continued at fixed dose for 7 days. - Dose adjusted based on ovarian response (u/s and E2) - Ovulation triggered when E2 1,000-4,500 pg/mL + at least 4	**Age:** Mean (SD): rFSH 40.9 (1.6); uFSH 41.3 (1.3) Range: 39-43 **Race/ethnicity (n [%]): NR** **Diagnoses (n [%]):** Unexplained infertility: 16% Endometriosis: 17% **Inclusion criteria:** - Age > 39 - Scheduled for IVF - Day 3 FSH < 10, E2<60 **Exclusion criteria:** **-** PCOS	**Definition(s) of outcome(s):** Pregnancy: Gestational sac 4 weeks after transfer Live birth: NR Multiples: NR Complications: NR	1) Pregnancy: <table><tr><th></th><th>Preg +</th><th>Preg -</th><th></th></tr><tr><td>uFSH</td><td>**23**</td><td>**106**</td><td>129</td></tr><tr><td>rFSH</td><td>**21**</td><td>**107**</td><td>128</td></tr><tr><td></td><td>44</td><td>213</td><td>257</td></tr></table> <table><tr><th></th><th></th><th>Lower 95% CI</th><th>Upper 95 % CI</th></tr><tr><td>**Rel risk**</td><td>1.09</td><td>0.63</td><td>1.86</td></tr></table> 2) Lower cumulative dose for uFSH	**Comments:** Primary outcome amount of FSH used **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	follicles > 16 mm mean diameter				
Montag, van der Ven, Dorn, et al., 2006 **#54250**	**Geographical location:** Bonn, Germany **Study dates:** Jan 2001-March 2001 **Size of population (no. of patients):** 273 **Number of cycles analyzed:** 273 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Randomized to transfer on (a) Day 3, (b) Day 4, (c) Day 5 Only 3 embryos cultured	**Age:** Median: 34.5; no differences between groups **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Age < 40 years - Oocyte retrieval for IVF/ICSI **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Clinical pregnancy, Day 4 vs Day 3 (intention-to-treat): Preg + / Preg - / Total Day 4: **21** / **74** / 95 Day 3: **33** / **57** / 90 54 / 131 / 185 Rel risk: 0.60 (Lower 95% CI 0.38, Upper 95 % CI 0.96) 2) Clinical pregnancy, Day 5 vs Day 3: Preg + / Preg - / Total Day 5: 13 / 75 / 88 Day 3: 33 / 57 / 90 46 / 132 / 178 Rel risk: 0.40 (Lower 95% CI 0.23, Upper 95 % CI 0.71)	**Comments:** Randomization based on week, not subject **Quality assessment:** Randomization method: - Blinding: Dropout rate < 20%: Adequacy of randomization concealment:
Moon, Choi, Ku, et al., 2007 **#71990**	**Geographical location:** Seoul, South Korea **Study dates:** Nov 2004-Aug 2005 **Size of population (no. of patients):** 97	**Age:** Mean (SD): DA-3801: 31.4 (3.2) Follitropin: 30.8 (2.7) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):**	**Definition(s) of outcome(s):** Pregnancy: Fetal heart rate on ultrasound 4 weeks after transfer Live birth: Yes	1) Clinical pregnancy: Preg + / Preg - / Total DA-3801: **9** / **40** / 49 Follitropin: **12** / **36** / 48 Total: 21 / 76 / 97 Value (Lower 95% CI, Upper 95% CI)	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Number of cycles analyzed: 97 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** GnRH antagonist (Cetrorelix) COH, randomized to new recombinant FSH (DA-3801) vs. follitropin-α	Endometriosis: 8 (8.1%) Male factor: 20 (20.6%) Tubal factor: 24 (24.7%) "Other/unknown": 34 (35.0%) Mixed: 11 (11.3%) **Inclusion criteria:** - Age 20-38 years - BMI 17-29 - Regular menses - No more than 2 previous attempts - No clomiphene or gonadotropins within 1 month of consent **Exclusion criteria:** - Systemic disease Cardiovascular/hepatic/ renal disease - Abnormal endocrine test - PCOS - Severe endometriosis - History of poor response in previous IVF/ICSI	Multiples: NR Complications: NR	**Rel risk** 0.73 0.34 1.58 2) Live birth: Live + / Live - / Total DA-3801: **9** / **40** / 49 Follitropin: **11** / **37** / 48 Total: 20 / 77 / 97 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.80 0.37 1.76	
Moon, Park, Lee, et al., 2004 **#12300**	**Geographical location:** Busan, Korea **Study dates:** March 1988-Feb 200 **Size of population (no. of patients):** 188 **Number of cycles**	**Age:** Mean (SD): Piroxicam 32.7 (4.3), placebo 33.2 (4.7) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 31	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Clinical pregnancy, piroxicam vs placebo: Preg + / Preg - / Lower / Upper Piroxicam: 44 / 50 / 94 Placebo: 26 / 68 / 94 70 / 118 / 188	**Comments:** Randomization apparently stratified by fresh or frozen embryo **Quality assessment:** Randomization method: - (NR) Blinding: + Dropout rate < 20%: - Adequacy of randomization concealment: - (NR)

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	analyzed: 188 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** - All underwent COH with GnRH agonist suppression, hpFSH - Piroxicam (NSAID): 10 mg 1-2 hours prior to embryo transfer - Control: placebo 1-2 hours prior to embryo transfer	(16.5%) Endometriosis: 17 (9.0%) Male factor: 33 (17.6%) Tubal factor: 107 (56.9%) **Inclusion criteria:** - Scheduled for IVF - Tubal, male, endometriosis, or unexplained infertility **Exclusion criteria:** NR		**Rel risk** 1.69 (95% CI 1.14, 95 % CI 2.50)	
Morgia, Sbracia, Schimberni, et al., 2004 **#13050**	**Geographical location:** Rome, Italy **Study dates:** January 2000-July 2004 **Size of population (no. of patients):** 129-140 randomized but 11 randomized to natural cycle refused **Number of cycles analyzed:** 225 **Number of cycles per patient:** 1.74 **Study type:** RCT **Interventions:** - (a) no stimulation; daily monitoring of E2 and follicles; ovulation triggered by hCG when at least one follicle >16 mm	**Age:** Mean (SD): 39.3 (5.6) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 24 (18.6%) Male factor: 62 (48.1%) Tubal factor: 19 (14.7%) PCOS: 15 (11.6%) **Inclusion criteria:** - Age ≤ 43 years - Previous IVF cycle with ≤3 follicles recruited or cancelled cycle due to lack of follicle activation **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Pregnancy (cumulative, per patient): Preg + / Preg - / Total uFSH: 7 / 63 / 70 Natural cycle: 7 / 52 / 59 14 / 115 / 129 Rel risk 0.84 (Lower 95% CI 0.31, Upper 95 % CI 2.27) 2) % cycles going to transfer in 1st 2 cycles much higher in stimulated group, similar pregnancy per transfer. Natural cycle group more likely to undergo multiple cycles if not pregnant.	**Comments:** - Continued on allocated treatment for subsequent cycles - More likely to go to transfer in stimulated group, but higher drop out rate if not pregnant **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	- (b) 0.05 mg/BID buserelin starting day 1 of cycle and 600 IU purified FSH starting on day 3 - FSH dose adjusted starting day 7 - hCG when 2 follicles > 16 mm				
Morgia, Torti, Montigiani, et al., 2006 **#54280**	**Geographical location:** Rome, Italy **Study dates:** Jan 2002-Dec 2003 **Size of population (no. of patients):** 709 **Number of cycles analyzed:** 709 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Randomized to (a) medium buffered only with bicarbonate, vs (b) medium buffered with N-hydroxyethylpiperazine-N-ethanesulfonate (HEPES), for ICSI, sperm washing, and oocyte retrieval	**Age:** Mean (SD): HEPES: 35.4 (4.2); bicarbonate 36.1 (4.1) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Endometriosis: 19% Male factor: 34% Tubal factor: 25% PCOS: 16% Other: 5% **Inclusion criteria:** 1st ICSI cycle **Exclusion criteria:** Azoospermia	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Clinical pregnancy: Preg + / Preg - No HEPES: **135** / **222** = 357 HEPES: **99** / **252** = 351 234 / 474 = 708 Rel risk 1.34 (Lower 95% CI 1.08, Upper 95% CI 1.66)	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -
Nadir Ciray, Bener, Karagenc, et al., 2005 **#41210**	**Geographical location:** Istanbul, Turkey **Study dates:** NR **Size of population (no.**	**Age:** Mean (SD): Control 34.0 (3.7); hatching 33.1 (4.2) **Race/ethnicity (n [%]):**	**Definition(s) of outcome(s):** Pregnancy: Gestational sac with + FHR 4 weeks after transfer	1) Clinical pregnancy: Preg + / Preg - Assisted hatching: **17** / **43** = 60	**Comments:** None **Quality assessment:** Randomization method: + Blinding: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results				Comments/Quality Scoring
	of patients): 90 **Number of cycles analyzed:** 90 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Randomized to (a) control or (b) laser assisted hatching day 3	NR **Diagnoses (n [%]):** Endometriosis: 100% **Inclusion criteria:** < 40 - Stage 3-4 endometriosis based on laparoscopy at least 3 months previously **Exclusion criteria:** - Zona ≥ 15 µm - No transfer	Live birth: NR Multiples: NR Complications: NR	Control **Rel risk**	**12** 29 0.71	**18** 61 Lower 95% CI 0.39	30 90 Upper 95 % CI 1.28	Dropout rate < 20%: + Adequacy of randomization concealment: -
Nagy, Taylor, Elliott, et al., 2005 **#39370**	**Geographical location:** Atlanta, GA **Study dates:** 7/04 - 1/05 **Size of population:** Grp 1: 44 no LCR Grp 2: 44 LCR **Number of cycles analyzed:** 88 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** LCR = lysed cell removal Women with frozen embryos were randomized to 2 grps. The no LCR grp had embryos replaced as usual. The LCR group had	**Age:** Grp 1: Mean (SD): 35.6 [4.89] Grp 2: Mean (SD): 35.8 [5.12] **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Women with embryos previously frozen on day 3 after an IVF cycle **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: +FHR Live birth: NR Multiples: NR Complications: NR	1) Pregnancy rate grp 1 vs 2: LCR + assisted hatching No LCR **Rel risk**	Preg + **24** **10** 34 2.40	Preg - **20** **34** 54 Lower 95% CI 1.31	44 44 88 Upper 95 % CI 4.41	**Comments:** - No diagnoses, no info as to pregnancy outcome in fresh cycle. - No control for effect of assisted hatching **Quality assessment:** Randomization method: NR Blinding: NR Dropout rate < 20%: + Adequacy of randomization concealment: NR

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	assisted hatching with removal of fragmented blastomeres.				
Ng, Chui, Tang, et al., 2001 **#58420**	**Geographical location:** Hong Kong, China **Study dates:** June 1999-March 2000 **Size of population (no. of patients):** 150 **Number of cycles analyzed:** 150 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Oocyte retrieval with (a) paracervical block + placebo, or (b) paracervical block with conscious sedation	**Age:** Mean (SD): 35.0 Range: 27-43 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Previous attempt of transvaginal retrieval at study unit - Presence of follicles in both ovaries **Exclusion criteria:** - First IVF cycle - General anesthesia requested by patient - < 3 dominant follicles present - Presence of dominant follicles in one ovary only - History of sensitivity to lignocaine	**Definition(s) of outcome(s):** Main outcome pain measured by visual analog scale Pregnancy: Not defined Live birth: NR Multiples: NR Complications: Pain	1) Pregnancy: Preg + / Preg - / Total Sedation: **18** / **57** / 75 Placebo: **19** / **56** / 75 Total: 37 / 113 / 150 Rel risk: Value 0.95; Lower 95% CI 0.54; Upper 95% CI 1.66 2) Pain levels during procedure significantly higher without sedation. Overall satisfaction similar.	**Comments:** None **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +
Ng, Lau, Yeung, et al., 2001 **#58430**	**Geographical location:** Hong Kong, China **Study dates:** NR **Size of population (no. of patients):** 40 **Number of cycles analyzed:** 40 **Number of cycles per patient:** 1.0	**Age:** Mean: hMG: 33.0 rFSH: 34.0 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Male factor: 40 (100%) **Inclusion criteria:** - Age < 40	**Definition(s) of outcome(s):** Pregnancy: Gestational sac on ultrasound 28 days post-transfer Live birth: NR Multiples: NR Complications: NR	1) Pregnancy: Preg + / Preg - / Total rFSH: **4** / **16** / 20 hMG: **5** / **15** / 20 Total: 9 / 31 / 40 Rel risk: Value 0.80; Lower 95% CI 0.25; Upper 95% CI 2.55	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Study type: RCT **Interventions:** Long protocol GnRH, ICSI for male factor, randomized to COH with (a) hMG (b) rFSH	- FSH < 10 on day 2 - Regular cycles - Severe oligospermia **Exclusion criteria:** - Smokers - History of ovarian surgery - Testicular sperm extraction			
Ng, Miao, Cheung, et al., 2003 **#58440**	**Geographical location:** Hong Kong, China **Study dates:** Aug 2000-June 2001 **Size of population (no. of patients):** 60 **Number of cycles analyzed:** 60 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Cyclogest vaginal suppositories 400 mg twice daily vs. Crinone 8% vaginal gel once daily for 14 days	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Long protocol of pituitary down-regulation used - Serum oestradiol (E2) level on the day of HCG > 10,000 pmol/l or number of oocytes obtained > 15 **Exclusion criteria:** - History of using any vaginal P preparations in previous IVF/ET cycles - Cancellation of ET because of no oocytes obtained - Absent fertilization - E2 on the day of HCG ≥ 30,000 pmol/l	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Pregnancy: Preg + / Preg - / Total Gel: **7** / **23** / 30 Suppository: **9** / **21** / 30 Total: 16 / 44 / 60 Value (Lower 95% CI – Upper 95% CI) **Rel risk** 0.78 (0.33 – 1.82) 2) Patient-rated inconvenience, leaking less with gel than suppositories	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +
Ng, Naveed, Lau, et al., 2005 **#9340**	**Geographical location:** Hong Kong, China **Study dates:** 5/2003 – 5/2004	**Age:** Grp 1: Mean (SD): 34 Range: 25-40 Grp 2:	**Definition(s) of outcome(s):** Pregnancy: gest sac on USD or + POC on D+C Ongoing: +FCM at 10-12	1) Pregnancy rate: Preg + / Preg neg / Total Laser zona: **10** / **70** / 80	**Comments:** - Preg was not primary outcome and insufficient power - # of embryos replaced was statistically diff between the 2 grps

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Size of population: Grp 1: 80 Grp 2: 80 **Number of cycles analyzed:** 160 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Grp 1: Laser zona pellucida (ZP) thinning prior to FET. Grp 2: No ZP thinning Protocols used for FET included normal cycles, clomid induced cycles and HRT cycles	Mean (SD): 34 Range: 26-40 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Grp 1: Unexplained infertility:9 [11.2] Endometriosis: 10 [12.5] Male factor: 43 [53.8] Tubal factor: 16 [20] Mixed: 2 [2.5] Grp 2: Unexplained infertility:6 [7.5] Endometriosis: 7 [8.7] Male factor: 43 [53.8] Tubal factor: 20 [25] Mixed: 4 [5] **Inclusion criteria:** 2 or more frozen embryos **Exclusion criteria:** > 3 previous IVF cycles	wks EGA Live birth: NR Multiples: Yes Complications: NR	thinning Control **12** **68** 80 Total 22 138 160 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.83 0.38 1.82 2) Multiple pregnancies: Multiple / Singleton / Total Laser zona thinning **6** **4** 10 Control **2** **10** 12 Total 8 14 22 Value / Lower 95% CI / Upper 95% CI **Rel risk** 3.60 0.92 14.06	**Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +
Nyboe Andersen, Popovic-Todorovic, Schmidt, et al., 2002 **#2780**	**Geographical location:** Braedstrup, Denmark **Study dates:** 3/1999 – 4/2000 **Size of population:** Grp 1: 150 Grp 2: 153 **Number of cycles analyzed:** 203 **Number of cycles per patient:** 1.00	**Age:** Grp 1: Mean (SD): 32.1 (4.1) Grp 2 Mean (SD): 32.2 (4.3) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Grp 1 Unexplained infertility:50 [33.3] Endometriosis: 0	**Definition(s) of outcome(s):** Pregnancy: Ongoing pregnancy with +FCM at 7 wks Live birth: Yes Multiples: Yes Complications: SAB	1) Ongoing preg: Preg + / Preg - Study drug **139** **14** 153 Control **133** **17** 150 272 31 303 Lower 95% CI / Upper 95 % CI **Rel risk** 1.02 0.95 1.11 2) Delivery:	**Comments:** Powered to detect a 10.7% difference in delivery rate **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		Male factor: 50 [33.3] Tubal factor: 52 [34.7] PCOS: 13 [8.7]		Birth + / Birth - Study drug: **126** / **27** (153) Control: **118** / **32** (150) 244 / 59 (303) Rel risk 1.05 (Lower 95% CI 0.94, Upper 95 % CI 1.17) 3) No difference in multiple preg rate 4) No difference in SAB rate	
	Study type: RCT **Interventions:** Grp 1: Stopped supplemental progesterone at time of + hCG Grp 2: Continued progesterone for 3 wks after + hCG Pts with +hCG from IVF/ICSI using a long GnRH downregulation and rFSH	Grp 2 Unexplained infertility:35 [22.8] Endometriosis: 0 Male factor: 56 [3.7] Tubal factor: 58 [37.9] PCOS: 16 [10.4] Total >100 due to multiple diagnoses reported for some couples **Inclusion criteria:** Serum or urine hCG > 25 IU 14d after transfer **Exclusion criteria:** More than slight vaginal bleeding before or at the time of hCG measurement			
Ohl, Lefebvre-Maunoury, Wittemer, et al., 2002 **#930**	**Geographical location:** France **Study dates:** NR **Size of population:** Grp 1: 70 Grp 2: 68 **Number of cycles analyzed:** 138 **Number of cycles per patient:** 1.00 **Study type:** RCT	**Age:** Grp 1 Mean (SD): 34.2 (2.1) Grp 2: Mean (SD): 34.5 (3.6) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Grp 1 Unexplained infertility: 2 [2.8] Endometriosis: 4 [5.7] Male factor: 45 [64.3]	**Definition(s) of outcome(s):** Pregnancy: Clinical +FCM at 6 wks EGA Live birth: Yes Multiples: Yes Complications: SAB	1) Clinical pregnancy rate: Preg + / Preg - (Total) Grp 1: **16** / **54** (70) Grp 2: **18** / **50** (68) Total: 34 / 104 (138) Rel risk Value 0.86 (Lower 95% CI 0.48, Upper 95% CI 1.55) 2) NTG related to first-trimester SAB: SAB+ / SAB- (Total) NTG: **1** / **69** (70)	**Comments:** - Looks at birth weight in the 2 grps - Originally powered for 25% diff in preg rate by patches became unavailable during trial resulting in a power of 53% to detect a 25% diff. **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Interventions: Grp 1: 5 mg NTG patch applied day before transfer until preg test or onset of period Grp 2: placebo patch All wore patches from morning until bedtime All patients had IVF/ICSI with GnRH long protocol and rFSH stimulation	Tubal factor: 16 [22.8] PCOS: 0 Other (specify): 3 [4.3] Grp 2 Unexplained infertility: 5 [7.3] Endometriosis: 2 [2.9] Male factor: 37 [54.4] Tubal factor: 18 [26.5] PCOS: 0 Other (specify): 6 [8.8] **Inclusion criteria:** Hx of 2 or more implantation failures during fresh IVF despite good embryo quality. At least 2 good quality embryos available for transfer **Exclusion criteria:** Hypersensitivity to NTG, heart failure, severe anemia, high intracranial or intra-ocular blood pressure		placebo 1 67 68 Total 2 136 138 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.97 0.06 15.22 3) NTG related to ectopic pregnancy: ect+ / ect- / Total NTG 1 69 70 placebo 1 67 68 Total 2 136 138 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.97 0.06 15.22 4) Also compared weights for singletons and for twins; no difference.	
Olivennes, Belaisch-Allart, Emperaire, et al., 2000 **#8670**	**Geographical location:** France **Study dates:** NR **Size of population:** Grp 1: 115 Grp 2: 39 **Number of cycles analyzed:** 154 **Number of cycles per patient:** 1.00 **Study type:** RCT	**Age:** Grp 1: Mean (SD): 31.4 (3.7) Median: NR Range: NR Grp 2: Mean (SD): 31.8 (3.8) Median: NR Range: NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: NR Endometriosis: NR	**Definition(s) of outcome(s):** Pregnancy: Clinical: +FCM Ongoing: + FCM after 12 wks EGA Live birth: NR Multiples: NR Complications: OHSS	1) Clinical pregnancy rate: preg + / preg neg / Total Grp 1 26 89 115 Grp 2 11 28 39 Total 37 117 154 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.80 0.44 1.47 2) Grp 2 had a greater number of oocytes and embryos but the # of embryos transferred was the same 3) No difference in OHSS rates	**Comments:** - The response rate of GnRH antagonist therapy was the primary outcome. - Study was not powered for pregnancy differences **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: Grp 1 8.7% Grp 2: 9.3% Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Interventions: Grp 1: Depot GnRH antagonist on day 7 of HMG stim. If ovulation trigger not done within 4 days, then daily GnRH antagonist given until trigger. Grp 2: Depot GnRH agonist during luteal phase All received IVF/ICSI with HMG stimulation Randomized in a 3:1 ratio	Male factor: NR Tubal factor: NR PCOS: NR **Inclusion criteria:** Age 18-39, cycles of 24-35 d with individual variation of ± 3 d, day 3 FSH < 10, nl uterus, ≤ 3 previous IVF attempts. **Exclusion criteria:** Women with PCOS or stages 3-4 endometriosis			
Orvieto, Kerner, Krissi, et al., 2002 **#350**	**Geographical location:** Tel Aviv, Israel **Study dates:** NR **Size of population (no. of patients):** 52 **Number of cycles analyzed:** 52 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** Leuprolide 3.75 mg depot	**Age:** Mean (SD): 28.7 ± 4.08 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Age < 37 years, normal uterine cavity, and no hydrosalpinges **Exclusion criteria:** Chronic illness or receiving chronic medical treatment or repeated IVF failures (> 3 previous	**Definition(s) of outcome(s):** Pregnancy: Clinical pregnancy, visualization of a gestational sac by ultrasound and elevation of serum hCG levels. Live birth: NR Multiples: NR Complications: Various (see right)	1) Clinical pregnancy: Preg + / Preg - / Total Triptorelin: **5** / **21** / 26 Leuprolide: **12** / **14** / 26 17 / 35 / 52 Rel risk: 0.42 (Lower 95% CI 0.17, Upper 95 % CI 1.02) 2) There were no cancellations of cycles due to poor response and no case of spontaneous LH surge in either group. None of the patients developed moderate or severe ovarian hyperstimulation syndrome. There was one case of early missed abortion in the leuprolide	**Comments:** None **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	formulation on day 21-23 of the menstrual cycle. Triptorelin 3.75 mg depot formulation on day 21-23 of the menstrual cycle.	cycles)		group and one case of extrauterine pregnancy in the triprorelin group.	
Out, David, Ron-El, et al., 2001 **#5100**	**Geographical location:** Haifa, Zerifin, Afula, Tel-Hashomer, and Petach Tiqva, Israel **Study dates:** May 1997 and June 1999 **Size of population (no. of patients):** 180 **Number of cycles analyzed:** 180 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** Fixed dose of 100 or 200 IU of rFSH (follatropin beta, Puregon ®; NV Organon, Oss, The Netherlands)	**Age:** Mean (SD): 27.5 (4) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Male factor: 180 (100%) Tubal factor: Tubal factor also present in 7 subjects **Inclusion criteria:** Age ≥ 18 and ≤ 37, male infertility, normal regular cycles with mean length between 24 and 35 days, presence of two ovaries, good physical and mental health, body mass index between 18 and 29 kg/m^2. **Exclusion criteria:** Female cause for infertility except mild endometriosis or a mechanical factor, previous IVF or ICSI cycles(s) after which less than 3 oocytes were retrieved, previous IVF or ICSI cycles(s) with hospitalization due to ovarian hyperstimulation syndrome, more than four previous IVF or ICSI cycles, total fertilization failure in a previous IVF or ICSI cycle, LH/FSH ratio at screening ≥ 3,	**Definition(s) of outcome(s):** Pregnancy: Vital pregnancy: intrauterine pregnancy with positive heart action. Live birth: NR Multiples: NR Complications: OHSS based on investigator report	1) Clinical pregnancy: Preg + / Preg - / Total Study drug: **21** / **70** / 91 Control: **22** / **67** / 89 43 / 137 / 180 Rel risk: 0.93 (Lower 95% CI 0.55; Upper 95 % CI 1.57) 2) Ongoing pregnancy: Preg + / Preg - / Total 100 IU: **17** / **74** / 91 200 IU: **15** / **74** / 89 32 / 148 / 180 Rel risk: 1.11 (Lower 95% CI 0.59; Upper 95 % CI 2.08) 3) OHSS requiring hospitalization was reported in four cases, all in the high dose group. One ectopic pregnancy occurred in the high dose group.	**Comments:** None **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		chronic cardiovascular, hepatic, renal, or pulmonary disease, history within 12 mo or current abuse of alcohol or drugs, and administration of non-registered investigational drugs within 3 mo prior to screening.			
Out, Rutherford, Fleming, et al., 2004 **#14220**	**Geographical location:** Bristol, UK **Study dates:** 6/2000 – 12/2001 **Size of population:** Grp 1: 131 Grp 2: 126 **Number of cycles analyzed:** 257 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Grp 1: 150 IU rFSH Grp 2: 200 IU rFSH All received IVF/ICSI with GnRH antagonist starting on day 6. After day 5 dose could be adjusted down to 100 IU.	**Age:** Grp 1: Mean (SD): 32.7 (3.6) Grp 2 Mean (SD): 32.2 (3.5) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Grp 1 Unexplained infertility:28 [21.4] Endometriosis: 7 [5.3] Male factor: 43 [32.8] Tubal factor: 40 [30.5] PCOS: 0 Mixed: 13 [10] Grp 2 Unexplained infertility:27 [21.4] Endometriosis: 15 [11.9] Male factor: 49 [38.9] Tubal factor: 28 [22.2] PCOS: 0 Mixed: 7 [5.6] **Inclusion criteria:** Age 18-39, cycles 24-35 d, BMI 18-29, weight 50-90 kg. **Exclusion criteria:**	**Definition(s) of outcome(s):** Pregnancy: Vital preg: +FCM Live birth: Yes Multiples: NR Complications: SAB rate	1) Live birth rate (intent-to-treat): Preg + / Preg - Study drug: **32** / **100** — 132 Control: **41** / **91** — 132 73 / 191 — 264 **Rel risk** 0.78 (Lower 95% CI 0.53, Upper 95 % CI 1.16) 2) Greater # of oocytes in grp 2 but no difference in good quality embryos 3) No difference in SAB rate	**Comments:** - Study powered to detect a 2.06 difference in # of oocytes recovered. - Preg not a primary outcome **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		PCOS, elevated follicular FSH or LH, ovary or abdominal abnl precluding visualization of at least 1 ovary, only one ovary present, use of hormones within 1 mo, alcohol or drug abuse within 12 mo, other investigational study within 3 mo			

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Pabuccu, Onalan, and Kaya, 2007 **#72120**	**Geographical location:** Ankara, Turkey **Study dates:** Nov 2002-Feb 2006 **Size of population (no. of patients):** 266 **Number of cycles analyzed:** 266 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Randomized to (a) long protocol GnRH agonist (triptorelin) vs, (b) GnRH antagonist (Cetrorelix) Stratified by endometriosis diagnosis (a) Stage I-II (b) resected endometrioma (c) active endometrioma	**Age:** Mean (SD): 30.9 (4.1) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Endometriosis: 100% **Inclusion criteria:** - Endometriosis - Normal uterus/tubes **Exclusion criteria:** - Hydrosalpinx - Documented tuberculosis - Male factor infertility - Thaw cycles	**Definition(s) of outcome(s):** Pregnancy: Fetal heart rate on ultrasound Live birth: NR Multiples: NR Complications: NR	1) Pregnancy, Stage I-II endometriosis: Preg + / Preg - / Total GnRH antag: **15** / **35** / 50 GnRH agonist: **15** / **33** / 48 Total: 30 / 68 / 98 Value (Lower 95% CI, Upper 95% CI) **Rel risk** 0.96 (0.53, 1.74) 2) Pregnancy, resected endometrioma: Preg + / Preg - / Total GnRH antag: **11** / **29** / 40 GnRH agonist: **16** / **25** / 41 Total: 27 / 54 / 81 Value (Lower 95% CI, Upper 95% CI) **Rel risk** 0.70 (0.37, 1.33) 3) Pregnancy, active endometrioma: Preg + / Preg - / Total GnRH antag: **7** / **27** / 34 GnRH agonist: **8** / **25** / 33 Total: 15 / 52 / 67 Value (Lower 95% CI, Upper 95% CI) **Rel risk** 0.85 (0.35, 2.08) 4) Pregnancy, all subjects: Preg + / Preg - / Total GnRH: **33** / **91** / 124	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				antag GnRH agonist **39** **83** 122 Total 72 174 246 **Rel risk** Value 0.83, Lower 95% CI 0.56, Upper 95% CI 1.23	
Pacchia-rotti, Aragona, Gaglione, et al., 2007 **#72140**	**Geographical location:** Rome, Italy **Study dates:** June 2005-March 2006 **Size of population (no. of patients):** 119 **Number of cycles analyzed:** 119 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** GnRH agonist long-protocol, randomized to (a) urinary FSH for 6 days, followed by rFSH until hCG administration, or (b) rFSH from day 2 through hCG	**Age:** Mean (SD): uFSH/rFSH: 34.1 (2.5) rFSH: 35.1 (3.1) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 16 (13.4%) Male factor: 47 (39.5%) Tubal factor: 53 (44.5%) **Inclusion criteria:** _ Infertility attributable to tubal factor, male factor or idiopathic infertility - Serum hormonal profile (FSH and LH <12 mIU/ml, E2 < 50 pg/ml and prolactin < 30 ng/ml) within the normal range - Regular ovulatory menstrual cycles - Presence of normal uterine cavity; - BMI ≥20–≤26 kg/m^2 - First IVF treatment - Age 27-39 **Exclusion criteria:** - Previous poor response to gonadotropins	**Definition(s) of outcome(s):** Pregnancy: Not defiined Live birth: NR Multiples: NR Complications: NR	1) Pregnancy: Preg + / Preg - / Total uFSH/rFSH **25** **33** 58 rFSH only **13** **48** 61 Total 38 81 119 **Rel risk** Value 2.02, Lower 95% CI 1.15, Upper 95% CI 3.56	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		- History of severe OHSS - Current PCOS - Male partner had azoospermia - Clinical signs of infection detected in semen analysis within 12 months before treatment			
Pakkila, Rasanen, Heinonen, et al., 2005 **#41520**	**Geographical location:** Oulu, Kuopio, and Tampere, Finland **Study dates:** 2000-2003 **Size of population (no. of patients):** 374 **Number of cycles analyzed:** 374 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** - COH with long GnRH agonist protocol, 100 mg aspirin or placebo beginning on first day of gonadotropins until menses or negative pregnancy test	**Age:** Mean (SD): Aspirin 32.0, placebo 31.3 Range: aspirin 24-39, placebo 22-39 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 21% Endometriosis: 20% Male factor: 28% Tubal factor: 14% Other female: 10%, multiple: 6% **Inclusion criteria:** - Scheduled for IVF (n=235), ICSI (n=12), or both (n=19) **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: NR Live birth: Yes Multiples: NR Complications: NR	1) Live birth (intention-to-treat): Preg + / Preg - / Lower 95% CI / Upper 95 % CI Study drug: 32 / 154 / 186 Control: 37 / 151 / 188 69 / 305 / 374 **Rel risk**: 0.87 / 0.57 / 1.34	**Comments:** - Powered to detect 15% difference in pregnancy rate **Quality assessment:** Randomization method:+ Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Pantos, Makrakis, Stavrou, et al., 2004 **#13900**	**Geographical location:** Athens, Greece **Study dates:** June 2002-Dec 2002 **Size of population (no. of patients):** 243 **Number of cycles analyzed:** 243 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Randomized to ET on (a) day 2, (b) day 3, or (c) day 6	**Age:** Mean (SD): Day 2: 32.4 (6.3), Day 3: 31.3 (5.2), Day 6: 33.1 (5.1) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - female age ≤40 years, - ≤ 3previous unsuccessful ART attempts - IVF or ICSI - COH with long or short protocol, using GnRH agonist and recombinant FSH. **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Pregnancy detected by ultrasound Ongoing pregnancy: beyond 12 weeks Live birth: NR Multiples: Yes Complications: NR	1) Clinical pregnancy, Day 2 vs Day 3: Preg + / Preg - / Total Day 2: **38** / **43** / 81 Day 3: **39** / **42** / 81 77 / 85 / 162 Rel risk: 0.97 (Lower 95% CI 0.70, Upper 95 % CI 1.35) 2) Clinical pregnancy, Day 6 vs Day 3: Preg + / Preg - / Total Day 6: **30** / **51** / 81 Day 3: **39** / **42** / 81 69 / 93 / 162 Rel risk: 0.77 (Lower 95% CI 0.54, Upper 95 % CI 1.11) 3) Ongoing pregnancy, Day 2 vs Day 3: Preg + / Preg - / Total Day 2: 33 / 48 / 81 Day 3: 35 / 46 / 81 68 / 94 / 162 Rel risk: 0.94 (Lower 95% CI 0.66, Upper 95 % CI 1.35) 4) Ongoing pregnancy, Day 6 vs Day 3: Preg + / Preg - / Total Day 6: **20** / **61** / 81 Day 3: **35** / **46** / 81 55 / 107 / 162 Rel risk: 0.57 (Lower 95% CI 0.36, Upper 95 % CI 0.90) 5) Similar numbers of twins, higher-order	**Comments:** No adjustment for multiple comparisons **Quality assessment:** Randomization method: - (not described) Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment:-

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				multiples	
Papanikolaou, Camus, Kolibianakis, et al., 2006 **#54790**	**Geographical location:** Brussels, Belgium **Study dates:** July 2003-Nov 2004 **Size of population (no. of patients):** 351 **Number of cycles analyzed:** 351 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Randomized to single embryo transfer at (a) day 3 vs (b) day 5; randomization at initial visit, before start of treatment	**Age:** Mean (SD): Day 3: 30.5 (3.2); Day 5: 30.4 (3.6) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 31 (8.8%) Male factor: 196 (55.8%) Male + female combined: 21 (6.0%) "Female" factor: 85 (24.2%) **Inclusion criteria:** < 36 years - 1st or 2nd ART cycle - Day 3 FSH ≤ 12 IU/L **Exclusion criteria:** PGD	**Definition(s) of outcome(s):** Pregnancy: Clinical pregnancy: + FHR at 7 weeks Ongoing pregnancy: + FHR after 12 weeks Live birth: Yes Multiples: NR Complications: NR	1) Clinical pregnancy: Preg + / Preg - / Lower 95% CI / Upper 95 % CI Day 5: **58** / **118** / 176 Day 3: **41** / **134** / 175 99 / 252 / 351 **Rel risk** 1.41 (1.00 – 1.98) 2) Ongoing pregnancy: Preg + / Preg - / Lower 95% CI / Upper 95 % CI Day 5: **58** / **118** / 176 Day 3: **38** / **137** / 175 96 / 255 / 351 **Rel risk** 1.52 (1.07 – 2.16) 3) Live birth: Live birth + / Live birth - / Lower 95% CI / Upper 95 % CI Day 5: **56** / **120** / 176 Day 3: **38** / **137** / 175 94 / 257 / 351 **Rel risk** 1.47 (1.03 – 2.09)	**Comments:** - Powered to detect 10% absolute difference - Stopped at interim analysis based on pre-specified stopping rules **Quality assessment:** Randomization method: + Blinding:- Dropout rate < 20%: + Adequacy of randomization concealment: +
Papaniko-	**Geographical location:**	**Age:**	**Definition(s) of**	1) Pregnancy rate grp 1 vs 2:	**Comments:**

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Iaou, D'haeseleer, Verheyen, et al., 2005 **#39670**	Brussels, Belgium **Study dates:** 1/01 - 11/03 **Size of population:** Grp 1: 84 - day 3 Grp 2: 80 - day 5 **Number of cycles analyzed:** 164 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Women with at least 4 good quality embryos on day 3 were randomized to day 3 vs day 5 transfer. Good quality was defined as a min of 6 blastomeres, max of 20% fragmentation, no multinucleated blastomeres.	Grp 1 Mean (SD): 29.6 [0.4] Grp 2: Mean (SD): 29.9 [0.4] **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Grp 1: Unexplained infertility: 4 [4.8] Male factor: 46 [55.4] Female factor: 25 [30.1] Combined factors: 8 [9.6] Grp 2: Unexplained infertility: 7 [8.8] Male factor: 43 [53.8] Female factor: 21 [26.3]] Combined factors: 9 [11.3] **Inclusion criteria:** Age ≤ 37, rank trial ≤ 3, day 3 FSH ≤ 12, use of ejaculated sperm **Exclusion criteria:** Oocyte donation, PGD	**outcome(s):** Pregnancy: +FCM Live birth: Yes Multiples: Yes Complications: NR	Preg + / Preg - / Lower 95% CI / Upper 95 % CI Day 5: **42** / **38** / 80 Day 3: **27** / **57** / 84 69 / 95 / 164 **Rel risk** 1.63 (1.12, 2.37) 2) Live birth rate: Birth + / Birth - / Lower 95% CI / Upper 95 % CI Day 5: 38 / 42 / 80 Day 3: 23 / 61 / 84 61 / 103 / 164 **Rel risk** 1.73 (1.14, 2.63) 3) Multiples: Mult + / Mult - / Lower 95% CI / Upper 95 % CI Day 5: 24 / 18 / 42 Day 3: 19 / 8 / 27 43 / 26 / 69 **Rel risk** 0.81 (0.57, 1.16)	None **Quality assessment:** Randomization method: + Blinding: no Dropout rate < 20%: + Adequacy of randomization concealment: no
Pellicano,	**Geographical location:**	**Age:**	**Definition(s) of**	1) Clinical pregnancy:	**Comments:**

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Zullo, Florentino, et al., 2001 **#3740**	Naples and Catanzaro, Italy **Study dates:** NR **Size of population (no. of patients):** 80 **Number of cycles analyzed:** NR **Number of cycles per patient:** NR **Study type:** RCT **Interventions:** For minilaparoscopic gamete intra-fallopian transfer either: CS: Conscious sedation GA: General anesthesia	Mean (SD): 31 (3.2) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Infertility duration ≥ 2 years, 3-6 failed IUIC, one patent tube on hysterosalpingography, normal uterine cavity by hysteroscopy, no pelvic pathology on ultrasound, and no metabolic or cardiorespiratory disorders. **Exclusion criteria:** NR	**outcome(s):** Pregnancy: Clinical pregnancy: ultrasound visualization of a gestational sac. Ongoing pregnancy: not defined Live birth: NR Multiples: NR Complications: Ectopic pregnancy, anesthesia complication (not defined)	 Clin preg + / Clin preg - / Total CS **14** **26** 40 GA **16** **24** 40 Total 30 50 80 Value (Lower 95% CI, Upper 95% CI) **Rel risk** 0.88 (0.50, 1.54) 2) Ongoing pregnancy: Ongoing preg + / Ongoing preg - / Total CS **11** **29** 40 GA **11** **29** 40 Total 22 58 80 Value (Lower 95% CI, Upper 95% CI) **Rel risk** 1.00 (0.49, 2.04) 3) No difference in operative time, lower discharge time, higher proportion discharged by 2 hr, and lower need for additional anesthesia for CS. 4) No difference in ectopic rate (1 in each group) and no anesthesia complications.	None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -
Petersen, Mauri, Baruffi, et al., 2002 **#290**	**Geographical location:** SP, Brazil **Study dates:** NR **Size of population:** Grp 1: 50 Grp 2: 50 **Number of cycles analyzed:** 100 **Number of cycles per**	**Age:** Grp 1 Mean (SD): 39.8 (1.3) Median: NR Range: NR Grp 2 Mean (SD): 40 (1.9) Median: NR Range: NR **Race/ethnicity (n [%]):** NR	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: Yes Multiples: NR Complications: SAB rate	1) Pregnancy rate: preg + / preg neg / Total Zona thinning **8** **42** 50 Control **11** **39** 50 Total 19 81 100 Value (Lower 95% CI, Upper 95% CI) **Rel risk** 0.73 (0.32, 1.65) 2) Delivery rate:	**Comments:** No power calculations **Quality assessment:** Randomization method: - Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	patient: 1.00 **Study type:** RCT **Interventions:** Grp 1: ZP laser thinning Grp 2: control All received ICSI with GnRH long protocol downregulation and rFSH stimulation for male factor ZP thinned at 4 sites 60-90%	**Diagnoses (n [%]):** NR **Inclusion criteria:** Age ≥ 38, male factor infertility **Exclusion criteria:** NR		preg + / preg neg / Total Zona thinning: **5** / **45** / 50 Control: **5** / **45** / 50 Total: 10 / 90 / 100 Rel risk: Value 1.00, Lower 95% CI 0.31, Upper 95% CI 3.24 3) No difference in SAB rate	
Petersen, Mauri, Baruffi, et al., 2005 **#9850**	**Geographical location:** Sao Paulo, Brazil **Study dates:** Jan 2002-July 2003 **Size of population (no. of patients):** 150 **Number of cycles analyzed:** 150 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Randomized to (a) control or (b) ¼ zona laser assisted hatching	**Age:** Mean (SD): 34.1-35.7 all 4 groups **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 11 (7.3%) Male factor: 61 (40.7%) Other: Female: 47 (31.3%) Mixed: 31 (20.7%) **Inclusion criteria:** - ICSI - history of at least one previous failed ART cycle (randomization stratified by number of previous failures) **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Gestational sac with + FHR 4 weeks after transfer Live birth: Yes Multiples: NR Complications: NR	1) Clinical pregnancy, 1 previous failure: Preg + / Preg - / Assisted hatching: **11** / **24** / 35 Control: **10** / **25** / 35 21 / 49 / 70 Rel risk: 1.10, Lower 95% CI 0.54, Upper 95 % CI 2.25 2) Live birth, 1 previous failure: LB + / LB - / Assisted hatching: **8** / **27** / 35 Control: **10** / **25** / 35 18 / 52 / 70 Rel risk: 0.80, Lower 95% CI 0.36, Upper 95 % CI 1.79 3) Clinical pregnancy, 2 previous failures: Preg + / Preg -	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

Assisted hatching	**10**	**30**	40
Control	**3**	**37**	40
	13	67	80

		Lower 95% CI	Upper 95 % CI
Rel risk	3.33	0.99	11.22

4) Live birth, 2 previous failures:

	LB +	LB -	
Assisted hatching	**9**	**31**	40
Control	**3**	**37**	40
	12	68	80

		Lower 95% CI	Upper 95 % CI
Rel risk	3.00	0.88	10.27

5) Clinical pregnancy, all subjects

	Preg +	Preg -	
Assisted hatching	**21**	**54**	75
Control	**13**	**62**	75
	34	116	150

		Lower 95% CI	Upper 95 % CI
Rel risk	1.62	0.87	2.98

6) Live birth, all subjects

	LB +	LB -	
Assisted hatching	**17**	**58**	75
Control	**13**	**62**	75
	30	120	150

		Lower 95% CI	Upper 95 % CI
Rel risk	1.31	0.68	2.50

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Pinheiro, Cavagna, Baruffi, et al., 2003 **#14350**	**Geographical location:** Ribeirao Preto, Brazil. **Study dates:** NR **Size of population (no. of patients):** 225 **Number of cycles analyzed:** 225 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** - All underwent long protocol GnRH, fixed stimuation with rFSH Group A: 10 mg terbutaline/day for 15 days starting day of oocyte retrieval Group B: 20 mg/day ritrodrine, same schedule Group C: no treatment	**Age:** Mean (SD): Terbutaline 34.6 (0.5), ritodrine 33.5 (0.7), control: 34.7 (0.7) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Male factor: 100% **Inclusion criteria:** - Scheduled for ICSI for male factor **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: + hCG; Ultrasound confirmed FHR 14 days after + hCG Live birth: NR Multiples: NR Complications: AEs	1) Pregnancy, terbutaline vs control (intention to treat): Preg + / Preg - / Total Terbutaline: **26** / **64** / 90 Control: **13** / **32** / 45 39 / 96 / 135 Rel risk: 1.00 (Lower 95% CI 0.57 – Upper 95 % CI 1.75) 2) Pregnancy, ritodrine vs control (intention to treat): Preg + / Preg - / Total Ritodrine: **20** / **70** / 90 Control: **13** / **32** / 45 33 / 102 / 135 Rel risk: 0.77 (Lower 95% CI 0.42 – Upper 95 % CI 1.40) 3) 30/90 (33%) of ritodrine subjects discontinued because of side effects, 3/90 (3%) of terbutaline subjects	**Comments:** - No adjustment for multiple comparisons - unclear if reported pregnancy rate is based on hCG or ultrasound results **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: Adequacy of randomization concealment: -
Platteau, Laurent,	**Geographical location:** Brussels, Belgium	**Age:** Grp 1:	**Definition(s) of outcome(s):**	1) Clinical pregnancy rate:	**Comments:** - Study powered to detect a 3.6

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Albano, et al., 2003 **#16630**	**Study dates:** 9/2000 – 12/2001 **Size of population:** Grp 1: 96 Grp 2: 104 **Number of cycles analyzed:** 200 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Grp 1: Follitropin β with pen device Grp 2 Follitropin α with conventional syringe All underwent IVF/ICSI with long protocol of GnRH agonist followed by 150-225 of Follitropin α or 150-200 of Follitropin β for the first 5d	Mean (SD): 31.3 (4.1) Grp 2 Mean (SD): 31.7 (3.5) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Grp 1 Unexplained infertility: 14 [15] Endometriosis: 0 Male factor: 58 [60] Tubal factor: 15 [16] PCOS: 0 Other (specify): 9 [9] Grp 2 Unexplained infertility: 12 [12] Endometriosis: 0 Male factor: 63 [61] Tubal factor: 20 [19.5] PCOS: 0 Other (specify): 8 [7.5] **Inclusion criteria:** Age 18-39, ovulatory cycles of 24-35 d, BMI 18-29. **Exclusion criteria:** Previous IVF in which less than 3 oocytes retrieved, ovarian abnl precluding adequate stimulation, hx hospitalization for severe OHSS, hx of EtOH or drug abuse within 12 mo and previous enrollment in this study.	Pregnancy: Clinical not defined Live birth: Yes Multiples: NR Complications: NR	difference in # of oocytes. - Preg not a primary outcome **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

	preg +	preg neg	Total
Injector	**34**	**62**	96
Syringe	**36**	**68**	104
Total	70	130	200

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.02	0.70	1.49

2) Live birth rate:

	preg +	preg neg	Total
Injector	**31**	**65**	96
Syringe	**34**	**70**	104
Total	65	135	200

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.99	0.66	1.47

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Poehl, Holag-schwandt-	**Geographical location:** Vienna, Austria	**Age:** Grp 1 Mean (SD): 33 (NR)	**Definition(s) of outcome(s):**	1) Ongoing pregnancy rate: Preg + Preg - Total	**Comments:** Low power

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
ner, Bichler, et al., 2001 **#4830**	**Study dates:** NR **Size of population:** Grp 1: 45 Grp 2: 44 **Number of cycles analyzed:** 89 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Grp 1: Conventional IVF Grp 2: ICSI All underwent GnRH agonist flare with rFSH stimulation	Grp 2: Mean (SD): 32.7 (NR) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Age 18-39, tubo-peritoneal factor infertility, nl uterine cavity, nl day 3 FSH, E, Prl, TSH, nl semen analysis within 6 mo **Exclusion criteria:** NR	Pregnancy: Ongoing pregnancy rate: not defined Live birth: NR Multiples: NR Complications: NR	Grp 1 **15** **30** 45 Grp 2 **10** **34** 44 Total 25 64 89 Value / Lower 95% CI / Upper 95% CI **Rel risk** 1.47 0.74 2.91	**Quality assessment:** Randomization method: NR Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -
Popovic-Todorovic, Loft, Bredkjaeer, et al., 2003 **#15070**	**Geographical location:** Copenhagen, Denmark **Study dates:** 1/2002 – 1/2003 **Size of population:** Grp 1: 131 Grp 2: 131 **Number of cycles analyzed:** 262 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Grp 1: Individualized rFSH dosing based on normogram	**Age:** Grp 1 Mean (SD): 31.9 (3.9) Grp 2 Mean (SD): 32.7 (3.7) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Grp 1 Unexplained infertility:18 [13.7] Endometriosis: 0 Male factor: 75 [57.3] Tubal factor: 38 [29] PCOS: 0 Other (specify): 4 [3.1] Grp 2 Unexplained infertility:18 [13.7]	**Definition(s) of outcome(s):** Pregnancy: Ongoing: not defined Live birth: NR Multiples: NR Complications: NR	1) Ongoing pregnancy rate: preg + / preg neg / Total Individualized **48** **83** 131 Standard **32** **99** 131 Total 80 182 262 Value / Lower 95% CI / Upper 95% CI **Rel risk** 1.50 1.03 2.18 2) SAB rate: SAB yes / SAB no / Total Individualized **0.5** **48** 48.5 Standard **5** **27** 32 Total 5.5 75 80.5 Value / Lower 95% CI / Upper 95% CI	**Comments:** - Sig greater number of embryos transferred in grp 2. - Sig higher SAB rate in grp 2 contributing to higher ongoing preg rate in grp 1 **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Grp 2: Standard FSH dosing IVF/ICSI with GnRH agonist long downregulation. Normogram in grp 1 based on antral follicle ct, ovarian volume, ovarian Doppler score, age, smoking.	Endometriosis: 0 Male factor: 79 [60.3] Tubal factor: 36 [27.5] PCOS: 0 Other (specify): 1 [0.8] **Inclusion criteria:** 1st IVF cycle, basal FSH < 12.5, both ovaries, cycles 21-35, max age 39. **Exclusion criteria:** Ovarian cysts, inaccessible ovaries		**Rel risk** 0.07 (0.00 – 1.17)	
Primi, Senn, Montag, et al., 2004 **#11230**	**Geographical location:** Lausanne, Switzerland; Bonn, Germany; Paris, France; Barcelona, Spain **Study dates:** NR **Size of population (no. of patients):** 246 in Groups I and II **Number of cycles analyzed:** 246 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Two sets of patients: (I) first cycle frozen-thawed embryos (II) poor prognosis (age > 37 or basal FSH >10 IU/L) undergoing 1st cycle of fresh embryos, randomized to 1 of 3 groups: (a) no assisted hatching	**Age:** Mean (SD): Group I: 31.7-32.8; Group II: 38.3-40.1 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 28 (11.4%) Male factor: 117 (49.4%) Other: Female: 78 (32.9%) Mixed: 16 (6.8%) **Inclusion criteria:** (i) 20 -45 years old, (ii) having at least one functional ovary, (iii) having normal FSH (between 3 and 12 IU/l) and prolactin (<30 mg/l) (iv) having no clinically significant abnormal findings within 6 months before treatment start, (v) no pelvic inflammatory disease between the previous	**Definition(s) of outcome(s):** Pregnancy: Gestational sac with + FHR Live birth: Yes Multiples: NR Complications: NR	1) Group I (frozen-thawed), control vs assisted hatching + placebo: Preg + / Preg - / Hatching + placebo: **1** / **61** / 62 Control: **8** / **45** / 53 9 / 106 / 115 Rel risk 0.11 (Lower 95% CI 0.01 – Upper 95 % CI 0.83) 2) Group I (frozen-thawed), control vs assisted hatching + methylprednisolone + doxycycline: Preg + / Preg - / Hatching + drugs: **6** / **50** / 56 Control: **8** / **45** / 53 14 / 95 / 109 Rel risk 0.71 (Lower 95% CI 0.26 – Upper 95 % CI 1.91) 3) Group II (poor prognosis, fresh embryo), control vs assisted hatching + placebo:	**Comments:** - In group 2, mean age of hatching + active drug (40.1) higher than placebo (38.3)—although not statistically significant, may be clinically relevant **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	+ placebo (b) assisted hatching + placebo (c) assisted hatching + methylprednisone + doxycycline 2 days prior through 5 days post transfer	assessment and study entry, (vi) having a normal uterine cavity as documented within 5 years prior to treatment assignment by a hysteroscopy, hysterosalpingography or hysterosonography, **Exclusion criteria:** NR		Preg + / Preg - Study drug: **3** / **19** (22) Control: **5** / **16** (21) 8 / 35 (43) **Rel risk** 0.57 (Lower 95% CI 0.16; Upper 95 % CI 2.10) 4) Group II (poor prognosis, fresh embryo), control vs assisted hatching + methylprednisolone + doxycycline: Preg + / Preg - Study drug: **5** / **18** (23) Control: **5** / **16** (21) 10 / 34 (44) **Rel risk** 0.91 (Lower 95% CI 0.31; Upper 95 % CI 2.71) 5) Patterns similar for live birth; sample size too small to draw conclusions	
Propst, Bates, Robinson, et al., 2006	**Geographical location:** San Antonio, TX **Study dates:** NR	**Age:** Mean (SD): Constant dose 31.8 (3.1); step-up 31.4 (3.1)	**Definition(s) of outcome(s):** Pregnancy: Not defined	1) Clinical pregnancy: Preg + / Preg - Step-up: 18 / 12 (30)	**Comments:** None **Quality assessment:**

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#55060	**Size of population (no. of patients):** 60 **Number of cycles analyzed:** 60 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** **-** OCPs on cycle prior to COH - rFSH 150-300 IU/day on day 5 - Follicular monitoring beginning 4 days later - GnRH antagonist (citrorelix) when lead follicles 13-14 mm - Randomized to (a) same starting dose of rFSH (b) addition of 75 IU rFSH at night for at least 2 days - Ovulation induction with hCG	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - ≤ 37 years - Undergoing IVF/ET **Exclusion criteria:** - PCOS - BMI > 33 - Day 3 FSH > 14.1 mIU/mL - History of poor response - Untreated submucosal polyps, fibroids, hydrosalpinges	Live birth: Yes Multiples: NR Complications: NR	Constant dose: 21 / 9 / 30 39 / 21 / 60 **Rel risk** 0.86 (Lower 95% CI 0.59, Upper 95 % CI 1.25) 2) Live birth: Preg + / Preg - Step-up: 18 / 12 / 30 Constant dose: 17 / 13 / 30 35 / 25 / 60 **Rel risk** 1.06 (Lower 95% CI 0.69, Upper 95 % CI 1.62)	Randomization method: + Blinding: - Dropout rate < 20%: - Adequacy of randomization concealment: +
Propst, Hill, Ginsburg, et al., 2001 **#58470**	**Geographical location:** Boston, MA **Study dates:** Oct 1998-Dec 1999	**Age:** NR **Race/ethnicity (n [%]):** NR	**Definition(s) of outcome(s):** Pregnancy: Gestational sac on ultrasound	1) Pregnancy: Preg + / Preg - / Total Gel: **31** / **71** / 102	**Comments:** Study stopped early because of excess vaginal bleeding in gel arm **Quality assessment:**

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Size of population (no. of patients): 201 **Number of cycles analyzed:** 201 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Crinone 8% gel vs.IM progesterone	**Diagnoses (n [%]):** Unexplained infertility: 30% Endometriosis: 9% Male factor: 26% Tubal factor: 24% PCOS: 10% **Inclusion criteria:** Undergoing IVF **Exclusion criteria:** - Donor oocytes - Cryopreserved embryos	Live birth: Yes Multiples: NR Complications: NR	IM **48** **51** 99 Total 79 122 201 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.63 0.44 0.90 2) Live birth: Live birth + / Live birth - / Total Gel **25** **77** 102 IM **39** **60** 99 Total 64 137 201 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.62 0.41 0.95	Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +
Qublan, Amarin, Tahat, et al., 2006 **#55080**	**Geographical location:** Irbid, Jordan **Study dates:** Jan 2002-Dec 2003 **Size of population (no. of patients):** 122 **Number of cycles analyzed:** 122 (cancelled cycles not included in analysis in paper) **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** - Long GnRH agonist protocol - Ultrasound on 3rd day of	**Age:** Mean (SD): 31.8 (5.2) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 4 (3.3%) Endometriosis: 23 (18.8%) Male factor: 35 (28.7%) Tubal factor: 14 (11.4%) PCOS: 17 (13.9%) **Inclusion criteria:** functional ovarian cyst (thin-walled intraovarian sonolucent structure with a mean diameter of ≥15 mm and E2 levels of ≥50 pg/) on day 3 of bleeding after GnRH administration	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Pregnancy, intention-to-treat: Preg + / Preg - Cyst aspiration 6 70 76 Control 3 43 46 9 113 122 Lower 95% CI / Upper 95 % CI **Rel risk** 1.21 0.32 4.61	**Comments:** - Randomization scheme unclear-?intentional 2:1 - Overall pregnancy rate in patients with cysts considerably lower than rate in patients without cysts (29%) **Quality assessment:** Randomization method: - Blinding: - Dropout rate < 20%:+ Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	bleeding after start of GnRH agonist - If cyst detected, randomized to aspiration or no treatment	**Exclusion criteria:** NR			
Quinn and Cooke, 2004 **#13070**	**Geographical location:** Sydney, Australia **Study dates:** NR **Size of population (no. of patients):** 60 **Number of cycles analyzed:** 60 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Randomized to media optimized to maintain pH of 7.2 to 7.3 at 1 atmosphere with (a) 6% CO2 vs (b) 5% CO2	**Age:** Mean (SD): 32.7 (3.3) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** NR **Exclusion criteria:** - Age ≥ 40 years - No embryos generated - Testicular/surgically retrieved sperm	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Pregnancy: Preg + / Preg - 5% CO2: **17** / **13** (30) 6% CO2: **13** / **17** (30) 30 / 30 (60) Rel risk 1.31 (Lower 95% CI 0.78, Upper 95 % CI 2.19)	Comments: Minimal difference to determine non-inferiority not stated **Quality assessment:** Randomization method: Blinding: Dropout rate < 20%: Adequacy of randomization concealment:
Ragni, Alagna, Brigante, et al., 2004	**Geographical location:** Milan, Italy **Study dates:** 9/01-5/02	**Age:** Mean (SD): A. 33.1 (3.0) B. 32.2 (6.6)	**Definition(s) of outcome(s):** Pregnancy: Not defined	1) Pregnancy rate: Out + / Out - / Total Daily rFSH: **11** / **21** / 32	**Comments:** None **Quality assessment:** Randomization method: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results				Comments/Quality Scoring
#14240	**Size of population:** 66 **Number of cycles analyzed:** 66 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Compare to different dosage of Gonadotropins use for GnRH antagonist protocol in pts undergoing IUI. Study divided in to 2 grps Gr A. Receive 50 units of rFSH daily. Gr. B. Receive 50 units of rFSH on alternate day.	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: A. 68.8 B. 64.7 Endometriosis: NR Male factor: A. 12.5 B. 11.8 Tubal factor: NR PCOS: NR Other (specify): Mixed A. 15.6 B. 17.6 Other (endometriosis and PCOS) A. 3.1 B. 5.9 **Inclusion criteria:** 1. Unexplained infertility or mild male factor 2. Infertility last longer than 24 mos 3. Age<38 yo 4. BMI 19-30 5. Normal prolactin, TSH 6. Normal uterine cavity and bilateral tubal patency. 7. Pt with endometriosis stage I or II who has at least 6 mo of treatment. **Exclusion criteria:** NR	Live birth: NR Multiples: NR Complications: NR	Alternate day FSH RR	**2** 13 Value 5.84	**32** 53 Lower 95% CI 1.40	34 66 Upper 95% CI 24.35	Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +
Rama Raju, Shashi Kumari, Krishna, et al., 2006	**Geographical location:** Andrha Pradesh, India **Study dates:** Jan 2002-Feb 2005	**Age:** Range: 26-30 **Race/ethnicity (n [%]):** NR	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: Yes	1) Clinical pregnancy: Office hysteroscopy	Preg + 109	Preg - 146	255	**Comments:** - Prevalence of abnormalities in patients with 2 prior failed cycles may be higher than in all women undergoing initial evaluation1

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#55160	**Size of population (no. of patients):** 520 **Number of cycles analyzed:** 520 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Randomized - Office hysteroscopy with treatment of diagnosed abnormalities (37% of group), followed by repeat IVF or ICSI - No hysteroscopy, repeat IVF or ICSI - Long protocol COH	**Diagnoses (n [%]):** Endometriosis: 36% Male factor: 32% Tubal factor: 17% PCOS: 45% **Inclusion criteria:** - 2 or more previous failed IVF cycles - primary infertility - normal hysterosalpingogram **Exclusion criteria:** NR	Multiples: NR Complications: NR	Control 69 196 265 178 342 520 Lower 95% CI / Upper 95 % CI **Rel risk** 1.64 1.28 2.10 2) Live birth: Preg + / Preg - Office hysteroscopy 72 183 255 Control 44 221 265 116 404 520 Lower 95% CI / Upper 95 % CI **Rel risk** 1.70 1.22 2.37 3) Pathology found in 95/255 (37.2%) of hysteroscopy group	**Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: - (NR)
Rhodes, Higdon, and Boone, 2007 **#55240**	**Geographical location:** Greenville, SC **Study dates:** Sep 2003-Oct 2005 **Size of population (no. of patients):** 99 (1 randomized subject not analyzed due to non-study catheter use) **Number of cycles analyzed:** 99 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** - All embryos transferred	**Age (mean [SD]):** E-W: 33.0 (4.3) Cook: 32.0 (4.3) **Race/ethnicity (n [%]):** Caucasian: 79 (79%) African-American: 9 (9%) Asian: 11 (11%) **Diagnoses (n [%]):** Endometriosis: 20 (20.0%) Male factor: 15 (15.2%) Tubal factor: 12 (12.1%) PCOS: 9 (9%) Combination or “other”: 43 (43%) **Inclusion criteria:** Age < 40; BMI 20-35; fresh sperm or oocytes; 3 or more embryos for	**Definition(s) of outcome(s):** Pregnancy: Gestational sac on transvaginal U/S at 6-7 weeks Live birth: NR Multiples: NR Complications: NR	1) Pregnancy: Preg + / Preg - E-W 29 21 50 Cooke 31 18 49 60 39 99 Lower 95% CI / Upper 95 % CI **Rel risk** 0.92 0.67 1.26	**Comments:** None **Quality assessment:** Randomization method: - (NR) Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: - (NR)

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	on day 3 after assisted hatching - Edwards-Wallace or Cook catheter used for transfer	transfer; no previous ART **Exclusion criteria:** NR			
Rickes, Nickel, Kropf, et al., 2002 **#58500**	**Geographical location:** Magdeburg, Germany **Study dates:** May 1999-May 2001 **Size of population (no. of patients):** 110 **Number of cycles analyzed:** 110 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Post-surgery for stage II-IV endometriosis, randomized to (a) 6 months GnRH agonist followed by 3 cycles ART, or (b) immediate therapy with 3 cycles ART ART – IUI, IVF, or ICSI	**Age:** Range: 23-40 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Endometriosis: 100% **Inclusion criteria:** Stage II-IV endometriosis **Exclusion criteria:** - Lack of desire to conceive - Age > 40 - Dependence on testicular sperm in ART	**Definition(s) of outcome(s):** Pregnancy: Gestational sac on ultrasound Live birth: NR Multiples: NR Complications: NR	1) Pregnancy, IUI: GnRH agonist: **24** / **3** / 27 No Rx: **22** / **14** / 36 Total: 46 / 17 / 63 Rel risk: Value 1.45, Lower 95% CI 1.09, Upper 95% CI 1.95 2) Pregnancy, IVF/ICSI: GnRH agonist: **21** / **7** / 28 No Rx: **9** / **10** / 19 Total: 30 / 17 / 47 Rel risk: Value 1.58, Lower 95% CI 0.94, Upper 95% CI 2.66	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +
Rombauts, Healy, Norman, et al., 2006 **#58510**	**Geographical location:** Woodville, Australia **Study dates:** NR **Size of population (no. of patients):** 234	**Age:** Mean (SD): Agonist: 32.2 (4.0) Antagonist: 32.1 (3.7) Antag + OCP: 32.7 (3.9) **Race/ethnicity (n [%]):**	**Definition(s) of outcome(s):** Pregnancy: Ultrasound 12-16 weeks after transfer Live birth: NR	1) Pregnancy (per randomized subject), GnRH agonist vs.antagonist alone: Antag: **23** / **94** / 117 Agonist: **26** / **91** / 117 Total: 49 / 185 / 234	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Number of cycles analyzed: 234 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Randomized to (a) GnRH agonist long protocol (b) ganirelix alone (c) ganirelix after 2-4 weeks oral contraceptive treatment	NR **Diagnoses (n [%]):** Unexplained infertility: 69 (20.8%) Endometriosis: 25 (7.5%) Male factor: 127 (38.2%) Tubal factor: 69 (20.8%) Combined: 15 (4.5%) **Inclusion criteria:** - Healthy females of infertile couples - Age at time of screening 18-39 - BMI 18-29 kg/m^2 - Body weight ≤ 90 kg - Normal menstrual cycle with a range of 24–35 days and an intra-individual variation of < 3 days **Exclusion criteria:** - Contraindications for the use of gonadotrophins - Endocrine abnormalities (e.g., PCOS) - > 3 unsuccessful controlled ovarian stimulation cycles - History of low or no ovarian response during FSH/HMG treatment - Clinically relevant abnormal laboratory values (including hormones) or medical examination findings	Multiples: NR Complications: Side effects, OHSS		concealment: +
Rufas-Sapir, Stein, Orvieto, et	**Geographical location:** Tel Aviv, Israel	**Age:** Range: < 35: 34.8%; 35-40:	**Definition(s) of outcome(s):**	1) Clinical pregnancy: Preg + Preg -	**Comments:** Randomization method not described

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.88	0.54	1.46

2) Pregnancy (per randomized subject), GnRH agonist vs.antagonist + OCP:

	Preg +	Preg -	Total
Antag + OCP	**18**	**99**	117
Agonist	**26**	**91**	117
Total	44	190	234

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.69	0.40	1.19

3) Fewer side effects in ganirellix group, lower OHSS (but only 12 total)

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results				Comments/Quality Scoring
al., 2004 **#12760**	**Study dates:** NR **Size of population (no. of patients):** 207 **Number of cycles analyzed:** 207 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Randomized to (a) control vs (b) mechanical hatching (day 2-3)	35.7%; >40: 29.5% **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** ≥ 3 previous failed cycles Normal menses Normal endocrine/anatomical evaluation **Exclusion criteria:** Male factor Recurrent abortion Clinically relevant systemic disease	Pregnancy: Gestational sac on ultrasound with + hCG Live birth: NR Multiples: NR Complications: NR	Assisted hatching Control **Rel risk**	**22** **28** 50 0.78	**82** **75** 157 Lower 95% CI 0.48	104 103 207 Upper 95 % CI 1.27	**Quality assessment:** Randomization method: - Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -
				2) Pregnancy rates significantly lower with assisted hatching in women < 35 (15% vs 35%); higher with hatching in women 41 and older (30% vs 22%)				

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Sagoskin, Levy, Tucker, et al., 2007 **#55380**	**Geographical location:** Rockville, MD **Study dates:** Aug 2001-March 2005 **Size of population (no. of patients):** 199 (4 not analyzed due to protocol violation (3) or loss to follow-up (1) **Number of cycles analyzed:** 199 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Randomized to (a) control or (b) laser assisted hatching	**Age:** Mean: 34.0 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** -first or second autologous IVF–embryo transfer cycles - Age < 40 -maximum baseline FSH 10 mIU/mL, -maximum baseline E2 75 pg/mL, -ovulatory menstrual cycles, - no uterine abnormality or communicating hydrosalpinx, -good embryo quality. **Exclusion criteria:** -diminished ovarian reserve, (PCOS), -uterine or egg factor infertility - >1 previous unsuccessful IVF attempt	**Definition(s) of outcome(s):** Pregnancy: Clinical pregnancy: gestational sac with +FHR Live birth: Yes Multiples: NR Complications: NR	1) Clinical pregnancy: Preg + / Preg - / Hatching: **63** / **55** / 118 Control: **44** / **37** / 81 107 / 92 / 199 **Rel risk** 0.98 (Lower 95% CI 0.76, Upper 95 % CI 1.28) 2) Live birth: Preg + / Preg - / Study drug: **55** / **63** / 118 Control: **37** / **44** / 81 92 / 107 / 199 **Rel risk** 1.02 (Lower 95% CI 0.75, Upper 95 % CI 1.39)	**Comments:** 2:1 randomization reported, but ratio of active: control 1.5 **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Sauer, Thornton, Schoolcraft, et al., 2004 **#11070**	**Geographical location:** NY, NY; Engelwood CO; Providence, RI **Study dates:** NR **Size of population (no. of patients):** 74 **Number of cycles analyzed:** 74 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** Group A: leuprolide acetate (Lupron®: TAP Pharmaceuticals) for pituitary downregulation and r-hFSH (Gonal-f® in multi-dose vials of 450 IU or 1050 IU: Serono Inc.) for ovarian stimulation. Group B: Cetrorelix (Cetrotide®: Serono Inc.) for down-regulation and r-hFSH for ovarian stimulation. Group C: Cetrorelix and r-hFSH together with mid-cycle r-hLH (Luveris®; Serono).	**Age:** Mean (SD): 32.6 (4) Range: 22 - 39 **Race/ethnicity (n [%]):** Caucasian: 51/73 (69.9%) **Diagnoses (n [%]):** Male factor: 56/73 (76.7%) Tubal factor: 18/73 (24.7%) **Inclusion criteria:** All of the following criteria were satisfied within three menstrual cycles prior to randomization: regular menstrual cycles, body mass index (BMI) < 35 kg/m-. both ovaries present, no clinical signs of pelvic or uterine abnormalities, normal cervical cytology, wash-out period completed for any previous IVF drug protocols and FSH concentrations in the normal range. All women were also required to be willing and able to comply with the study protocol. **Exclusion criteria:** Clinically significant systemic disease, HIV, hepatitis C or B, presence of endometriosis or medical conditions likely to interfere with the study drug, previous assisted reproduction cycles had failed through insufficient response to gonadotrophin	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: OHSS	1) Clinical pregnancy: |	Clin preg +	Clin preg -	Total
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Leupro-lide	**11**	**14**	25
Cetro-relix	**21**	**28**	49
Total	32	42	74 | |	Value	Lower 95% CI	Upper 95% CI
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Rel risk	1.03	0.59	1.78	 By the three groups: Group A: 11/25 Group B: 11/25 Group C: 10/24 2) One patient in each treatment group had OHSS.	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - (open label) Dropout rate < 20%: Adequacy of randomization concealment: - (open label)

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		stimulation or absence of motile spermatozoa, or if ≥ 3 consecutive assisted reproduction cycles without a clinical pregnancy, or had a history of extrauterine pregnancy or abnormal gynecological bleeding.			
Sbracia, Farina, Poverini, et al., 2005 **#40220**	**Geographical location:** Rome, Italy **Study dates:** 1/99 - 7/2001 **Size of population:** Grp 1: short protocol, 110 Grp 2: long protocol, 110 **Number of cycles analyzed:** 220 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Women undergoing first ICSI cycle age ≥ 40 randomized to short protocol with a GnRH agonist vs long protocol with a GnRH agonist. Used buserelin and FSH	**Age:** Grp 1: Mean (SD): 41.6 [1.4] Grp 2: Mean (SD): 42.4 [1.5] **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Grp 1: Unexplained infertility: 35 [12.8] Endometriosis: 6 [12.8] Male factor: 46 [41] Tubal factor: 19 [23.1] PCOS: 4 [10.2] Grp 2: Unexplained infertility: 36 [19.3] Endometriosis: 4 [12.9] Male factor: 49 [29.0] Tubal factor: 13 [22.6]] PCOS: 5 [16.1] **Inclusion criteria:** Age ≥ 40, day 3 FSH ≤ 10 and E2 ≤ 60, first cycle, all nulliparous **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Gestational sac Live birth: NR Multiples: NR Complications: NR	1) Pg rate grp 1 vs 2: preg + / preg neg / Total Grp 1: **12** / **98** / 110 Grp 2: **25** / **85** / 110 Total: 37 / 183 / 220 Value / Lower 95% CI / Upper 95% CI **Rel risk**: 0.48 / 0.25 / 0.91	**Comments:** None **Quality assessment:** Randomization method: NR Blinding: NO Dropout rate < 20%: + Adequacy of randomization concealment: NO
Schats,	**Geographical location:**	**Age:**	**Definition(s) of**	1) Delivery rate:	**Comments:**

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Sutter, Bassil, et al., 2000 **#7390**	Multicenter: - Amsterdam, The Netherlands - Gent, Belgium - Brussels, Belgium - Nijmegen, The Netherlands **Study dates:** 11/96 - 8/98 **Size of population:** 496 **Number of cycles analyzed:** 496 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Compare the efficacy of rFSH (Gonal-F) and highly purified urine hFSH (Metrodin HP) in women undergoing ovarian stimulation for IVF/ICSI.	Mean (SD): Gonal-F 31.4 (3.4) Metrodin 31.3 (3.7) Range: 18-38 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Male factor: 50 Tubal factor: 23 **Inclusion criteria:** - Regular, spontaneous menstrual cycle of 25d-35d - Aged 18-38 - Infertility attributable to any of the following criteria Tubal factor Grade I/II endometriosis Male factor Unexplained infertility - Normal FSH and LH - Prolactin < 20 ng/ml - Testosterone<3.5 nmol/l - No more than 2 previous ART cycles - BMI > or = 18 but < or=28 - Presence of both ovaries and normal uterine cavity - No treatment with clomiphene citrate or gonadotrophins in the mo prior to the study - Willing to participate in the study and to comply with procedures. **Exclusion criteria:** - Abnormal gyn bleeding of undetermined origin Previous IVF or ICSI failure due to a poor response to gonadotropins	**outcome(s):** Pregnancy rate: Positive pregnancy test Live birth: NR Multiples: Yes Complications: NR	Preg + / Preg - / Lower 95% CI / Upper 95 % CI hp_uFSH: 43 / 206 / 249 rFSH: 56 / 191 / 247 99 / 397 / 496 **Rel risk** 0.76 (0.53, 1.09) 2) Multiple pregnancies: Preg + / Preg - rFSH: 16 / 46 / 62 Control: 19 / 31 / 50 35 / 77 / 112 **Rel risk** 0.68 (0.39, 1.18)	None **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		or a previous ICSI failure due to problems of sperm fertilization - previous history of severe OHHS - A male partner with azoospermia and clinical signs of infection detected in a semen analysis within the past 12 mos - A clinically significant condition/disease - Microsurgical epididymal sperm aspiration, testicular sperm extraction or percutaneous epididymal sperm aspiration procedures			
Scholtes, Schnittert, van Hoog-straten, et al., 2004 **#13440**	**Geographical location:** Dusseldorf, Germany **Study dates:** NR **Size of population (no. of patients):** 102 **Number of cycles analyzed:** 102 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** - Long protocol GnRH agonist downregulation - Randomized to (a) 450 IU rFSH every 3 days, or (b) 150 IU rFSH every day Dose adjusted in both groups starting day 6	**Age:** Mean (SD): Daily 30.7; q 3 days 31.6 Range: 19-39 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Male factor: 93 (91.1%) Tubal factor: 13 (12.7%) **Inclusion criteria:** - no more than three previous IVF/ICSI treatment cycles, - menstrual cycle of ≤35 days -no previous ovarian surgery - BMI ≤ 30 **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: OHSS	1) Clinical pregnancy: Preg + / Preg - Every 3 days: 13 / 38 — 51 Daily: 7 / 44 — 51 20 / 82 — 102 Rel risk 1.86 (Lower 95% CI 0.81; Upper 95 % CI 4.27) 2) OHSS: Preg + / Preg - Study drug: 5 / 46 — 51 Control: 6 / 45 — 51 11 / 91 — 102 Rel risk 0.83 (Lower 95% CI 0.27; Upper 95 % CI 2.56) 3) Biochemical pregnancy rate significantly	**Comments:** None **Quality assessment:** Randomization method: + Blinding:- Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Ovulation triggered when at least 1 follicle 18 mm, 2 or more 16 mm			higher in 3 day dosage group (33.3% vs 15.7%)	
Selman, De Santo, Sterzik, et al., 2002 **#660**	**Geographical location:** 3 institutions -Brindisi, Italy -Florance, Italy -Ulm, Germany **Study dates:** 12/98 - 11/00 **Size of population:** 267 **Number of cycles analyzed:** 267 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Compare the effectiveness of highly purify urinary follicle stimulation hormone (Fostimon) and Recombinant FSH (Gonal-F)	**Age:** Mean (SD): Fostimon: 32 (4) Gonal-F: 31.8 (6) Range: 18-38 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Infertility attributable to tubal factor, male factor, or unexplained infertility - Normal serum level of FSH, LH and prolactin - Regular ovulatory cycle every 25-35 days - Normal uterine cavity - No treatment with gonadotropins in the month before study entry - presentation for the first IVF cycle - BMI >or= 18 but < or=26 - Willingness to participate in the study and to comply with the procedures **Exclusion criteria:** - Had gynecologic abnormalities or diseases - Previous poor response to gonadotropins used for IUI - History of severe OHHS PCOS - Male partner had azoospermia	**Definition(s) of outcome(s):** Pregnancy: Clinical pregnancy rate; confirm pregnancy by u/s 6 wks after embryo transfer Live birth: Yes Multiples: Yes Complications: NR	1) Clinical pregnancy: Highly purified uFSH: **61** / **70** / 131 rFSH: **49** / **84** / 133 110 / 154 / 264 **Rel risk** 1.26 (95% CI 0.95 – 1.69) 2) Live birth: fostimon: **52** / **79** / 131 Gonal F: **41** / **92** / 133 93 / 171 / 264 **Rel risk** 1.29 (95% CI 0.93 – 1.79) 3) There was no difference in multiple pregnancy rates (29.5% vs 22.4%)	**Comments:** None **Quality assessment:** Randomization method: NR Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment:+

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		- Clinical signs of infection in semen analysis within 12 mo before treatment			
Serafini, Yadid, Motta, et al., 2006 **#55590**	**Geographical location:** Sao Paulo and Rio de Janeiro, Brazil **Study dates:** NR **Size of population (no. of patients):** 323 **Number of cycles analyzed:** 323 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** - All received rFSH on sliding scale (150-350 IU) based on age (a) Long protocol GnRH agonist down regulation, rFSH started when E2 ≤60 pg/mL with dose adjusted based on response beginning day 6 (b) rFSH on day 2-3 of menstrual cycle, adding GnRH antagonist (citrorelix) when either 2 follicles 13 mm or day 6 (c) rFSH on day 2-3 of menstrual cycle, adding GnRH antagonist (citrorelix) + 200 IU hCG + decreasing rFSH to 75 IU when either 2 follicles 13 mm or day 6	**Age:** Mean (SD): GnRH agonist: 33.4 (0.3) GnRH antagonist: 34.4 (0.4) Antagonist + hCG: 33.5 (0.4) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** 1. the presence of a standard indication for either IVF or intracytoplasmic sperm injection (ICSI) treatment; 2. age 21 to 39 years; 3. the presence of two functional ovaries; 4. the presence of an anatomically normal uterine cavity on the basis of recent hysterosalpingographic or hysteroscopic evaluation (≤6 months); 5. history of ≤3 attempts at IVF/ICSI; 6. early follicular phase (day 2 or 3) serum FSH levels ≤15 IU/L and E2 levels ≥60 pg/mL; 7. no history of low ovarian response in previous IVF/ICSI treatment; 8. body mass index (BMI)	**Definition(s) of outcome(s):** Pregnancy: Gestational sac with FHR Live birth: NR Multiples: NR Complications: OHSS	1) Clinical pregnancy, GnRH antagonist vs GnRH agonist: Preg + / Preg - / Antag: 38 / 55 / 93; Agonist: 43 / 55 / 98; 81 / 110 / 191 Rel risk: 0.93 (Lower 95% CI 0.67, Upper 95 % CI 1.30) 2) Clinical pregnancy, GnRH antagonist + hCG vs GnRH agonist: Preg + / Preg - / Antag + hCG: 58 / 48 / 106; Agonist: 43 / 55 / 98; 101 / 103 / 204 Rel risk: 1.25 (Lower 95% CI 0.94, Upper 95 % CI 1.66) 3) Clinical pregnancy, GnRH antagonist + hCG vs GnRH antagonist only: Preg + / Preg - / Antag + hCG: 58 / 48 / 106; Antag: 38 / 55 / 93; 96 / 103 / 199 Rel risk: 1.34 (Lower 95% CI 0.99, Upper 95 % CI 1.81) 4) OHSS 6.1% GnRH agonist, 4.1% antagonist, 2.9% antagonist + hCG outcome]:	**Comments:** None **Quality assessment:** Randomization method:+ Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	- Ovulation triggered according to same protocol in all 3 groups	≤25 kg/m2; 9. no untreated endocrinologic disease; 10. no treatment with gonadotropin therapy for ≥3 months preceding the study; and 11. male partner should have ejaculated spermatozoa with ≥1% strict morphology. **Exclusion criteria:** NR			
Sifer, Sellami, Poncelet, et al., 2006 **#55700**	**Geographical location:** Paris, France **Study dates:** Jan 2004-Dec 2004 **Size of population (no. of patients):** 125 **Number of cycles analyzed:** 125 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Randomized to (a) control vs (b) assisted hatching (pronase)	**Age:** Mean (SD): Control 32.0 (4.4); hatching 32.2 (4.0) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Endometriosis: 63 (50.4%) Male factor: 20 (24.0%) Tubal factor: 8 (6.4%) Other (not specified): 14 (11.2%) **Inclusion criteria:** 1st frozen-thawed embryo cycle **Exclusion criteria:** Donor cycles	**Definition(s) of outcome(s):** Pregnancy: Gestational sac with + FHR at 5-6 weeks post-transfer Live birth: NR Multiples: NR Complications: NR	1) Clinical pregnancy: Preg + / Preg - / Study drug: **11** / **50** / 61 Control: **12** / **52** / 64 23 / 102 / 125 Rel risk 0.96 (Lower 95% CI 0.46, Upper 95 % CI 2.01)	**Comments:** More endometriosis (59% vs 41%) fewer male factor(23% vs 41%) in assisted hatching group **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -
Simons, Roelofs, Schmout-ziguer, et al., 2005	**Geographical location:** 3 hospitals in the Netherlands **Study dates:** 2/2000 - 2/2002	**Age:** Mean (SD): S: 31.9 (3.0) M: 31.6 (3.6) L: 32.1 (3.6) Range: 18-38	**Definition(s) of outcome(s):** Pregnancy: Positive urine or serum hCG 2-3 with after embryo transfer	1) Pregnancy rate between short and long protocol: Out + / Out - / Total Short: **17** / **41** / 58	**Comments:** No adjustments made for multiple comparisons **Quality assessment:** Randomization method: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#9890	**Size of population:** 178 **Number of cycles analyzed:** 178 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Study the effectiveness of 3 GnRH agonist protocol Grp L: Pts received the traditional long protocol: Mid luteal started triptorelin (the study GnRH agonist) was continued up to and including the day of hCG. Grp M: Midluteal started triptorelin and continue up to and including day 4 of hMG administration. Grp S: Stop triptorelin On the day of hMG started. Grp M and S continued treatment with placebo injections from the day after stopping triptorelin up to and including the day of hCG administration	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Eligibility for IVF/ICSI treatment - History of s spontaneous regular cycle between 24-35 days - 18-38 yo - BMI < or = to 32 **Exclusion criteria:** - PCOS - Incipient ovarian failure - Ovulation induction or IVF/ICS in the 2 mos before this study - Poor stimulation response in prior cycle - Treatment with GnRH within 3 mos before the study - Previous inclusion of this study - History or suspicion of non compliance to medical regimens - Treatment with oral contraceptives within 1 mo before this study	Ongoing pregnancy: positive pregnancy test at 10-12 wks of gestation Live birth: NR Multiples: NR Complications: Premature LH surge	Long **13** **45** 58 30 86 116 Value / Lower 95% CI / Upper 95% CI **Rel risk** 1.31 0.70 2.44 2) Pregnancy rate between medium and long protocol: Out + / Out - / Total Medium **20** **42** 62 Long **13** **44** 58 33 86 119 Value / Lower 95% CI / Upper 95% CI **Rel risk** 1.41 0.78 2.57 3) Ongoing pregnancy rate between short and long protocol: Out + / Out - / Total Short **16** **42** 58 Long **12** **46** 58 28 88 116 Value / Lower 95% CI / Upper 95% CI **Rel risk** 1.33 0.69 2.56 4) Ongoing pregnancy rate between medium and long protocol: Out + / Out - / Total Medium **15** **47** 62 Long **12** **46** 58 27 93 120 Value / Lower 95% CI / Upper 95% CI **Rel risk** 1.17 0.60 2.28 5) NO premature LH surge (which is the main complication that might happen with short and	Blinding: + Dropout rate < 20%:+ Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				medium protocol) occurred during study.	
Smith, Coyle, and Norman, 2006 **#55800**	**Geographical location:** Adelaide, Australia **Study dates:** May 2003-Jan 2005 **Size of population (no. of patients):** 228 (pregnancy outcomes available for 221) **Number of cycles analyzed:** 228 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** - 3 sessions of acupuncture (active or sham): day 9 of stimulation, immediately before and immediately after embryo transfer - acupuncture: administered based on traditional Chinese medicine diagnosis - sham—acupuncture performed close to, but not on, same points, using blunt placebo needle	**Age:** Mean (SD): Acupuncture 35.9 (4.7); sham: 36.1 (4.8) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 51 (22.3%) Endometriosis: 54 (23.7%) Male factor: 105 (46.0%) Tubal factor: 89 (39.0%) Unspecified "other":82 (36.0%) **Inclusion criteria:** - Planned IVF or ICSI **Exclusion criteria:** - Previous cycle in this trial	**Definition(s) of outcome(s):** Pregnancy: Fetal heart rate on ultrasound Ongoing pregnancy: live fetus at 18 weeks Live birth: NR Multiples: NR Complications: NR	1) Pregnancy: Preg + / Preg - / Total Study drug: 34 / 76 / 110 Control: 27 / 81 / 108 61 / 157 / 218 Rel risk: 1.24 (Lower 95% CI 0.80; Upper 95 % CI 1.90) 2) Ongoing pregnancy: Preg + / Preg - / Total Study drug: 31 / 79 / 110 Control: 22 / 86 / 108 53 / 165 / 218 Rel risk: 1.38 (Lower 95% CI 0.86; Upper 95 % CI 2.23) 3) Relaxation more common in control group; no changes in any of SF-36 domains	**Comments:** None **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +
Staessen, Platteau, Van Assche, et al., 2004 **#58530**	**Geographical location:** Brussels, Belgium **Study dates:** Mar 2000-Dec 2003	**Age:** Mean (SD): Control: 39.9 (2.4) PGD: 40.1 (2.4) **Race/ethnicity (n [%]):**	**Definition(s) of outcome(s):** Ongoing pregnancy: Gestational sac with FHR 6 weeks post-transfer	1) Ongoing pregnancy: Preg + / Preg - / Total PGD: **22** / **126** / 148 Control: **29** / **112** / 141	**Comments:** Randomization method not described **Quality assessment:** Randomization method: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Size of population (no. of patients): 400 randomized, 289 to oocyte retrieval **Number of cycles analyzed:** 289 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** ICSI with blastocyst transfer, randomized to preimplantation genetic diagnosis	NR **Diagnoses (n [%]):** Unexplained infertility: 53 (18%) Male factor: 113 (39%) Tubal factor: 57 (20%) Combined: 67 (23%) **Inclusion criteria:** - Maternal age ≥ 37 - Need for ICSI - Motile sperm - Both partners with a normal karyotype **Exclusion criteria:** NR	Live birth: NR Multiples: NR Complications: NR	Total 51 238 289 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.72 0.44 1.20 2) Significantly fewer embryos transferred with PGD	Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -
Stener-Victorin, Walden-strom, Wikland, et al., 2003 **#16350**	**Geographical location:** Gothenberg, Malmo, and Stockholm, Sweden **Study dates:** 1999 to 2001 **Size of population (no. of patients):** 286 **Number of cycles analyzed:** 274 **Number of cycles per patient:** 1 **Study type:** RCT **Interventions:** EA and PCB: electro-acupuncture plus a paracervical block Alfentanil and PCB	**Age:** Mean (range): 32.9 (22-38) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 68 (25%) Endometriosis: 43 (16%) Male factor: 121 (44%) Tubal factor: 45 (16%) PCOS: 14 (5%) Other: 10 (4%) 2 causes: 27 (10%) **Inclusion criteria:** Aged <38 years, with a body mass index (BMI) <28 kg/m^2, who had four or more follicles of an expected size >18 mm at the time of hCG injection, and who had undergone no more than three IVF	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: Pain by VAS	1) Pregnancy: Preg + / Preg - / Total EA and PCB **43** **93** 136 Alfenta-nil and PCB **49** **89** 138 Total 92 182 274 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.89 0.64 1.24 2) No difference in pain by VAS	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%:+ Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		treatments previously, were accepted for the study. **Exclusion criteria:** NR			
Stephenson and Fluker, 2000 **#6430**	**Geographical location:** Vancouver, Canada **Study dates:** March 1995-July 1998 **Size of population (no. of patients):** 51 **Number of cycles analyzed:** 51 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** - COH with GnRH agonist, gonadotropins - Randomized to placebo or intravenous immunoglobulin infusion (500 mg/kg over 4-6 hours) within 72 hours preceding embryo transfer, repeated 4 weeks later if + FHR	**Age:** Mean (SD): 36 Range: 28-44 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - At least 2 previous failed transfers, with at least 2 good quality embryos/transfer **Exclusion criteria:** - Age <18 or >44 years - IgA deficiency - Immunoglobulin hypersensitivity - + serology for hepatitis B, C, HIV, HTLV	**Definition(s) of outcome(s):** Pregnancy: Positive fetal heart rate Live birth: Yes Multiples: NR Complications: NR	1) Live birth: Preg + / Preg - / Lower 95% CI / Upper 95 % CI Study drug: 4 / 22 / 26 Control: 3 / 22 / 25 7 / 44 / 51 **Rel risk**: 1.28 / 0.32 / 5.16	**Comments:** None **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +
Stern, Chamley, Norris, et al., 2003 **#15940**	**Geographical location:** Victoria, Australia & Epsom, New Zealand **Study dates:** 1994-1997 **Size of population (no.**	**Age:** Mean (SD): 35.2 (4.6%) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):**	**Definition(s) of outcome(s):** Pregnancy: NR Live birth: Yes	1) Live birth rate (1st cycle only): Preg + / Preg - Heparin/ aspirin: 11 / 63 / 74 Control: 10 / 59 / 69 21 / 122 / 143	**Comments:** Crossover design makes it impossible to calculate cumulative per patient pregnancy rate **Quality assessment:** Randomization method: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	of patients): 143 **Number of cycles analyzed:** 300 **Number of cycles per patient:** 2.1 **Study type:** RCT **Interventions:** - Beginning on day of embryo transfer through hCG results, randomized to self-administered (a) heparin 5000 U sc twice daily plus 100 mg aspirin daily, or (b) placebo heparin and aspirin - monitored with aPTT and platelet counts - if no pregnancy, treatment alternated in subsequent cycle	Unexplained infertility: 44 (30%) Endometriosis: 11 (8%) Male factor: 41 (29%) Tubal factor: 33 (23%) PCOS: 6 (4%) **Inclusion criteria:** - Women seropositive for at least one antiphospholipid (APA), antinuclear (ANA), or beta 2 glycoprotein I autoantibody, - >10 embryos transferred without achieving pregnancy **Exclusion criteria:** - abnormal findings on hysteroscopic evaluation of the uterine cavity - osteoporosis, - known hematological/thrombotic disorders including thrombophilia, platelet dysfunction, or previous thrombosis	Multiples: NR Complications: NR	 **Rel risk** 1.03 (Lower 95% CI 0.46, Upper 95 % CI 2.26) 2) Results similar for analysis on per-cycle basis	Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +
Strehler, Abt, El-Danasouri, et al., 2001 **#58550**	**Geographical location:** Ulm, Germany **Study dates:** Jan 1998-June 1999 **Size of population (no. of patients):** 578	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 36 (5%)	**Definition(s) of outcome(s):** Pregnancy: Gestational sac on ultrasound at 6 weeks Live birth: NR	1) Pregnancy (per randomized subject): rFSH: Preg + **78**, Preg- **218**, Total 296 hMG: Preg + **80**, Preg- **202**, Total 282 Total: Preg + 158, Preg- 420, Total 578	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		Endometriosis: 21 (3%) Male factor: 462 (80%) Tubal factor: 137 (24%) Non-mutually exclusive categories **Inclusion criteria:** - Scheduled for IVF/ICSI - Age ≤ 40 - ≤ 4 previous attempts **Exclusion criteria:** NR	Multiples: NR Complications: NR	Value 0.93; Lower 95% CI 0.71; Upper 95% CI 1.21 (Rel risk)	concealment: -
Surrey, Silverberg, Surrey, et al., 2002 **#58560**	**Geographical location:** Englewood, CA; Austin, TX; Beverly Hills, CA **Study dates:** NR **Size of population (no. of patients):** 51 **Number of cycles analyzed:** 51 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Endometriosis, scheduled for IVF/ET, randomized to (a) 3 months GnRH agonist (leuprolide) vs.(b) no treatment	**Age:** Mean (SD): Agonist: 33.1 (0.7) No treatment: 32.6 (0.6) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Endometriosis: 100% **Inclusion criteria:** - Infertile patients with endometriosis documented at laparoscopy or laparotomy within 60 months of cycle initiation (range, 2-55 months) - Regular menses (every 26–33 days) - Candidates for autologous IVF-ET undergoing fresh embryo transfer only **Exclusion criteria:** - GnRH agonist in	**Definition(s) of outcome(s):** Pregnancy: Gestational sac with FHR on ultrasound Live birth: NR Multiples: NR Complications: NR	1) Pregnancy: Preg + / Preg - / Total GnRH: **20** / **5** / 25 No Rx: **14** / **12** / 26 Total: 34 / 17 / 51 Value 1.49; Lower 95% CI 0.99; Upper 95% CI 2.23 (Rel risk)	**Comments:** Not clear if randomization stratified by center **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		previous 12 months - FSH > 12 - Ovarian endometrioma			
Tang, Glanville, Orsi, et al., 2006 **#56080**	**Geographical location:** Leeds, UK **Study dates:** 2001-2004 **Size of population (no. of patients):** 101 **Number of cycles analyzed:** 101 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** - Long GnRH agonist protocol - Randomized to (a) metformin 850 mg or (b) placebo BID from first day of down-regulation until egg retrieval	**Age:** Mean (SD): metformin 31.3, placebo 31.1 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** PCOS: 100% **Inclusion criteria:** - PCOS, normal FSH - ages 20-39 - Undergoing IVF/ICSI **Exclusion criteria:** - concurrent hormone therapy within the previous 6 weeks - any chronic disease that could interfere with the absorption, distribution, metabolism or excretion of metformin - renal or liver disease. - significant systemic disease or diabetes (type 1 or 2)	**Definition(s) of outcome(s):** Pregnancy: Clinical pregnancy > 12 weeks Live birth: > 24 weeks Multiples: NR Complications: Side effects, severe OHSS (symptomatic, or embryos frozen because considered high risk)	1) Clinical pregnancy: Preg + / Preg - / Study drug: 17 / 35 / 52 Control: 8 / 41 / 49 25 / 76 / 101 Rel risk: 2.00 (Lower 95% CI 0.95, Upper 95 % CI 4.21) 2) Live birth: Preg + / Preg - / Metformin: 17 / 35 / 52 Placebo: 6 / 43 / 49 23 / 78 / 101 Rel risk: 2.67 (Lower 95% CI 1.15, Upper 95 % CI 6.22) 3) Severe OHSS: Preg + / Preg - / Metformin: 2 / 50 / 52 Placebo: 10 / 39 / 49 12 / 89 / 101 Rel risk: 0.19 (Lower 95% CI 0.04, Upper 95 % CI 0.82) 4) Side effects: Preg + / Preg - / Study drug: 23 / 29 / 52 Control: 1 / 41 / 42	**Comments:** None **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization +concealment:

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				24 70 94 Lower Upper 95% CI 95 % CI **Rel risk** 18.58 2.62 131.94	
Tang, Ng, So, et al., 2001 **#3720**	**Geographical location:** Hong Kong, China **Study dates:** 9/1999 - 10/2000 **Size of population:** 800 **Number of cycles analyzed:** 800 **Number of cycles per patient:** 1.00 **Study type:** RCT **Interventions:** Ultrasound-guided ET vs. Clinical touch method	**Age:** Mean (SD):34.3 (3.8) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility:79(9.9) Endometriosis: 60(7.5) Male factor: 354(44.3) Tubal factor: n/a PCOS: n/a Other (specify): Tuboperitoneal: 228(28.5) Mixed 51(6.4) **Inclusion criteria:** NR **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Clinical pregnancy: Positive uhCG and +gestational sac on u/s, irrespective of whether it was intra- or extrauterine, by u/s examination Ongoing pregnancy: +FCA at 10 wks gestation Live birth: NR Multiples: Yes Complications: NR	1) Clinical pregnancy: Out + Out - Total u/s guided **104** **296** 400 clinical touch **90** **310** 400 Total 194 606 800 Value Lower 95% CI Upper 95% CI **Rel risk** 1.16 0.90 1.48 2) Ongoing pregnancy: Out + Out - Total u/s guided **94** **306** 400 clinical touch **76** **324** 400 Total 170 630 800 Value Lower 95% CI Upper 95% CI **Rel risk** 1.24 0.95 1.62 3) Multiple pregnancy: Out + Out - Total u/s guided **31** **73** 104 clinical touch **20** **70** 90 Total 51 143 194 Value Lower 95% CI Upper 95% CI	**Comments:** Powered to detect 8% absolute difference in pregnancy rates **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Rel risk 1.34 (0.82 – 2.18)	
Tarlatzis, Tavmergen, Szama-towicz, et al., 2006 **#58570**	**Geographical location:** 6 centers in Greece, Israel, Poland, Turkey **Study dates:** NR **Size of population (no. of patients):** 114 **Number of cycles analyzed:** 114 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Down-regulation with GnRH agonist, rFSH until lead follicle 14 mm, then randomized to (a) rFSH + placebo (b) rFSH + rLH up to 10 days prior to ooycte retrieval	**Age:** Mean (SD): FSH only: 30.3 (3.6) FSH + LH: 30.5 (3.5) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Male factor: 64 (56%) Tubal factor: 41 (36%) Other: 9 (8%) **Inclusion criteria:** - Age 18-37 - Normal uterus and two ovaries - Scheduled to undergo controlled ovarian stimulation prior to IVF with ICSI - Normal ovulatory cycles of 24-35 days - Maximum FSH and prolactin concentrations of 12 IU/l and 1040 mIU/l, respectively, during early follicular phase (days 2–6) - No evidence of other gynecological pathology (except tubal) based on ultrasonography and laboratory investigations **Exclusion criteria:** Previous cycle with < 2 oocytes retrieved	**Definition(s) of outcome(s):** Pregnancy: FHR on ultrasound 35 days after retrieval Live birth: Yes Multiples: NR Complications: NR	1) Pregnancy: Preg + / Preg - / Total FSH + LH: **9** / **46** / 55 FSH: **14** / **45** / 59 Total: 23 / 91 / 114 Value (Lower 95% CI – Upper 95% CI) **Rel risk** 0.69 (0.32 – 1.46) 2) Live birth: Live birth + / Live birth - / Total FSH + LH: **6** / **49** / 55 FSH: **10** / **49** / 59 Total: 16 / 98 / 114 Value (Lower 95% CI – Upper 95% CI) **Rel risk** 0.64 (0.25 – 1.65)	**Comments:** None **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +
Tay and Lenton,	**Geographical location:** Sheffield, UK	**Age:** Mean (SD): 32.2 (4.5)	**Definition(s) of outcome(s):**	1) Clinical pregnancy:	**Comments:** None

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
2003 **#15090**	**Study dates:** Jan 1998-Jan 1999 **Size of population (no. of patients):** 63 **Number of cycles analyzed:** 63 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** GnRH agonist COH; randomized to (a) progesterone 200 mg BID vaginally vs (b) Progesterone + 2mg E2 valerate daily	Range: 22-39 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** -No previous infertility treatment - Infertility at least 2 years **Exclusion criteria:** Basal FSH >10	Pregnancy: +FHR Live birth: NR Multiples: NR Complications: NR	Preg + / Preg - Study drug: **5** / **28** = 33 Control: **7** / **28** = 35 12 / 56 = 68 Rel risk 0.76 (Lower 95% CI 0.27; Upper 95 % CI 2.15)	**Quality assessment:** Randomization method: - Blinding: - Dropout rate < 20%: - Adequacy of randomization concealment: -
Tay and Lenton, 2005 **#40970**	**Geographical location:** Sheffield, UK **Study dates:** NR **Size of population (no. of patients):** 168 **Number of cycles analyzed:** 168	**Age:** Mean (SD): Overall mean 32.4 Range: 21-41 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:**	**Definition(s) of outcome(s):** Pregnancy: Ongoing pregnancy—greater than 14 weeks Live birth: NR Multiples: NR	1) Ongoing pregnancy, rectal progesterone vs progesterone capsules: Preg + / Preg - Rectal: **12** / **35** = 47 Capsule: **19** / **55** = 74 31 / 90 = 121 Lower 95% CI; Upper 95 % CI	**Comments:** No adjustment for multiple comparisons **Quality assessment:** Randomization method: - Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: -

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Number of cycles per patient: 1.0 **Study type:** RCT **Interventions:** (a) micronized progesterone 200 mg rectally twice daily, from day 4 post retrieval for 14 days (b) micronized progesterone 8% gel once daily from day 4 post retrieval for 14 days (c) micronized progesterone capsules, varying dosage, from day 4 post retrieval for 14 days (d) 1500 IU hCG days 4 and 7	- BMI 19-20 - Day 3 FSH <12 **Exclusion criteria:** Pre-ovulatory E2 >15,000 pmol/L and/or >15 follicles	Complications: NR	**Rel risk** 0.99 (0.53, 1.85) 2) Ongoing pregnancy, progesterone gel vs progesterone capsules: Gel: **13** / **36** / 49 Capsule: **19** / **55** / 74 32 / 91 / 123 **Rel risk** 1.03 (Lower 95% CI 0.56, Upper 95 % CI 1.89) 3) Ongoing pregnancy, hCG vs progesterone capsules: hCG: **12** / **35** / 47 Capsule: **19** / **55** / 74 31 / 90 / 121 **Rel risk** 0.99 (Lower 95% CI 0.53, Upper 95 % CI 1.85)	
Tesarik, Hazout, and Mendoza, 2005 **#41280**	**Geographical location:** Granada, Spain and Paris, France **Study dates:** NR **Size of population (no. of patients):** 100 **Number of cycles**	**Age:** Mean (SD): GH: 42.2 (1.1), placebo 42.3 (1.0) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:**	**Definition(s) of outcome(s):** Pregnancy: NR Live birth: Yes Multiples: NR Complications: NR	1) Live birth: GH: 11 / 39 / 50 Placebo: 2 / 48 / 50 13 / 87 / 100 **Rel risk** 5.50 (Lower 95% CI 1.28, Upper 95 % CI 23.56)	**Comments:** None **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	analyzed: 100 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** - Long GnRH agonist protocol with rFSH - On day 7 of ovarian stimulation, randomized to (a) 8 IU growth hormone or (b) placebo until day after ovulation triggering dose of hCG	-Women aged 41-44 **Exclusion criteria:** - day 3 serum FSH >14 IU/l - day 3 inhibin B <30 pg/ml.			
Tesarik, Hazout, Mendoza-Tesarik, et al., 2006 **#56160**	**Geographical location:** Granada, Spain **Study dates:** Sep 2003-Sep 2005 **Size of population (no. of patients):** 600 **Number of cycles analyzed:** 600 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** 300 GnRH agonist, 300 GnRH antagonist COH Randomized to (a) placebo, or (b) single dose GnRH agonist 3 days after embryo transfer All received E2 +	**Age:** Mean (SD): **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** ICSI **Exclusion criteria:** - Age > 40 - Need for testicular sperm extraction	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: NR	1) Ongoing pregnancy, GnRH agonist downregulation: Preg + / Preg - / Total GnRH a: 66 / 84 / 150 Placebo: 54 / 96 / 150 120 / 180 / 300 Rel risk: 1.22 (Lower 95% CI 0.92, Upper 95 % CI 1.62) 2) Ongoing pregnancy, GnRH antagonist down regulation: Preg + / Preg - / Total GnRH a: 65 / 85 / 150 Placebo: 46 / 104 / 150 111 / 189 / 300 Rel risk: 1.41 (Lower 95% CI 1.04, Upper 95 % CI 1.91) 3) Ongoing pregnancy, both groups combined: Preg + / Preg -	**Comments:** None **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	progesterone for luteal support			GnRHa **131** **169** 300 Placebo **110** **190** 300 241 359 600 Lower 95% CI / Upper 95 % CI **Rel risk** 1.19 0.98 1.45	
Thompson, Murray, MacLennan, et al., 2000 **#58580**	**Geographical location:** Aberdeen, UK **Study dates:** NR **Size of population (no. of patients):** 112 **Number of cycles analyzed:** 112 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** Randomized to inhalational (isodex) or IV (fentanyl/midazolam) analgesia for oocyte retrieval	**Age:** Mean (SD): Inhalational: 33.9 (4.0) IV: 32 (4.5) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Scheduled for oocyte retrieval for IVF/ICSI **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy: Not defined Live birth: NR Multiples: NR Complications: Pain	1) Pregnancy: Preg + / Preg - / Total IV **7** **48** 55 Inhala-tional **10** **47** 57 Total 17 95 112 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.73 0.30 1.77 2) Pain scores worse for inhalation; no significant difference in satisfaction	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +
Thurin, Hausken, Hillensjo, et al., 2004 **#10520**	**Geographical location:** Göteborg and Linköping, Sweden; Copenhagen, Denmark; Haugesund Norway. **Study dates:** May 2000 to Oct 2003 **Size of population (no.**	**Age:** Mean (SD): 30.8 (3.0) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Endometriosis: 96 Male factor: 319 Tubal factor: 130	**Definition(s) of outcome(s):** Pregnancy: Positive test for urinary HCG (> 20 IU/L) or serum HCG ≥2 IU 2 weeks after transfer Live birth: Yes	1) Pregnancy: Preg + / Preg - / Total SET **9** **321** 330 DET **16** **315** 331 Total 25 636 661 Value / Lower 95% CI / Upper 95% CI **Rel risk** 0.56 0.25 1.26	**Comments:** None **Quality assessment:** Randomization method: + Blinding: + Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	of patients): 661 **Number of cycles analyzed:** 661 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** SET: Transfer of a single fresh embryo and, if there was no live birth, subsequent transfer of a single frozen-and-thawed embryo DET: Single transfer of two fresh embryos	Other: Hormonal: 144 Unknown: 126 (More than one diagnosis per couple was possible; 513 couples had one, 140 had two, and 8 had three diagnoses.) **Inclusion criteria:** < 36 years of age, were undergoing their first or second in vitro fertilization cycle, and had at least two embryos of good quality available for transfer or freezing. [The original protocol stipulated that the patient had to be less than 35 years of age and have at least three good-quality embryos available, but these criteria were modified in an amendment after the first 215 patients were enrolled, owing to a change in usual clinical practice in Sweden.] **Exclusion criteria:** NR	Multiples: Yes Complications: NR	2) Live birth: Live birth + / Live birth - / Total SET: **158** / **172** / 330 DET: **174** / **157** / 331 Total: 332 / 329 / 661 Value: 0.91 (Lower 95% CI: 0.78; Upper 95% CI: 1.06) **Rel risk** 3) Multiple births: Multiple + / Multiple - / Total SET: **1** / **127** / 128 DET: **47** / **95** / 142 Total: 48 / 222 / 270 Value: 0.02 (Lower 95% CI: 0.00; Upper 95% CI: 0.17) **Rel risk**	
Tremellen, Valbuena, Landeras, et al., 2000 **#6470**	**Geographical location:** Adelaide, Australia, and Madrid and Murcia, Spain **Study dates:** June 1996-Dec 1998 **Size of population (no. of patients):** 478	**Age:** Mean (SD): 33 (pooled) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 17% Male factor: 47% Other:	**Definition(s) of outcome(s):** Pregnancy: +FHR Live birth: NR Multiples: NR Complications: NR	1) Pregnancy: Preg + / Preg - Intercourse: 47 / 195 / 242 Control: 39 / 197 / 236 86 / 392 / 478 Lower 95% CI; Upper 95 % CI	**Comments:** None **Quality assessment:** Randomization method: + Blinding: - Dropout rate < 20%: + Adequacy of randomization concealment: +

Evidence Table 2. Question 3 – Assisted Conception: IVF and ICSI (continued)

Study	Study Design	Patients	Clinical Presentation	Results				Comments/Quality Scoring
	Number of cycles analyzed: 478 **Number of cycles per patient:** 1.0 **Study type:** RCT **Interventions:** - Austraila: randomized to (a) intercourse at least once in the 4 day period 2 days before and 2 days after embryo transfer, or (b) abstaining -Spain: (a) intercourse at least twice, 12 hours before and 12 hours after embryo transfer, or (b) abstain during entire IVF cycle	"Female factor" 20% Combined: 15% **Inclusion criteria:** - 18-40 - stable relationship **Exclusion criteria:** - donor eggs/sperm - Hepatitis B, C, HIV		**Rel risk**	1.18	0.80	1.73	

Evidence Table 3. Question 4 – Longer-Term Outcomes

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Aboulghar, Aboulghar, Mansour, et al., 2001 **#4560**	**Geographical location:** Cairo, Egypt **Study dates:** Jan 1997 – Dec 1999 **Size of population:** 430 consecutive babies conceived by ICSI from 320 deliveries (220 singletons, 198 twins, 12 triplets), 430 babies conceived naturally from 418 deliveries (406 singletons, 12 twins) **Study type:** Cohort Prospective cohort of consecutive ICSI deliveries, compared to control grp of consecutive naturally-conceived pregnancies. Planned sample size had 80% power to detect 2.5% difference in chromosomal anomalies with 2-sided significance level of 0.05	**Age:** Mean (SD): ICSI 30 (5.2) Ctrl 28.5 (4.1) Range: ICSI 17-41 Ctrl 18-39 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Women who conceived through ICSi in this center who were observed by OB of this center and delivered at this hospital; consecutive deliveries. **Exclusion criteria:** Observed by another obstetrician	**Definition(s) of outcome(s):** Karyotype performed on cord blood or peripheral blood.	6 sex chromosome anomalies 8 autosomal anomalies 1 combined 1) Abnl karyotypes: Abnl karyo / Nl karyo / Total ICSI: **15** / **415** / 430 Natural: **0.5** / **430** / 430.5 Total: 15.5 / 845 / 860.5 Value (Rel risk): 30.03; Lower 95% CI: 1.80; Upper 95% CI: 501.13 2) Abnl kayotype by method of sperm collection (ejaculated vs surgically retrieved): Abnl karyo / Nl karyo / Total ICSI - ejac: **14** / **374** / 388 ICSI - surg: **1** / **41** / 42 Total: 15 / 415 / 430 Value (Rel risk): 1.52; Lower 95% CI: 0.20; Upper 95% CI: 11.24	**Comments:** - Significant consanguinity in both grps (9.7% ICSI, 11% ctrl), but similar. - Similar mat & pat ages in both grps. - Only 6/15 parents of infants with abnl karyotypes underwent karyotyping themselves; unclear whether these are de novo mutations or inherited. - 2/6 had abnl paternal karyotype **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for genomic test: NR Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Adler-Levy, Lunenfeld, and Levy, 2007 **#70280**	**Geographical location:** Beer Sheva, Israel **Study dates:** Jan 1988-Dec 2002 **Size of population (no. of patients):** 4730 **Study type:** Cohort	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** All twin deliveries ≥ 24 weeks, divided by ART, ovulation induction, or spontaneous **Exclusion criteria:** - Vanishing twins (n = 32) - Only 1 pregnancy used for 83 mothers with > 1 twin pregnancy (randomly selected)	**Definition(s) of outcome(s):** Diabetes Pregnancy induced hypertension Preterm delivery Birthweight Malformations	1) Small for gestational age, IVF vs. spontaneous: SGA + / SGA - / Total IVF: **93** / **465** / 558 Spont: **794** / **2900** / 3694 Total: 887 / 3365 / 4252 Value / Lower 95% CI / Upper 95% CI Rel risk: 0.78 / 0.64 / 0.94 2) Small for gestational age, ovulation induction vs. spontaneous: SGA + / SGA - / Total Ov Ind: **102** / **376** / 478 Spont: **794** / **2900** / 3694 Total: 896 / 3276 / 4172 Value / Lower 95% CI / Upper 95% CI Rel risk: 0.99 / 0.83 / 1.19 3) Malformation, IVF vs. spontaneous: Mal + / Mal - / Total IVF: **24** / **454** / 478 Spont: **274** / **3420** / 3694 Total: 298 / 3874 / 4172 Value / Lower 95% CI / Upper 95% CI Rel risk: 0.68 / 0.45 / 1.02 4) Malformation, ovulation induction vs. spontaneous: Mal + / Mal - / Total Ov ind: **67** / **491** / 558 Spont: **274** / **3420** / 3694 Total: 341 / 3911 / 4252	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: - Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Rel risk: Value 1.62, Lower 95% CI 1.26, Upper 95% CI 2.08 5) After adjustment for maternal age and nulliparity: - Increased risk for gest diabetes in both groups (IVF 2.41, 95% CI 1.77-3.29; induction 1.71, 95% CI 1.20-2.42) - Lower risk for preterm birth for IVF (0.91, 95% CI 0.88-0.94) but not induction (1.01, 95% CI 0.97-1.35) - Lower risk for malformations with induction (0.60, 95% CI 0.38-0.95)	
Agarwal, Loh, Lim, et al., 2005 **#40680**	**Geographical location:** Singapore **Study dates:** Aug 1998 - 1999 **Size of population:** 76 ICSI, 261 naturally conceived **Study type:** Cohort	**Age:** Mean (SD): ICSI 33.8 (5.7), ctrl 33.7 (5.6) **Race/ethnicity (n [%]):** ICSI 85% Chinese, 10% Malay, 5% Indian Ctrls 83% Chinese, 13% Malay, 4% indian **Diagnoses (n [%]):** NR **Inclusion criteria:** Eligible subjects identified retrospectively; liveborns conceived by ICSI, invited by mail & phone call. Controls naturally conceived during same study period, randomly selected using hospital database, matched for maternal age, sex, del date, race, plurality, parity. 3:1 controls: ICSI **Exclusion criteria:** No consent given, ectopic or early miscarriage, neonatal death	**Definition(s) of outcome(s):** Major malformation = resulted in functional impairment or required surgical correction BSID = Bayley Scale of Development II - MDI = mental developmental index - PDI = psychomotor developmental index - Mean scores for both 100 VABS = Vineland Adaptive Behaviour Scale Mean score 100 Exam at 2yo	1) C/S in singletons: CS+: ICSI 19, Ctrl 60, Total 79 CS-: ICSI 22, Ctrl 125, Total 147 Total: ICSI 41, Ctrl 185, Total 226 Rel risk: Value 1.43, Lower 95% CI 0.97, Upper 95% CI 2.11 2) Bayley MDI >115 (>2SD above mean): MDI > 115: ICSI 6, Ctrl 6, Total 12 MDI ≤ 115: ICSI 70, Ctrl 255, Total 325 Total: ICSI 76, Ctrl 261, Total 337 Rel risk: Value 3.43, Lower 95% CI 1.14, Upper 95% CI 10.34 Other developmental outcomes presented as continuous variables; no diff in any by whole grp, singletons, multiples, EXCEPT mean Bayley MDI for multiples higher in ICSI grp (92 vs. 86, p=0.03). Difference NS (and all others NS) when adjusted for maternal education,	**Comments:** - 10% study pts & 3% ctrls declined to participate - ICSI grp had higher income, but no signif diff in level of education - Small numbers **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: - Adequate description of the cohort: + Use of validated method for genomic test: NR Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				income, housing type, plurality, gestational age, presence of congenital malformation 3) Major malformations: ICSI: Malf+ **6**, Malf- **70**, Total 76 Ctrl: Malf+ **7**, Malf- **254**, Total 261 Total: Malf+ 13, Malf- 324, Total 337 Rel risk: Value 2.94, Lower 95% CI 1.02, Upper 95% CI 8.50	
Alikani, Ceklenial, Walters, et al., 2003 **#15800**	**Geographical location:** West Orange, NJ **Study dates:** 7 yr period (dates NR) **Size of population:** 4,305 cycles 81 cycles involved monozygotic (MZ) fetuses **Study type:** Case-control	**Age:** Mean (SD): MZ twin preg – 35.3 (0.49) Non-MZ twins – 34.5 (0.09) Singletons – 35.5 (0.09) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** IVF pts with confirmed pregnancy at 6 wks **Exclusion criteria:** Extra sacs w/o evidence of embryo development	**Definition(s) of outcome(s):** Incidence of MZ twinning	Overall incidence of MZ twinning 1.88% No sig diff (MZ versus non-MZ twins or singletons) in mat or pat age, # drug ampoules, # days gonadotropins, Peak E2, peak P, # oocytes retrieved, # embryos replaced. No categorical variables to analyze by 2x2 tables. Of 81 MZ twin pregnancies, 40 fetuses were selectively reduced.	**Comments:** Major strength is early ascertainment of cases through routine US at 6 wks (allows for inclusion of those MZ pregnancies that were later reduced) **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: + Verification that the control is free of cancer: NR Comparability of cases and controls with respect to potential confounders: Validated dietary assessment method: NR Appropriateness of statistical analyses: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Anthony, Buitendijk, Dorrepaal, et al., 2002 **#1350**	**Geographical location:** Nijmegen, Netherlands **Study dates:** 1995 - 1996 **Size of population:** 4,224 IVF children, 314,605 naturally-conceived children **Study type:** Cohort (retrospective)	**Age:** Mean (SD): IVF 33.3, ctrl 29.7 **Race/ethnicity (n [%]):** IVF 78.2% Dutch, Ctrl 78.6% Dutch **Diagnoses (n [%]):** NR **Inclusion criteria:** 3 national registries: National Perinatal Database for Primary Care (midwife births), National Perinatal Database for Secondary Care (OB births), National Neonatology Database (records admissions within 28d of life, and readmissions for neonatal problems). Reviewed for IVF coded as conception method. **Exclusion criteria:** Pregnancies <16wks not included in National Perinatal Databases.	**Definition(s) of outcome(s):** Congenital malformations. Coded by organ system. No definition given, either for congenital malformation or major/minor.	1) Overall congenital malformations: Malf + / Malf - / Total IVF: **137** / **4087** / 4224 Nat: **8526** / **306079** / 314605 Total: 8663 / 310166 / 318829 Value (Lower 95% CI – Upper 95% CI) Odds rat: 1.20 (1.01 – 1.43) When adjusted for confounders (mat age, parity, ethnicity), OR for all malformations became insignificant (1.03, 0.86-1.23). 2) Major malformations: Malf + / Malf - / Total IVF: **28** / **4196** / 4224 Nat: **1700** / **312905** / 314605 Total: 1728 / 317101 / 318829 Value (Lower 95% CI – Upper 95% CI) Odds rat: 1.23 (0.84 – 1.79) 3) Minor malformations: Malf + / Malf - / Total IVF: **54** / **4170** / 4224 Nat: **3445** / **311160** / 314605 Total: 3499 / 315330 / 318829 Value (Lower 95% CI – Upper 95% CI) Odds rat: 1.17 (0.89 – 1.53) Raw data not presented: By specific organ system, only cardiovascular malformations significantly more common (OR 1.56 [1.10-2.22]) in IVF grp. By specific malformation, SUA, inguinal hernia, club foot were more frequent in IVF grp. No adjustment for multiple comparisons though.	**Comments:** - Complete information from 85% of all Dutch births. - Includes pregnancies with gestational age of at least 16 wks. - Would not include terminations before then. - Same data source of malformations for both grps, not general population statistics. - However, only includes admissions within 28d, so would miss dx made as output or made after that time period. - No mention of terminations. - No distinction for ICSI kids. **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: + Use of validated method for genomic test: NR Use of validated method for ascertaining clinical outcomes: - Adequate follow-up period: - Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Bajoria, Ward, and Adegbite, 2006 **#50370**	**Geographical location:** Manchester, UK **Study dates:** 1986-2000 **Size of population (no. of patients):** ART-only triplets N= 106 sets trichorionic-triamniotic triplets (TCTA) N= 34 sets dichorionic-triamniotic triplets (DCTA) **Study type:** Cohort	**Age:** DCTA 33yrs (25-41) TCTA 32yrs (19-43) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** ART triplets **Exclusion criteria:** Spontaneous triplets Fetal reduction	**Definition(s) of outcome(s):** Preterm birth < 30 wks Very low bwt < 1000 gm Respiratory distress syndrome (RDS) Anemia in neonate Intraventricular hemorrhage (IVH) Perinatal mortality = stillbirth + neonatal death	1) PTB < 30wks by 2 triplet groups: PTB+ / PTB- / Total TCTA **16** **90** 106 DCTA **17** **17** 34 Total 33 107 140 Value (Lower 95% CI – Upper 95% CI) Rel risk 0.30 (0.17 – 0.53) 2) Very low birthweight by 2 triplet groups: vlbwt+ / vlbwt- / Total TCTA **34** **284** 318 DCTA **43** **59** 102 Total 77 343 420 Value (Lower 95% CI – Upper 95% CI) Rel risk 0.25 (0.17 – 0.37) 3) RDS by 2 triplet groups: RDS+ / RDS- / Total TCTA **41** **277** 318 DCTA **41** **61** 102 Total 82 338 420 Value (Lower 95% CI – Upper 95% CI) Rel risk 0.32 (0.22 – 0.46) 4) Anemia in neonate: anemia+ / anemia- / Total TCTA **5** **313** 318 DCTA **20** **82** 102 Total 25 395 420 Value (Lower 95% CI – Upper 95% CI) Rel risk 0.08 (0.03 – 0.21) 5) Intraventricular hemorrhage:	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

	IVH+	IVH-	Total
TCTA	**11**	**307**	318
DCTA	**28**	**74**	102
Total	39	381	420

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.13	0.07	0.24

6) Perinatal mortality:

	perinatal mortality +	perinatal mortality -	Total
TCTA	**23**	**295**	318
DCTA	**40**	**62**	102
Total	63	357	420

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.18	0.12	0.29

Belva, Henriet, Liebaers, et al., 2007

#50590

Geographical location: Brussels, Belgium

Study dates: Children with 8th birthday from Feb 2001-Dec 2003

Size of population (no. of patients):
150 ICSI
147 spontaneously conceived controls

Study type: Cohort

Age: maternal age at birth
Median: ICSI 32 (25-43); spontaneous: 30 (18-42)

Race/ethnicity (n [%]): NR

Diagnoses (n [%]): NR

Inclusion criteria:
- ICSI at institution for exposed, local schools for controls
- Born in appropriate time period
- singleton
- born at least 32 weeks of gestation.
Children with low

Definition(s) of outcome(s):

- Major malformations
- Minor malformations
- Pediatric hospitalizations
- NICU admissions
- Pregnancy complications (not specified)

Variable response rate for specific variables—only malformation rates (complete denominator) reported here

1) Major malformations:

	Out +	Out -	Total
Exp +	**15**	**135**	150
Exp -	**5**	**142**	147
Total	20	277	297

	Value	Lower 95% CI	Upper 95% CI
Rel risk	2.94	1.10	7.88

2) Minor malformations:

	Out +	Out -	Total
Exp +	**35**	**115**	150
Exp -	**25**	**127**	152
Total	60	242	302

	Value	Lower 95% CI	Upper 95% CI

Comments:
- Only 61% of cohort participated—16% lost to follow-up, 23% refused participation
- Medical/neurologic/psychological assessment not blinded
- Self-reported history not validated against medical records
- No multivariate analysis (but numbers small—unlikely to have sufficient power)
- Variable response rates for different outcomes within groups

Quality assessment:
Unbiased selection of the cohort (prospective recruitment of subjects): -
Large sample size: -
Adequate description of the

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		birthweight or major malformations were not *per se* excluded from the study. - Dutch-speaking **Exclusion criteria:** NR		Rel risk 1.42 (0.89, 2.25)	cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: - Analysis (multivariate adjustments) and reporting of results: -
Ben-Ami, Vaknin, Reish, et al., 2005 **#39230**	**Geographical location:** Tel Aviv, Israel **Study dates:** Jan 1997 - July 2004 **Size of population:** 380 **Study type:** Cohort (retrospective)	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Women admitted during study period for termination of pregnancy bc of severe fetal anom **Exclusion criteria:** NR	**Definition(s) of outcome(s):** All twins dichorionic	1) Anencephaly overall: Anen+ / Anen- / Total IVF: **1** / **12** / 13 Spont: **20** / **332** / 352 Total: 21 / 344 / 365 Odds rat: Value 1.38, Lower 95% CI 0.17, Upper 95% CI 11.18 2) Anencephaly in twins: Anen+ / Anen- / Total IVF: **1** / **7** / 8 Spont: **1** / **11** / 12 Total: 2 / 18 / 20 Odds rat: Value 1.57, Lower 95% CI 0.08, Upper 95% CI 29.41 3) Anencephaly overall, ICSI vs spont: Anen+ / Anen- / Total ICSI: **5** / **10** / 15 Spont: **20** / **332** / 352 Total: 25 / 342 / 367 Odds rat: Value 8.30, Lower 95% CI 2.59, Upper 95% CI 26.60 4) Anencephaly in twins, ICSI vs spont:	**Comments:** Excluded those who continued pregnancy, either because they chose to or because of failed or late dx **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: - Adequate description of the cohort: - Use of validated method for genomic test: NR Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Anen+ / Anen- / Total ICSI: **5** / **7** / 12 Spont: **1** / **11** / 12 Total: 6 / 18 / 24 Value / Lower 95% CI / Upper 95% CI Odds rat: 7.86 / 0.75 / 82.13 No diff in IVF vs ICSI Logistic regression used to determine influence of twinning or mode of conception, found correlation only between anencephaly and twinning.	
Ben-shushan, Paltiel, Brzezinski, et al., 2001 **#4380**	**Geographical location:** Jerusalem, Israel **Study dates:** Cases reported Jan 1989-Dec 1992 **Size of population:** 128 **Study type:** Case-control	**Age:** Mean at diagnosis (SD): Cases: 53.53 (6.37) Controls: 50.49 (7.82) **Race/ethnicity (n [%]):** European/American (cases 45.3%, ctrls 24.7%) **Diagnoses (n [%]):** NR **Inclusion criteria:** - Histologically-confirmed diagnosis of endometrial CA - First diagnosed and reported to Israel Cancer Registry 1989-92 - Born 1929-57 (because fertility drugs first used in Israel in 1960) - Living Controls were randomly telephoned within same area codes as cases, same DOB range	**Definition(s) of outcome(s):** Ascertainment of exposure to any infertility drug based on interview	1) Use of any infertility drug: Cases / Ctrls / Total Infertility drug: **7** / **10** / 17 None: **121** / **245** / 366 Total: 128 / 255 / 383 Value / Lower 95% CI / Upper 95% CI Odds rat: 1.42 / 0.53 / 3.81	**Comments:** - 21.6% potential cases had died before or during study period - Of those living, interviewed only 39% (unable to locate pt or physician, illness, refusal by pt or physician) – non-response bias - More cases European-American, hypertensive, obese - Did not verify use of fertility drugs **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: - Appropriateness of the control population: + Verification that the control is free of cancer: - Comparability of cases and controls with respect to potential confounders: - Validated dietary assessment method: NR Appropriateness of statistical analyses: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		Exclusion criteria: - Women who had undergone hysterectomy excluded as controls - Had to contact women through their physicians – physicians obtained consent to interview patient			
Boerrigter, de Bie, Mannaerts, et al., 2002 **#1370**	**Geographical location:** Oss, Netherlands **Study dates:** NR (published 2002) **Size of population:** 340 pregnancies after ganireliex (a GnRH antagonist),, 134 after treatment with GnRH agonist **Study type:** Cohort Pooled results from 5 trials, 4 of which were RCTs	**Age:** Mean (SD): Ganirelix 31.4 (3.8), agonist 31.3 (4.1) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Pregnancies ≥ 16wks from 5 clinical trials of ganirelix. Inclusion criteria not described in detail. **Exclusion criteria:** Pregnancies < 16wks, frozen embryo transfer (except for one trial in which frozen were allowed)	**Definition(s) of outcome(s):** Pregnancy info collected at trial site directly, or through questionnaire. Info about children collected at birth "and, optionally, until 8 wks after birth." Congenital malformations classified by single person using 2 different definitions: Definition A: reduces viability or compromises quality of life and requires medical treatment. Def B: causes functional impairment or requires surgical intervention.	Btw 16-26wks, 8 losses in ganirelix grp (6 SAB, 2 selective/induced AB – one for cardiac malformation, one for meningomyelocele), 3 in agonist grp (all spont, unknown cause). After 26wks, 5 IUFD's in ganirelix grp, 2 in agonist. No major differences in rates of preterm birth, LBW, etc. Higher rates of preterm birth, VLBW, C/S with higher multiplicity in both grps. 1) Any pregnancy complication: Preg complic + / Preg complic - / Total Ganirelix: **159** / **181** / 340 Agonist: **69** / **65** / 134 Total: 228 / 246 / 474 Value: Rel risk 0.91 (Lower 95% CI 0.74, Upper 95% CI 1.11) 2) Cesarean: C/S / Other / Total Ganirelix: **147** / **184** / 331 Agonist: **59** / **73** / 132 Total: 206 / 257 / 463 Value: Rel risk 0.99 (Lower 95% CI 0.79, Upper 95% CI 1.24)	**Comments:** Sponsored by Organon - Information collected at birth and optionally up to 8wks after birth **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: - Use of validated method for genomic test: NR Use of validated method for ascertaining clinical outcomes: - Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				3) Congenital malformations after 26 wks: Malf + / Malf - / Total Ganirelix: **32** / **392** / 424 Agonist: **10** / **171** / 181 Total: 42 / 563 / 605 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.37 / 0.69 / 2.72	
Bonduelle, Bergh, Niklasson, et al., 2004 **#11510**	**Geographical location:** Brussels, Belgium; Göteborg, Sweden; and New York, NY **Study dates:** NR **Size of population:** 300 cases, 266 controls **Study type:** Consecutive intracytoplasmic sperm injection (ICSI) cases matched with spontaneous conception (SC) controls; medical records reviewed & exam at age 5	**Age:** Mean (SD): 5.2 cases, 5.4 controls Range: 4.0-6.3 cases, 4.3-6.1 controls **Race/ethnicity (n [%]):** 100% Caucasian from 2 European sites; 4/102 cases and 7/55 controls from NY were "non-Caucasian" **Diagnoses (n [%]):** NR **Inclusion criteria:** Singletons born after ICSI (cases) or SC (controls). Cases consecutively recruited at age 5, controls matched for sex, age, maternal age. **Exclusion criteria:** Multiple birth, birth < 32 wk, maternal or child language different from national language. No donor sperm used.	**Definition(s) of outcome(s):** Chronic illness = disorder of ≥ 3 mos duration during the last yr that interfered with daily functioning and/or required treatment Neuro exam included tone, CN status, DTRs, walking, running, jumping Malformations classified by ICD; major malformation caused functional impairment and/or required surgical correction Main endpoint was growth (stature)	1) Stature (height in cm, median [range]): ICSI 112.4 (97.0-128.9) SC 112.0 (98.0-126.0) 2) Major malformations: Major malform + / Major malform - / Total ICSI: **20** / **280** / 300 SC: **8** / **258** / 266 Total: 28 / 538 / 566 Value / Lower 95% CI / Upper 95% CI Odds rat: 2.30 / 1.00 / 5.32 3) Chronic illness: Chronic illness + / Chronic illness - / Total ICSI: **24** / **276** / 300 SC: **18** / **248** / 266 Total: 42 / 524 / 566 Value / Lower 95% CI / Upper 95% CI Odds rat: 1.20 / 0.64 / 2.26 4) LBW (< 2500 g):	**Comments:** None **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: +/ - (SC population younger [mat & pat], less likely primiparous) Verification that the control is free of cancer: NA Comparability of cases and controls with respect to potential confounders: +/- (see above) Validated dietary assessment method: NA Appropriateness of statistical analyses: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

	LBW +	LBW -	Total
ICSI	**32**	**268**	300
SC	**10**	**256**	266
Total	42	524	566

	Value	Lower 95% CI	Upper 95% CI
Odds rat	3.06	1.47	6.35

5) Cesarean delivery (C/S):

	C/S +	C/S -	Total
ICSI	**74**	**226**	300
SC	**38**	**228**	266
Total	112	454	566

	Value	Lower 95% CI	Upper 95% CI
Odds rat	1.96	1.28	3.03

Bonduelle, Liebaers, Deketelaere, et al., 2002

#2650

Geographical location: Brussels, Belgium

Study dates: ICSI Jun 1991-Dec 1999; IVF Jan 1983-Dec 1999

Size of population: ICSI 3073 pregnancies, 2889 births; IVF 3,329 pregnancies, 2995 births

Study type: Cohort

No correction for multiple comparisons because aiming to investigate safety of ICSI

Mat Age: Mean (SD): ICSI sing: 32.7 (4.3); ICSI multi: 32.8 (4.3); IVF sing: 32.4 (4.2); IVF multi: 31.7 (3.7)

Race/ethnicity (n [%]): NR

Diagnoses (n [%]): NR

Inclusion criteria: All pregnancies obtained by IVF or ICSI in single center

Exclusion criteria: ICSI: 2.4% lost for f/u; IVF 2.6% lost

Definition(s) of outcome(s):

Perinatal outcomes obtained from ob/gyn in charge; if any problem, detailed info obtained from peds.

Babies born at "our hosp" had detailed exam and routine US of brain kidneys, and heart. For those born elsewhere, exam by geneticist done after 2 mo when possible.

2 mo f/u with parents to verify neonatal data, and collect info on illness & development. When possible, exam. 12mo & 2 y f/u as well.

No difference in LBW, VLBW between singletons by IVF/ICSI. No diff in total perinatal death rates, major malformations in EABs and IUFDs.

The following 2 use livebirths as denominator.

1) VLBW multiples:

	VLBW +	VLBW -	Total
ICSI	**103**	**1238**	1341
IVF	**139**	**1260**	1399
Total	242	2498	2740

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.77	0.61	0.99

2) Prematurity < 37wks multiples (holds for total, but similar rates in singletons):

	Prem +	Prem -	Total
ICSI	**776**	**565**	1341

Comments:
- IVF group collected starting earlier; may bias outcomes in favor of ICSI because of advances since then
- Complete data given comparing rates of biochemical, ectopic pregnancies, SAB, EAB, IUFD, multiples - similar rates in both groups.
- More nullips & smokers in ICSI group
- Routine testing led to higher detection rates for malformations in IVF pts – difference disappeared when these patients excluded

Quality assessment:
Unbiased selection of the cohort (prospective recruitment of subjects): +
Large sample size: +
Adequate description of the cohort: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
			Major malformation = causes functional impairment or requires surgical correction. Minor malformation distinguished from normal if occurs in ≤ 4% of infants of same ethnic group	IVF **727** **672** 1399 Total 1503 1237 2740 Value / Lower 95% CI / Upper 95% CI Rel risk 1.11 1.04 1.19 3) Major malformations: Major malf + / Major malf - / Total ICSI **96** **2744** 2840 IVF **112** **2843** 2955 Total 208 5587 5795 Value / Lower 95% CI / Upper 95% CI Rel risk 0.89 0.68 1.17 No difference when separately analyzing or adding in EABs, IUFDs. No difference by method of sperm collection. No difference by sperm morphology. Higher rates of major malformation with sperm motility < 50%, but raw data not shown (3.77% vs 1.86% for motility ≥ 50%).	Use of validated method for genomic test: NR Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -
Bonduelle, Wennerholm, Loft, et al., 2005 **#9680**	**Geographical location:** Brussels, Belgium; Göteborg, Sweden; Copenhagen, Denmark; Thessaloniki, Greece; and London, UK **Study dates:** Nov 2000 – Nov 2002 **Size of population:** 1515 total 540 ICSI 437 IVF 538 NC (natural conception)	**Age:** Mean (SD): ICSI: 5.0 (0.3) IVF: 5.1 (0.3) NC: 5.1 (0.3) **Race/ethnicity (n [%]):** Caucasian 100 **Diagnoses (n [%]):** NR **Inclusion criteria:** - Age 4.5-5.5 yr - Singleton - Caucasian - Born ≥ 32 wk gestation - 1st or 2nd born	**Definition(s) of outcome(s):** Illnesses & anomalies classified according to ICD Malformations classified into major & minor by geneticist blinded to mode of conception Major malformation = causes functional impairment or requires surgical correction	ANOVA was used by investigators to compare 3 grps, but results here presented with NC grp as referent grp 1) Weight & height were similar among grps. 2) Any surgery (ICSI vs. NC controls): Any surg + / Any surg - / Total ICSI **128** **412** 540 NC **73** **465** 538 Total 201 877 1078 Value / Lower 95% CI / Upper 95% CI Odds rat 1.98 1.44 2.72	**Comments:** ICSI, IVF cases recruited from fertility clinics; unclear exactly how, and unclear whether some may have refused participation (perhaps those with more problems were more likely to enroll) **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + (although see above) Appropriateness of the control population: + Verification that the control is free of cancer: NA Comparability of cases and controls

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Study type: 5-yr-old children conceived by ICSI, IVF, or NC were examined by pediatricians, & history taken from parents. NC controls matched for age, sex, maternal education, parental SES.	- Mother tongue English, Dutch, Danish, Swedish, or Greek **Exclusion criteria:** NR		3) Any surgery (IVF vs. NC controls): Any surg + / Any surg - / Total IVF: **95** / **342** / 437 NC: **73** / **465** / 538 Total: 168 / 807 / 975 Value / Lower 95% CI / Upper 95% CI Odds rat: 1.77 / 1.27 / 2.47 4) Major malformations (ICSI vs. NC controls): Major malform + / Major malform - / Total ICSI: **33** / **507** / 540 NC: **12** / **526** / 538 Total: 45 / 1033 / 1078 Value / Lower 95% CI / Upper 95% CI Odds rat: 2.85 / 1.46 / 5.59 5) Major malformations (IVF vs. NC controls): Major malform + / Major malform - / Total ICSI: **18** / **419** / 437 NC: **12** / **526** / 538 Total: 30 / 945 / 975 Value / Lower 95% CI / Upper 95% CI Odds rat: 1.88 / 0.90 / 3.95 6) Cesarean delivery (C/S – ICSI vs. NC controls): C/S + / C/S - / Total ICSI: **155** / **385** / 540 NC: **95** / **443** / 538	with respect to potential confounders: - (NC group mat & pat age younger, less likely married, less likely to have any maternal chronic illness) Validated dietary assessment method: NA Appropriateness of statistical analyses: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Total 250 828 1078 Value / Lower 95% CI / Upper 95% CI Odds rat 1.88 1.41 2.51 7) Cesarean delivery (IVF vs. NC controls): C/S + / C/S - / Total IVF **119** **318** 437 NC **95** **443** 538 Total 214 761 975 Value / Lower 95% CI / Upper 95% CI Odds rat 1.75 1.29 2.37	
Brinton, Kruger Kjaer, Thomsen, et al., 2004 **#13420**	**Geographical location:** Copenhagen, Denmark **Study dates:** NR; mothers diagnosed with infertility 1960 - 1996 **Size of population:** 54,379 women identified with diagnosis of infertility 1960 - 1996 51,063 children born to 30,364 women from that cohort: - 16,786 born before mother entered cohort (i.e., before diagnosis of infertility) - 34,277 born after entry into cohort Total of 105 children diagnosed with cancer: - 54 born before entry into cohort.	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Women with diagnosis of infertility and the children born to those women **Exclusion criteria:** Stillbirths, foreign adoptions, Danish adoptions, births with uncertain nationality	**Definition(s) of outcome(s):** Expected number of tumors = person-yrs of observations * age-, sex-, and calendar-specific incidence rates for tumor occurrence SIR = standardized incidence ratio = ratio of observed/expected number of tumors	1) CA risk of cases was found to be comparable to that of the general population in Denmark: Observed: 51 Expected: 44.7 SIR = 1.14 (95% CI 0.8 to 1.5) 2) "Case-cohort" portion – childhood tumors by maternal exposure to ovulation-stimulating drugs: CA / Controls / Total Ovul stim + **15** **334** 349 Ovul stim - **30** **524** 554 Total 45 858 903 Value / Lower 95% CI / Upper 95% CI Odds rat 0.78 0.42 1.48 No difference if broken down by clomid, hMG, or number of cycles of each. Some had unknown ovulation-stimulation, clomid, hMG status	**Comments:** - Little bias – few records could not be obtained - National database **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: + Verification that the control is free of cancer: NA Comparability of cases and controls with respect to potential confounders: - (not assessed) Validated dietary assessment method: NA Appropriateness of statistical analyses: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	- 51 born after **Study type:** Study compared rate of CA in above-described cohort of children to rate in the general population Also compared those with CA to children of "random subcohort" of 868 children (case-cohort)				
Brinton, Lamb, Moghissi, et al., 2004 **#13110**	**Geographical location:** Boston, MA; New York, NY; Chicago, IL; Detroit, MI; San Francisco, CA **Study dates:** Patients seen between 1965-1988 **Size of population (no. of patients):** 8429 analyzed (original pool 12,193) **Study type:** Cohort	**Age:** Age at evaluation < 30: 47.5% ≥ 30: 52.5% **Race/ethnicity (n [%]):** White: 6658 (79.0%) African-American: 393 (4.6%) Other: 471 (5.6%) Unknown: 908 (10.8%) **Diagnoses (n [%]):** Unexplained infertility: Endometriosis: 1893 (22.5%) Male factor: 1942 (23.0%) Tubal factor: 2954 (35.0%) PCOS: 2304 (27.3%) Uterine/cervical: 1516 (18.0%) Categories not mutually exclusive **Inclusion criteria:** -evaluated for infertility at 1 of the participating clinics between 1965 and 1988, -had a U.S. address at the	**Definition(s) of outcome(s):** Cancer cases ascertained by questionnaire, medical records, and cancer registries; confirmed if possible by medical records/registry/death certificate	1) Standardized Incidence Ratios: SIR 95% CI All subjects 1.98 1.4, 2.6 Ever exposed: Clomiphene No 2.09 1.4,3.0 Yes 1.79 1.0,3.0 Gonadotropins No 1.95 1.4,2.7 Yes 2.26 0.7,5.3 2) Adjusted within-group risks non-significantly higher in women with > 12 cycles clomiphene (OR 1.54, 95% CI 0.5, 5.1) or >9 cycles gonadotropins (OR 1.21, 95% CI 0.4, 3.9); or more than 15 years since exposure (clomiphene OR 1.48, 95% CI 0.7, 3.2; gonadotropin OR 2.46, 95% CI 0.7, 8.3). Risk also increased in women who were still nulliparous at follow-up (OR 1.75, 95% CI 0.5, 5.7). No other adjusted ORs above 1.2.	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		time of evaluation, -were seen more than once or had been referred by another physician who provided relevant medical information. **Exclusion criteria:** Evaluated for reversal of tubal ligation			
Brinton, Lamb, Moghissi, et al., 2004 **#12620**	**Geographical location:** Boston, MA; New York, NY; Chicago, IL; Detroit, MI; San Francisco, CA **Study dates:** Patients seen between 1965-1988 **Size of population (no. of patients):** 8429 analyzed (original pool 12,193) **Study type:** Cohort	**Age:** Age at evaluation < 30: 47.5% ≥ 30: 52.5% **Race/ethnicity (n [%]):** White: 6658 (79.0%) African-American: 393 (4.6%) Other: 471 (5.6%) Unknown: 908 (10.8%) **Diagnoses (n [%]):** Unexplained infertility: Endometriosis: 1893 (22.5%) Male factor: 1942 (23.0%) Tubal factor: 2954 (35.0%) PCOS: 2304 (27.3%) Uterine/cervical: 1516 (18.0%) Categories not mutually exclusive **Inclusion criteria:** - evaluated for infertility at 1 of the participating clinics between 1965 and 1988, - had a U.S. address at the time of evaluation,	**Definition(s) of outcome(s):** Cancer cases ascertained by questionnaire, medical records, and cancer registries; confirmed if possible by medical records/registry/death certificate	1) Standardized Incidence Ratios: SIR 95% CI Type of infertility Primary 2.73 1.8,4.0 Secondary 1.44 0.9,2.2 Cause of infertility Endometriosis 2.48 1.3,4.2 Anovulation 1.94 1.0,3.4 Tubal disease/adhesions 2.04 1.2,3.3 Male factor 1.88 0.9,3.5 Cervical factor 1.32 0.2,4.8 Uterine factor 2.2 0.8,4.8 2) Within-group adjusted rate ratio higher for women with primary infertility. Highest risk seen with endometriosis (RR 2.72, 95% CI 1.1, 6.7)	**Comments:** May be variability in accuracy of exposure categorization (e.g., laparoscopic dx of endometriosis), but unlikely to be any bias in ascertainment between cases and non-cases **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		- were seen more than once or had been referred by another physician who provided relevant medical information. **Exclusion criteria:** Evaluated for reversal of tubal ligation			
Brinton, Scoccia, Moghissi, et al., 2004 **#11150**	**Geographical location:** Boston, MA; New York, NY; Chicago, IL; Detroit, MI; San Francisco, CA **Study dates:** Patients seen between 1965-1988 **Size of population (no. of patients):** 8431 included in followup analysis (original pool 12,193) **Study type:** Cohort (retrospective)	**Age:** Age at evaluation < 30: 47.5% ≥ 30: 52.5% **Race/ethnicity (n [%]):** White: 6658 (79.0%) African-American: 393 (4.6%) Other: 471 (5.6%) Unknown: 908 (10.8%) **Diagnoses (n [%]):** *Without/with CA (8139/292):* Endometriosis: 1864/57 Male factor: 1875/78 Tubal factor: 2897/102 PCOS: 2238/85 Categories not mutually exclusive **Inclusion criteria:** - Evaluated for infertility at participating clinic between 1965 and 1988 - U.S. address at the time of evaluation - Seen more than once or referred by physician who provided relevant medical information - Primary or secondary infertility	**Definition(s) of outcome(s):** Cancer cases ascertained by questionnaire, medical records, and cancer registries; confirmed if possible by medical records/registry/death certificate Standardized incidence ratios (SIRs) comparing breast cancer within infertility cohort with rates for U.S. women; observed/expected events based on age-, race-, and calendar-yr-specific incidence disease rates for females from CA registry rates through SEER. Standardized mortality ratios (SMRs) also calculated.	1) Standardized Incidence Ratios – breast cancer: SIR 95% CI All subjects 1.29 1.1, 1.4 Ever exposed: Clomiphene No 1.28 1.1,1.5 Yes 1.29 1.1,1.6 Gonadotropins No 1.28 1.1,1.4 Yes 1.40 0.9,2.0 SMR 1.58 (95% CI 1.1 to 2.2), with no higher risk for those who took clomid vs. not. Higher risk of breast CA associated with later ages at first birth, nulliparity, prior history of breast CA. No variation in risk across causes of infertility. 2) Adjusted within-group risks (adjusted for age at follow-up, calendar year, site, and family history): clomiphene 1.02 (0.8, 1.3); gonadotropins 1.07 (0.7, 1.6). Risk estimates higher 20 years after exposure (clomiphene 1.39 (0.9,2.1), gonadotropins 1.54 (0.8, 3.2)	**Comments:** - Retrospective – relied on review of medical records, unable to locate 20% of study pop, 11% refused permission to access records, 41% of those alive did not complete questionnaire - Incomplete infertility workups – but adjustment for cause of infertility did not change risks **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: - Analysis (multivariate adjustments) and reporting of results: +:

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		Exclusion criteria: - Evaluated for reversal of tubal ligation - Refused access to medical records			
Bruinsma, Venn, Lancaster, et al., 2000 **#8560**	**Geographical location:** Victoria, Australia **Study dates:** 1979-95 **Size of population:** 5249 births from 4,357 pregnancies **Study type:** Cohort Births conceived by ART linked to Victorian Cancer Registry	**Age at end of f/u:** Mean (SD): NR Median: 3yr, 9mos Range: 0-15yr **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Conceptions using ART at 2 clinics resulting in livebirth **Exclusion criteria:** Stillbirths, parents residing overseas or interstate	**Definition(s) of outcome(s):** Expected # cases = Victorian age-specific population-based cancer incidence 1982 - 1995 applied to person-yrs f/u in each age grp. Standardized incidence ratio (SIR) = observed:expected cases.	1) Expected vs observed cases of CA: CA+ / CA- / Total Observed: **6** / **5243** / 5249 Expected: **4.33** / **5244.67** / 5249 10487.6 Total: 10.33 / 7 / 10498 Value / Lower 95% CI / Upper 95% CI Odds rat: 1.39 / 0.40 / 4.77	**Comments:** - Reporting to this registry is mandated by law since 1981 – tiny # of births in series before then. - Not clear whether these 2 clinics are the only ones performing ART in this area – if not, may have missed some cases and understated risk. **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: + Verification that the control is free of cancer: NR Comparability of cases and controls with respect to potential confounders: - Validated dietary assessment method: NR Appropriateness of statistical analyses: +
Buckett, Chian, Holzer, et al., 2007 **#70550**	**Geographical location:** Montreal, Canada **Study dates:** Jan 1998-Dec 2003	**Age:** Mean (SD): 33 **Race/ethnicity (n [%]):** NR	**Definition(s) of outcome(s):** Major and minor anomalies	1) All malformations, in vitro maturation vs. spontaneous: Mal + / Mal - / Total IVM: **5** / **50** / 55	**Comments:** More multiples in ART pregnancies **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Size of population (no. of patients): 782 infants, 688 mothers **Study type:** Cohort All in vitro maturation (n = 55), in vitro fertilization (n = 217), ICSI (n = 16) pregnancies and age- and parity matched controls (n = 344)	**Diagnoses (n [%]):** NR **Inclusion criteria:** All pregnancies delivered at the McGill University Health Centre after assisted reproductive treatments (namely, IVM, IVF, or ICSI) with a birth weight of at least 500 g **Exclusion criteria:** NR		Spont **25** **325** 350 Total 30 375 405 Value / Lower 95% CI / Upper 95% CI Rel risk 1.27 / 0.51 / 3.18 2) All malformations, IVF vs. spontaneous: Mal + / Mal - / Total IVF **17** **200** 217 Spont **25** **325** 350 Total 42 525 567 Value / Lower 95% CI / Upper 95% CI Rel risk 1.10 / 0.61 / 1.98 3) All malformations, ICSI vs. spontaneous: Mal + / Mal - / Total ICSI **17** **143** 160 Spont **25** **325** 350 Total 42 468 510 Value / Lower 95% CI / Upper 95% CI Rel risk 1.49 / 0.83 / 2.68 4) All malformations, any ART vs. spontaneous: Mal + / Mal - / Total Any ART **39** **393** 432 Spont **25** **325** 350 Total 64 718 782 Value / Lower 95% CI / Upper 95% CI Rel risk 1.26 / 0.78 / 2.05	subjects): + Large sample size: - Adequate description of the cohort: + Use of validated method for ascertaining exposure: - Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -
Burkman, Tang,	**Geographical location:** Atlanta, Detroit, Los	**Age:** Cases, controls matched	**Definition(s) of outcome(s):**	1) Overall OR for fertility drug use, ever vs never, controlled for age, race, study site: 0.9	**Comments:** - Case control

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Malone, et al., 2003 **#16690**	Angeles, Philadelphia, and Seattle. **Study dates:** Jul 1994-Apr 1998 **Size of population (no. of patients):** Cases: 4575 (516 sought care for infertility) Controls: 4682 (617 sought care for infertility) **Study type:** Case-control	for age **Race/ethnicity (n [%]):** White: 65%, African-American: 35% (matched for race) **Diagnoses (n [%]):** NR **Inclusion criteria:** Cases: age 35 to 64 years; presence of histologically confirmed, primary invasive breast cancer with no prior invasive or in situ breast cancer history; US birth with residence at date of diagnosis in a study region; white or black race (including Hispanic ethnicity); a working telephone at the individual's residence at date of diagnosis; ability to be interviewed in English; and physical and mental capability to undergo the interview process Controls—same except for case-defining event **Exclusion criteria:** NR	Invasive breast cancer, confirmed by medical records	(0.8, 1.2) Restricted to diagnosis of infertility: 1.2 (0.8, 1.7) Risk increased in women treated with hMG ≥ 6 months/cycles (ORs for all subgroups >2.0, 95% CIs do not include 1.0)	- Exposure by self-report—potential for recall bias - Multiple comparisons **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: + Comparability of cases and controls with respect to potential confounders: + Appropriateness of statistical analyses: +
Cahill, Meadow-croft, Akande, et al., 2005	**Geographical location:** Bristol, UK **Study dates:** Jan 1987 - April 1991	**Age:** Mean (SD): 34.5 (5.4) Median: 34 respondents, 35 nonrespondents Range: 24-44	**Definition(s) of outcome(s):** Pregnancy following last contact with infertility center	19% of respondents conceived in 3 yrs. 1) Spont preg by age: > 38: Preg+ **1**, Preg- **24**, Total 25	**Comment:** - Response rate 44%. - No diff btw respondents & nonrespondents in age, duration of infertility, nulliparity, success from IVF at Centre

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#38890	**Size of population:** 154 couples **Study type:** Cohort ≥ 3 yr after last contact with Centre, questionnaire mailed. Nonresponders got 2nd questionnaire & phone call	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Couples who had treatment at study center **Exclusion criteria:** Stated desire for no further contact, non-UK address, known divorce or death of either partner, ongoing or previous legal proceedings between couple and Centre, current pts, h/o bilat tubal occlusion or azoospermia. After questionnaire, excluded 34/154 couples who had received tx elsewhere, and 4 with incomplete records		≤ 38: **27** / **64** / 91 Total: 28 / 88 / 116 Odds rat: Value 0.10, Lower 95% CI 0.01, Upper 95% CI 0.77 2) Spont preg by duration of infertility before IVF (y): ≥ 3: **18** / **73** / 91 < 3: **10** / **10** / 20 Total: 28 / 83 / 111 Odds rat: Value 0.25, Lower 95% CI 0.09, Upper 95% CI 0.68 3) Spont preg by primary vs secondary infertility: Prim: **17** / **52** / 69 Sec: **11** / **31** / 42 Total: 28 / 83 / 111 Odds rat: Value 0.92, Lower 95% CI 0.38, Upper 95% CI 2.22 4) Spont preg by unexplained infert vs all other: Unexp: **8** / **15** / 23 Other: **20** / **73** / 93 Total: 28 / 88 / 116 Odds rat: Value 1.95, Lower 95% CI 0.72, Upper 95% CI 5.24 5) Spont preg by tubal infert vs all other:	**Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: + Use of validated method for genomic test: NR Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: - Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Preg+ Preg- Total Tubal **2** **30** 32 Other **26** **58** 84 Total 28 88 116 Value Lower 95% CI Upper 95% CI Odds rat 0.15 0.03 0.67	
Cai, Izumi, Koido, et al., 2006 **#50830**	**Geographical location:** Japan **Study dates:** 1994-2003 **Size of population (no. of patients):** Twins N = 199 Spontaneous n = 97 Ovulation induction n = 28 IUI n = 24 IVF n = 50 **Study type:** Cohort	**Age:** Spontaneous 29.4 (4.6) Ovulation indx 30.8 (3.8) IUI 32.1 (2.4) IVF 33.5 (3.9) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Twins ≥ 25 wks **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Preterm birth ≤ 36 wks Intrauterine growth retardation <10th%ile for Japanese standards Birthweight discordance ≥ 25% difference Low birthweight < 2500 g	Grouped all ART for relative risk calculations here but results are provided for individual Art modalities, although small n for each subgroup 1) Preterm birth any ART v. spontaneous: ptb+ ptb- Total any ART **47** **55** 102 spontaneous **55** **42** 97 Total 102 97 199 Value Lower 95% CI Upper 95% CI Rel risk 0.81 0.62 1.07 2) IUGR any Art v. spontaneous: iugr+ iugr- Total any ART **26** **76** 102 spontaneous **14** **83** 97 Total 40 159 199 Value Lower 95% CI Upper 95% CI Rel risk 1.77 0.98 3.18	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: - Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
Cheang, Huang, Lee, et al., 2007	**Geographical location:** Macau, Sanchung, and Taipei, Taiwan	**Age:** NR **Race/ethnicity (n [%]):** NR	**Definition(s) of outcome(s):** Birth weight	1) Delivery prior to 28 weeks, twins reduced from higher order multiples vs. non reduced twins:	**Comments:** No adjustment for maternal age **Quality assessment:**

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#70640	**Study dates:** Jan 1998-Dec 2004 **Size of population (no. of patients):** 782 **Study type:** Cohort Comparison of twins resulting from ART to twins resulting from reduction from higher order multiples after ART	**Diagnoses (n [%]):** NR **Inclusion criteria:** Multiple pregnancy after ART during time period **Exclusion criteria:** NR	Preterm labor/delivery	< 28 weeks / > 28 weeks / Total Reduced: **16** / **337** / 353 Non-reduced: **7** / **382** / 389 Total: 23 / 719 / 742 Value / Lower 95% CI / Upper 95% CI Rel risk: 2.52 / 1.05 / 6.05 2) Delivery prior to 36 weeks: < 36 weeks / > 26 weeks / Total Reduced: **143** / **210** / 353 Non-reduced: **127** / **262** / 389 Total: 270 / 472 / 742 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.24 / 1.03 / 1.50 3) Risk increased with increasing number of fetus pre-reduction; risk of discordancy also significantly increased. No difference in perinatal morbidity/mortality	Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: - Adequate description of the cohort: - Use of validated method for ascertaining exposure: + Use of validated method for +ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -
Check, Choe, Katsoff, et al., 2005 **#41000**	**Geographical location:** Camden, NJ **Study dates:** Jan 1997-Nov 2003	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR	**Definition(s) of outcome(s):** NR	1) Ectopic pregnancy by fresh vs. frozen embryo transfer: Ect+ / Ect- / Total Frozen: **20** / **955** / 975 Fresh: **38** / **1407** / 1445	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Size of population: 1445 clinical pregnancies from fresh ET, 975 from frozen ET **Study type:** Cohort (retrospective)	**Inclusion criteria:** - All IVF pregnancies in women up to age 49, including donor oocytes - Transfers used 3d old embryos **Exclusion criteria:** Pregnancies resulting from blastocyst transfers		Total 58 2362 2420 Value / Lower 95% CI / Upper 95% CI Rel risk 0.78 0.46 1.33	subjects): - Large sample size: + Adequate description of the cohort: - Use of validated method for genomic test: NR Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -
Child, Henderson, and Tan, 2004 **#13790**	**Geographical location:** Montreal, Canada **Study dates:** 2000 **Size of population:** 801 infertility pts (460 women, 341 men) Response rate 55% & 46%, respectively **Study type:** Prospective questionnaire	**Age:** Mean (SD): Women: 35.5 (5.1) Men: 38.0 (6.4) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Male & female pts attending tertiary fertility clinic **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Asked whether pts considered that babies of multiple pregnancy are at increased risk compared with singletons Asked to state desired number of babies with next fertility treatment	1) Questionnaire results: Multiple logistic regression used to identify independent variables associated with desire for multiple pregnancy; another with recognition of increased risks of multiple pregnancy as dependent variable. 41% of all pts considered multiple pregnancy an ideal outcome. 38.9% women, 36.4% men reported twins would be ideal (2%, 0.9% for triplets; 0.7%, 1.5% for quads). Increasing duration of infertility or history of ART associated with increase, and previous children or recognition of risks with decrease in desire for multiple pregnancy. History of ART was only variable associated with recognition of increased risk in multiple pregnancy.	**Comment:** - Questionnaire completed alone, w/o consulting partner - 50% response rate **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): Large sample size: Adequate description of the cohort: Use of validated method for genomic test: Use of validated method for ascertaining clinical outcomes: Adequate follow-up period: Completeness of follow-up: Analysis (multivariate adjustments) and reporting of results:
Choi, Kim, and Roh, 2006 **#51090**	**Geographical location:** Seoul, S. Korea **Study dates:** 1994-2003 **Size of population (no. of patients):**	**Age:** Dichorionic Spontaneous 30.5 (3.9) IVF 32.9 (4.2) Monochorionic Spontaneous 30.0 (4.2)	**Definition(s) of outcome(s):** Preterm birth < 34wks Low birthweight < 2.5kg	1) Preterm birth, dichorionic twins: PTB+ / PTB- / Total IVF: **49** / **107** / 156 spontaneous: **45** / **148** / 193	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	TWINS Spontaneous 392 ART 206 **Study type:** Cohort	IVF 31.8 (2.8) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** NR **Exclusion criteria:** NR	NICU admission Respiratory distress syndrome	Total 94 255 349 Value / Lower 95% CI / Upper 95% CI Rel risk 1.35 0.95 1.90 2) Preterm birth, monochorionic twins: PTB+ / PTB- / Total IVF: **10** / **24** / 34 spontaneous: **37** / **117** / 154 Total 47 141 188 Value / Lower 95% CI / Upper 95% CI Rel risk 1.22 0.68 2.21 3) Low birthweight, dichorionic: lbwt+ / lbwt- / Total IVF: **235** / **77** / 312 spontaneous: **268** / **118** / 386 Total 503 195 698 Value / Lower 95% CI / Upper 95% CI Rel risk 1.08 0.99 1.19 4) Low birthweight, monochorionic: lbwt+ / lbwt- / Total IVF: **38** / **30** / 68 spontaneous: **212** / **96** / 308 Total 250 126 376 Value / Lower 95% CI / Upper 95% CI Rel risk 0.81 0.65 1.02 5) NICU admission, dichorionic: NICU+ / NICU- / Total	Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

IVF	**164**	**148**	312
spontaneous	**165**	**221**	386
Total	329	369	698

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.23	1.05	1.44

6) NICU admission, monochorionic:

	NICU+	NICU-	Total
IVF	**24**	**44**	68
spontaneous	**136**	**172**	308
Total	160	216	376

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.80	0.57	1.13

7) RDS, dichorionic:

	RDS+	RDS-	Total
IVF	**27**	**285**	312
spontaneous	**36**	**350**	386
Total	63	635	698

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.93	0.58	1.49

8) RDS, monochorionic:

	RDS+	RDS-	Total
IVF	**4**	**64**	68
spontaneous	**31**	**277**	308
Total	35	341	376

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.58	0.21	1.60

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Chow, Benson, Racowsky, et al., 2001 **#4760**	**Geographical location:** Boston, MA **Study dates:** May 1998-April 2000 **Size of population (no. of patients):** 464 **Study type:** Cohort	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - 1st trimester ultrasound - Multiple gestations - Mode of conception known **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Chorionicity of multiple gestation	1) Relative risk of monochorionic pair, spontaneous vs ART pregnancy: Out + / Out - / Total Spont: **31** / **79** / 110 ART: **19** / **335** / 354 Total: 50 / 414 / 464 Value (Lower 95% CI – Upper 95% CI) Rel risk: 5.25 (3.09 – 8.92)	**Comments:** Tertiary center—possibility of referral bias **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: - Adequate description of the cohort: - Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
Chung, Coutifaris, Chalian, et al., 2006 **#51140**	**Geographical location:** 2 sites in Pennsylvania, U.S. **Study dates:** 1999-2004 **Size of population (no. of patients):** 159 cases 276 controls **Study type:** Case-control	**Age:** Mean (SD): Cases: 33.25 (3.52) Controls: 33.41 (3.73) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - IVF-ET pregnancies reaching 10-12 wks gestation - Cases = preterm delivery < 37 weeks of gestation, LBW < 2500 g, or stillbirth after 1st trimester - Controls = normal weight, full-term live births **Exclusion criteria:**	**Definition(s) of outcome(s):** See definition of cases and controls	1) Association of OHSS with adverse outcome: Cases / Controls / Total OHSS +: **45** / **23** / 68 OHSS -: **114** / **253** / 367 Total: 159 / 276 / 435 Value (Lower 95% CI – Upper 95% CI) Odds rat: 4.34 (2.51 – 7.52) 2) Multiple gestation associated with adverse outcome: Cases / Controls / Total Twins/ triplets: **113** / **49** / 162 Single-tons: **46** / **227** / 273 Total: 159 / 276 / 435	**Comments:** None **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: + Comparability of cases and controls with respect to potential confounders: + Appropriateness of statistical analyses: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		- Spontaneous abortions - Ectopic pregnancies - Gestations with > 3 fetuses - Pregnancies resulting from other methods of ART		Value / Lower 95% CI / Upper 95% CI Odds rat 11.38 7.17 18.05	
Clayton, Schieve, Peterson, et al., 2006 **#60320**	**Geographical location:** U.S. – national registry **Study dates:** Jan 1999-Dec 2001 **Size of population (no. of patients):** 94,118 Demographics presented for fresh, non-donor cycles (n = 69,366) **Study type:** Cohort	**Age:** 55.0% < 35 years **Race/ethnicity (n [%]):** White: 53.6% African-American: 2.6% Asian: 2.9% Hispanic:3.7% Other: 0.1% Missing: 37.2% **Diagnoses (n [%]):** Unexplained infertility: 11.1% Endometriosis: 8.4% Male factor: 21.5% Tubal factor: 17.0% Ovulatory disorders: 6.3% Combined: 27.7% **Inclusion criteria:** Pregnancy reported to ART Registry within time period **Exclusion criteria:** Investigators excluded a small number of pregnancies that resulted from less common treatment options (< 1%). These uncommon options included: - Procedures in which any combination of IVF-ET, gamete intrafallopian transfer (GIFT), or zygote	**Definition(s) of outcome(s):** Intrauterine pregnancy: documentation of one or more gestational sacs in uterine cavity Ectopic pregnancy: documentation of one or more sacs outside the uterine cavity Heterotopic pregnancy: Criteria for both intrauterine and ectopic pregnancy met	1) Overall ectopic rate 2.1%; heterotopic rate 0.15% 2) In multivariate analysis, risk of ectopic significantly increased with: OR / Lower 95% CI / Upper 95% CI Tubal factor 2.01 1.68 2.41 Endometriosis 1.30 1.04 1.62 Non-tubal female factor 1.38 1.16 1.63 and significantly decreased with history of prior birth (OR 0.62, 95% CI 0.54, 0.72).	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		intrafallopian transfer (ZIFT) were used for transfer (n = 176) - Procedures in which both frozen-thawed and freshly fertilized embryos were transferred (n = 120) - Procedures in which embryos from both donor and patient oocytes were transferred (n = 109) - GIFT and ZIFT procedures that involved either donor oocytes or frozen-thawed embryos (n = 170) - Pregnancies for which the improbable transfer of 15 or more embryos was reported (n = 7)			
Clayton, Schieve, Peterson, et al., 2007 **#51210**	**Geographical location:** United States **Study dates:** 1999-2002 **Size of population (no. of patients):** 207 heterotopic 132,660 intrauterine-only **Study type:** Cohort	**Age:** IUP vs. heterotopic, N (%) < 30: 17,791 (13.4) vs. 30 (14.5) 30-34: 47,004 (35.4) vs. 84 (40.6) 35-37: 28,869 (21.8) vs. 45 (21.7) 38-40: 21,212 (16) vs. 31 (15.0) 41-43: 10,849 (8.2) vs. 11 (5.3) < 44: 6,935 (5.2) vs. 6 (2.9) **Race/ethnicity (n [%]):** IUP v. heterotopic, N (%) Black 3,013 (2.3) v. 9 (4.4) Hispanic 4,291 (3.2) v. 5 (2.4) Asian 3,698 (2.8) v. 6 (2.9) Other 109 (0.1) v. 0 Unknown 56,108 (42.3) v. 79 (38.2)	**Definition(s) of outcome(s):** Spontaneous abortion Preterm birth < 37 wk Low birthweight< 2500 gm	1) Sab by heterotopic vs. IUP-only: SAb+ / SAb- / Total Hetero-topic: **64** / **140** / 204 IUP: **20147** / **111297** / 131444 Total: 20211 / 111437 / 131648 Value: 2.05 (Lower 95% CI: 1.67; Upper 95% CI: 2.51) 2) Livebirth by heterotopic vs. IUP-only: Livebirth + / Livebirth - / Total Hetero-topic: **119** / **85** / 204 IUP: **109343** / **22101** / 131444 Total: 109462 / 22186 / 131648 Value / Lower 95% CI / Upper 95% CI	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		Diagnoses (n [%]): Tubal factor: 27,320 (20.6) v. 69 (33.3) Tubal Ligation: 3,339 (2.5) v. 6 (2.9) Endometriosis: 12,620 (9.5) v. 19 (9.2) Nontubal female factors: 64,344 (48.5) v. 95 (45.9) Male factor: 25,037 (18.9) v. 18 (8.7) **Inclusion criteria:** Reported to SART **Exclusion criteria:** NR		Rel risk 0.70 0.62 0.79 3) Low birthweight by heterotopic vs. IUP-only among singleton livebirths only: Lbwt + / Lbwt - / Total Hetero-topic: **10** / **88** / 98 IUP: **6400** / **64300** / 70700 Total: 6410 / 64388 / 70798 Value / Lower 95% CI / Upper 95% CI Rel risk 1.13 0.63 2.03 4) Preterm birth by heterotopic vs. IUP-only among singleton livebirths only: Preterm + / Preterm - / Total Hetero-topic: **19** / **79** / 98 IUP: **9834** / **60866** / 70700 Total: 9853 / 60945 / 70798 Value / Lower 95% CI / Upper 95% CI Rel risk 1.39 0.93 2.09 Results for twins presented but cannot exactly reconcile # livebirths and outcomes based on # pregnancies vs. #neonates.	
Cusido, Fabregas, Pere, et al., 2007 **#70740**	**Geographical location:** Barcelona, Spain **Study dates:** Jan 1982-Dec 2000 **Size of population (no. of patients):** 42 case,	**Age:** Mean (SD): Cases: 39.5 (13.6) Controls: 37.0 (8.2) **Race/ethnicity (n [%]):** NR	**Definition(s) of outcome(s):**	1) History of infertility: Border-line / Benign / Total Infert: **6** / **70** / 76 No infert: **36** / **187** / 223 Total: 42 / 257 / 299	**Comments:** - No multivariate analysis - Hospital-based controls **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	257 controls **Study type:** Case-control All borderline ovarian tumors vs. all benign pathology ovarian surgery	**Diagnoses (n [%]):** NR **Inclusion criteria:** Surgery for benign or borderline tumors during time period **Exclusion criteria:** NR		Value / Lower 95% CI / Upper 95% CI Odds rat 0.45 0.18 1.10 Borderline / Benign / Total Infert **5** **34** 39 No infert **37** **223** 260 Total 42 257 299 Value / Lower 95% CI / Upper 95% CI Odds rat 0.89 0.33 2.41	population: - Comparability of cases and controls with respect to potential confounders: - Appropriateness of statistical analyses: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Da Costa, Abdel-massih, de Oliveira, et al. **2001** **#5800**	**Geographical location:** Sao Paulo, Brazil **Study dates:** Jan 1996 – Dec 1999 **Size of population:** 943 pregnancies (129 from blastocyst transfers, 814 from 4-8cell) **Study type:** Cohort (retrospective)	**Age:** Mean (SD): 4-8cell grp 34.11 (3.53), Blastocyst 35.72 (4.67) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** 4-8cell grp, blastocyst grp Unexplained infertility: 233 (9), 27 (8) Endometriosis: 155 (6), 23 (7) Male factor: 956 (37), 131 (39) Tubal factor: 672 (26), 80 (24) PCOS: 465 (18), 54 (16) Other (specify): "other" 103 (4), 20 (6) **Inclusion criteria:** ICSI pregnancies **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Monozygotic twinning	1) Blastocyst versus 4-8cell transfer as risk factor for MZ twinning: MZ+ / MZ- / Total blastocyst: **5** / **124** / 129 4-8 cell: **6** / **808** / 814 Total: 11 / 932 / 943 Value (Lower 95% CI – Upper 95% CI) Rel risk: 5.26 (1.63 – 16.98)	**Comments:** Blastocyst transfer only performed during latter part of study period (from Sept 1998 on) **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: - Use of validated method for genomic test: n/a Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -
Daniel, Ochshorn, Fait, et al. **2000** **#6840**	**Geographical location:** Tel Aviv, Israel **Study dates:** Jan 1996 - Dec 1997 **Size of population:** 297 twin pregnancies (104 by ART, 193 by non-ART, of which 72 conceived by ovulation induction and 121 spontaneously) **Study type:** Cohort (retrospective)	**Age:** Mean (SD): ART 32 (4.8), non-ART 30.4 (4.9) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Twin pregnancies delivered ≥ 24wks. **Exclusion criteria:** HOM with or w/o IUFD, singletons with early	**Definition(s) of outcome(s):** PIH = persistent BP ≥ 140/90 > 20wks in previously normotensive Preex = same plus proteinuria ≥ 100mg/dL or 300mg/24h Preterm uterine ctx = regular ctxs requiring tocolytics (accompanied by progressive cvx change and/or dil > 1cm at	Note raw data not given, only percentages. 1) IUGR, ART vs non-ART: IUGR+ / IUGR- / Total ART: **8** / **99** / 107 non-ART: **5** / **188** / 193 Total: 13 / 287 / 300 Value (Lower 95% CI – Upper 95% CI) Odds rat: 3.04 (0.97 – 9.53) ART vs spont also ns	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: - Use of validated method for genomic test: n/a Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Compared all twins ≥ 24wks born at one hosp, ART versus NC	vanishing twins, twin pregnancies reduced to singletons	admission) Discordance > 25% birthwt IUGR < 3%ile or no wt gain in 2-3wks	2) Discordance, ART vs non-ART: disc+ / disc- / Total ART: **18** / **86** / 104 non-ART: **14** / **179** / 193 Total: 32 / 265 / 297 Value / Lower 95% CI / Upper 95% CI Odds rat: 2.68 / 1.27 / 5.63 3) Fetal reduction, ART vs non-ART: Red+ / Red- / Total ART: **23** / **81** / 104 non-ART: **5** / **188** / 193 Total: 28 / 269 / 297 Value / Lower 95% CI / Upper 95% CI Odds rat: 10.68 / 3.92 / 29.07 3) Fetal reduction, ART vs ovulation indxn: Red+ / Red- / Total ART: **23** / **81** / 104 OI: **5** / **67** / 72 Total: 28 / 148 / 176 Value / Lower 95% CI / Upper 95% CI Odds rat: 3.80 / 1.37 / 10.55 (no reductions in spontaneous grp) 4) Cesarean, ART vs non-ART: C/S+ / C/S- / Total ART: **45** / **59** / 104 non-ART: **65** / **128** / 193 Total: 110 / 187 / 297 Value / Lower 95% CI / Upper 95% CI Odds rat: 1.50 / 0.92 / 2.45	Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				5) PIH, ART vs non-ART: PIH+ / PIH- / Total ART: **19** / **85** / 104 non-ART: **18** / **175** / 193 Total: 37 / 260 / 297 Odds rat: Value 2.17, Lower 95% CI 1.08, Upper 95% CI 4.35	
de Boer, den Tonkelaar, Burger, et al., 2005 **#39440**	**Geographical location:** Amsterdam, Netherlands **Study dates:** Treated for IVF 1983-95 Questionnaire 1997-2000 **Size of population:** 7842 women, 4072 with regular menstrual cycles **Study type:** Cohort (retrospective) Questionnaire, and data abstracted retrospectively if consent given	**Age:** Mean (SD) at questionnaire, by cause of subfertility: Tubal: 33.3 (4.6) Male: 37.5 (4.4) Unexplained: 38.7 (4.3) Other: 38.6 (4.6) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** IVF-treated women participating in OMEGA study **Exclusion criteria:** - Did not consent - 1st cycle stimulation protocol unknown or Clomid - Donor oocytes - F/u period < 1yr Unable to assess menopausal status - OC's 1 yr before questionnaire - Induced menopause	**Definition(s) of outcome(s):** Women considered to be in menopause transition if 1) mean menstrual cycle length was < 21 d or > 35 d and next cycle was not predictable within 4 d OR 2) no menses in previous 3-11 mo OR 3) used hormone therapy to manage menopause symptoms Considered to have reached menopause when last VB occurred ≥ 12 mo before completion of questionnaire	1) Menopause transition or menopause, by tubal vs. all other causes: Men + / Men - / Total Tubal: **133** / **1260** / 1393 Other: **157** / **2375** / 2532 Total: 290 / 3635 / 3925 Rel risk: Value 1.54, Lower 95% CI 1.23, Upper 95% CI 1.92 2) Menopause transition or menopause, by male vs. all other causes: Men+ / Men- / Total Male: **64** / **1156** / 1220 Other: **226** / **2479** / 2705 Total: 290 / 3635 / 3925 Rel risk: Value 0.63, Lower 95% CI 0.48, Upper 95% CI 0.82 3) Menopause transition or menopause, by unexplained vs. all other causes: Men+ / Men- / Total Unexp: **57** / **829** / 886 Other: **233** / **2806** / 3039 Total: 290 / 3635 / 3925	**Comments:** - 71% response rate - No mention that those abstracting data were blinded to cause of subfertility **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: + Use of validated method for genomic test: NR Use of validated method for ascertaining clinical outcomes: - Adequate follow-up period: - Completeness of follow-up: - Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		- Pregnancy - Lactation			

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.84	0.63	1.11

De Neubourg, Gerris, Mangel-schots, et al., 2006 **#51450**	**Geographical location:** Belgium **Study dates:** 1998-2003 **Size of population (no. of patients):** N = 251 singletons SET N = 59,535 spontaneous singletons **Number of cycles analyzed:** 808 **Number of cycles per patient:** 3.2 cycles/patient **Study type:** Cohort	**Age:** Mean (SD): SET: 30.8 (3.6) Spontaneous: 29.3 (4.8) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 10% Female factor: 22.5% Male factor: 50% Mixed: 8.5% **Inclusion criteria:** Single embryo transfer (SET) with IVF+/-ICSI **Exclusion criteria:** - Incomplete data - Multiple gestations	**Definition(s) of outcome(s):** Low birthweight < 2.5 kg Very low bwt < 1.5 kg Preterm birth < 37 wk Very preterm birth < 32 wk	1) Low birthweight:	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -

	LBWT +	LBWT -	Total
SET	**15**	**236**	251
Spon-taneous	**3050**	**56485**	59535
Total	3065	56721	59786

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.17	0.71	1.91

2) Very low birthweight:

	VLBWT +	VLBWT -	Total
SET	**2**	**249**	251
Spon-taneous	**466**	**59069**	59535
Total	468	59318	59786

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.02	0.26	4.06

3) Preterm birth < 37 wk:

	PTB +	PTB -	Total
SET	**25**	**226**	251
Spon-taneous	**3669**	**55866**	59535
Total	3694	56092	59786

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.62	1.11	2.35

4) Very preterm birth:

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

	VPTB +	VPTB -	Total
SET	**2**	**249**	251
Spon-taneous	**468**	**59067**	59535
Total	470	59316	59786

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.01	0.25	4.04

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
De Neubourg, Mandel-schots, Van Royen, et al., 2004 **#11670**	**Geographical location:** Antwerp, Belgium **Study dates:** Jan 1998 – Dec 2002 **Size of population:** 27 cases OHSS in 2007 cycles, 21 during conception cycles 16/482 singleton 5/134 twin **Study type:** Retrospective cohort study	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** OHSS recorded in database, occurring in conception cycle **Exclusion criteria:** NR	**Definition(s) of outcome(s):** OHSS defined by Golan criteria; those with moderate or severe OHSS requiring hospitalization were recorded in database	1) OHSS – twins vs. singletons:	**Comment:** - Relies on OHSS cases being recorded into database - No info regarding severity of OHSS (different between twins & singletons?) - During this time period, single embryo transfer was "gradually introduced" – but no data presented to assess correlation between number of embryos transferred & OHSS **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: - Use of validated method for genomic test: NA Use of validated method for ascertaining clinical outcomes: (Golan criteria) Adequate follow-up period: NA Completeness of follow-up: NA Analysis (multivariate adjustments) and reporting of results: -

	OHSS +	OHSS -	Total
Twin	**5**	**129**	134
Single-ton	**16**	**366**	382
Total	21	495	516

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.89	0.33	2.38

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
De Sutter, Delbaere,	**Geographical location:** Finland	**Age:** Mean (SD):	**Definition(s) of outcome(s):**	1) Preterm birth:	**Comments:** None

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Gerris, et al., 2006 **#51480**	**Study dates:** 2000-4 **Size of population (no. of patients):** N = 404 single ET N =431 double ET **Study type:** Cohort	SET 31.6 (3.5) DET 33.2 (4.3) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** SET vs. DET groups: Unexplained infertility: 118 (29.6%), 81 (19%) Female: 66 (16.6%), 63 (14.8%) Male factor: 184 (46.2%), 244 (57.1%) Combined: 30 (7.5%), 39 (9.1%) **Inclusion criteria:** Single or double fresh embryo transfer in cycle 1-3, who delivered a singleton child of > 500 g **Exclusion criteria:** NR	Outcomes were not defined Preterm birth Low birthweight	PTB + / PTB - DET 45 / 386 = 431 SET 25 / 379 = 404 70 / 765 = 835 Rel risk 1.69 (Lower 95% CI 1.05, Upper 95 % CI 2.70) 2) Low birthweight: LBW / Preg - DET 50 / 381 = 431 SET 17 / 387 = 404 67 / 768 = 835 Rel risk 2.76 (Lower 95% CI 1.62, Upper 95 % CI 4.70) 3) Risks remained statistically significant and elevated after adjustment for relevant confounders (including gestational age for birthweight).	**Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: - Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
De Sutter, Veldeman, Kok, et al., 2005 **#41930**	**Geographical location:** Gent, Belgium **Study dates:** 1997-2001 **Size of population:** 126 pairs of pts (126 IVF, 126 IUI) **Study type:** Case-control Matched eligible IUI pts with IVF pts by maternal age, parity, plurality, del date	**Age:** Mean (SD): IVF: 31.7 (1.8) IUI: 30.3 (3.6) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Patients who conceived by IVF or IUI - Address available **Exclusion criteria:** - ICSI - Incomplete questionnaire - Non-respondents - No appropriate control	**Definition(s) of outcome(s):** PTB < 37 wk LBW < 2500 g Perinatal mortality= stillbirths ≥ 500 g and neonatal deaths in 7 d PIH not defined	No difference in C/S rate (raw #s not reported) 1) Preterm birth: PTB + / PTB - / Total IVF **21** / **105** = 126 IUI **19** / **107** = 126 Total 40 / 212 = 252 Value (Lower 95% CI, Upper 95% CI) Odds rat 1.13 (0.57, 2.22) 2) NICU stay: NICU + / NICU - / Total IVF **16** / **110** = 126 IUI **24** / **102** = 126 Total 40 / 212 = 252	**Comments:** - Only 47% of IUI pts responded to initial questionnaire - Small numbers – not able to detect rare outcomes - No mention of those collecting data being blinded to mode of conception **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: - Appropriateness of the control population: + Verification that the control is free of cancer: NR Comparability of cases and controls with respect to potential confounders: - (not matched for smoking, adverse pregnancy history, medical problems)

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Value / Lower 95% CI / Upper 95% CI Odds rat 0.62 0.31 1.23 3) PIH: PIH + / PIH - / Total IVF **19** **107** 126 IUI **12** **114** 126 Total 31 221 252 Value / Lower 95% CI / Upper 95% CI Odds rat 1.69 0.78 3.64	Validated dietary assessment method: NR Appropriateness of statistical analyses: +
Derom, Leroy, Vlietinck, et al., 2006 **#51560**	**Geographical location:** East Flanders, Belgium **Study dates:** 1964-2002 **Size of population (no. of patients):** 6208 twins, 170 triplets **Study type:** Cohort	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Included in provincial twin/triplet registry **Exclusion criteria:** - Selective reduction - Unknown mode of conception after 1985	**Definition(s) of outcome(s):** Zygosity of multiple gestation Chorionicity of multiple gestation	1) Monoyzygous vs dizygous twins, ovulation induction vs spontaneous: Mono / Di / Total Induction **57** **704** 761 Spon-taneous **2072** **2529** 4601 Total 2129 3233 5362 Value / Lower 95% CI / Upper 95% CI Rel risk 0.17 0.13 0.21 2) Monozygous vs dizygous, ART vs spontaneous: Mono / Di / Total ART **17** **738** 755 Spon-taneous **2072** **2529** 4601 Total 2089 3267 5356 Value / Lower 95% CI / Upper 95% CI Rel risk 0.05 0.03 0.08 3) Proportion of monozygous twins among	**Comments:** Not adjusted for birth year or maternal age **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: - Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				different infertility treatments highest for clomiphene citrate alone (12% vs 3.6%).	
Dokras, Baredziak, Blaine, et al., 2006 **#51610**	**Geographical location:** Iowa City, Iowa **Study dates:** Jan 1995-Apr 2005 **Size of population (no. of patients):** 1293 **Study type:** Cohort	**Age:** Mean age 31 across all 4 **Race/ethnicity (n [%]):** White non-Hispanic: 94% **Diagnoses (n [%]):** PCOS more common (> 27% vs. < 7%) in women with BMI ≥ 30, unexplained infertility less common (< 6% vs. 10-12%) **Inclusion criteria:** - Age < 38 years - 1st fresh IVF cycle **Exclusion criteria:** - Day 2 transfer cycles - Cryopreserved embryo transfers - Donor oocyte cycles - GIFT/ZIFT	**Definition(s) of outcome(s):** Preeclampsia Gestational diabetes Cesarean section	1) Trend for increasing rates of preeclampsia, gestational diabetes, preterm birth, cesarean section with increasing BMI, but insufficient power to show significant risk except for comparison of extremes (BMI < 25 vs BMI ≥ 40).	**Comments:** - Obstetric outcomes assessed by patient self-report - Single center **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: - Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: - Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
Dor, Lerner-Geva, Rabinovici, et al., 2002	**Geographical location:** Israel **Study dates:** Treated	**Age:** Mean (SD): at treatment: 34.0 (6.4); at follow-up 37.5 (7.1)	**Definition(s) of outcome(s):** Cancer cases reported to	1) Standardized Incidence Ratios: All cancers SIR 0.76 95% CI 0.5,1.1	**Comments:** - Subgroup analysis (by cause of infertility, # cycles) only done in 1524 subjects

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#2860	1981-1992, cases identified through December 1996 **Size of population (no. of patients):** 5026 **Study type:** Cohort	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Treated with IVF at sites during study time period - at least one cycle **Exclusion criteria:** NR	Israel National Cancer Registry	Breast 0.69 0.46,1.66 Ovary 0.57 0.01,3.2 Cervix 0.58 0.01,3.22 Endometrium 2.25 0.25,8.1 Other* 0.78 0.4,1.36) *Colon cancer (3 cases); melanoma (3 cases); and 1 case each of tongue cancer, thyroid cancer, stomach cancer, leukemia, lymphoma, and cancer of the peritoneum. 2) Total 27 cancers diagnosed 1 year or more after treatment. 13 diagnosed within 1 year, not included in analysis.	- ?Peritoneal cancer should be analyzed as ovary **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: - Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: - Completeness of follow-up: - (NR) Analysis (multivariate adjustments) and reporting of results: +
Doria-Rose, Lou Biggs, and Weiss, 2005 **#39770**	**Geographical location:** Seattle, WA **Study dates:** 1977 - 1983 **Size of population:** 329 cases, 675 controls **Study type:** Case-control	**Age:** NR **Race/ethnicity (n [%]):** 100% White **Diagnoses (n [%]):** NR **Inclusion criteria:** All cases of germ cell testicular CA dx'd 1977 - 1983 in western WA. Controls by random digit dialing. Only white men 20 - 69yo who spoke English and had telephone **Exclusion criteria:** Non-white, unable to locate, dead, refusal	**Definition(s) of outcome(s):** Testicular germ cell CA	1) No. of children fathered as risk factor for CA: CA ctrl Total 0 **173** **330** 503 any **156** **342** 498 Total 329 672 1001 Value Lower 95% CI Upper 95% CI Odds rat 1.15 0.88 1.50 2) Infertility as risk factor for CA: CA ctrl Total Infert **12** **10** 22 No infert **317** **662** 979 Total 329 672 1001 Value Lower 95% CI Upper 95% CI Odds rat 2.51 1.07 5.86	**Comment:** Recall bias **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: - Appropriateness of the control population: + Verification that the control is free of cancer: - (not stated specifically) Comparability of cases and controls with respect to potential confounders: + Validated dietary assessment method: n/a Appropriateness of statistical analyses: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
El Hage, Ghanem, Safi, et al., 2006 **#51680**	**Geographical location:** Beirut, Lebanon **Study dates:** Jan 1996-Dec 2001 **Size of population (no. of patients):** 780 IVF/ICSI birth (89.6% ICSI) 2168 spontaneous **Study type:** Cohort	**Age:** Mean (SD): IVF/ICSI: 32.0 (5.2); spontaneous 27.8 (5.2) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - IVF—successful pregnancy from 2 practitiioners - Spontaneous—ob patients followed by same practitioners **Exclusion criteria:** NR	**Definition(s) of outcome(s):** "Neuro-orthopedic" malformations—not specifically defined, includes range of diagnoses from neural tube defects to club feet not usually associated with syndrome	1) "Neuro-orthopedic" malformations, crude relative risk: IVF/ICSI + : Out + **7**, Out - **773**, Total 780 IVF - : Out + **7**, Out - **2161**, Total 2168 Total: Out + 14, Out - 2934, Total 2948 Rel risk: Value 2.78, Lower 95% CI 0.98, Upper 95% CI 7.90 Risk estimate reduced after adjustment for low birthweight, multiple gestation, primiparity (although apparently not adjusted for maternal age) 2) All malformations, crude relative risk: Exp + : Out + **19**, Out - **761**, Total 780 Exp - : Out + **23**, Out - **2145**, Total 2168 Total: Out + 42, Out - 2906, Total 2948 Rel risk: Value 2.30, Lower 95% CI 1.26, Upper 95% CI 4.19 Adjusted estimates not reported	**Comments:** Significantly more multiples, lower birthweight, primiparous, c-sections in IVF/ICSI gropu **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: - Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
Ellison, Hotamisligil, Lee, et al., 2005	**Geographical location:** Boston, MA **Study dates:** NR	**Age:** Mean (SD): Mothers: 35 (4) Children: 22 mo (8)	**Definition(s) of outcome(s):** Assessments of:	Data presented as % prevalence; calculated from %s 1) Difficulty meeting material needs:	**Comments:** - Response rate 64% - Higher for multiples (77% vs 52%)

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#40420	**Size of population:** 249 mothers of 128 singletons, 111 twins, 10 triplets **Study type:** Cohort Sent questionnaires to subjects who conceived by ART. Matched singleton mothers to multiple moms by children's yr of birth, maternal age, and parity.	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Subjects identified through 2 infertility clinics - Conceived by ART - Children ≥ 12 mo old - Residing in New England - Treated in MA **Exclusion criteria:** - Children > 48 mo old	- Meeting material needs (higher scores = increased unmet material needs) - Social stigma - Overall quality of life (Ferrans and Powers Quality of Life Index) - Marital satisfaction (Kansas Marital Satisfaction Scale) - Stress (Cohen Perceived Stress Scale) - Depression (Centers for Epidemiological Study-Depression Scale) - Children with health or developmental problems		**Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): Large sample size: Adequate description of the cohort: Use of validated method for ascertaining exposure: Use of validated method for ascertaining clinical outcomes: Adequate follow-up period: Completeness of follow-up: Analysis (multivariate adjustments) and reporting of results:

	Mat needs +	Mat needs -	Total
Twin	**20**	**91**	111
Single	**3**	**125**	128
Total	23	216	239

	Value	Lower 95% CI	Upper 95% CI
Odds rat	9.16	2.64	31.75

	Mat needs +	Mat needs -	Total
Triplet	**3**	**7**	10
Single	**3**	**125**	128
Total	6	132	138

	Value	Lower 95% CI	Upper 95% CI
Odds rat	17.86	3.04	105.06

2) Lower quality of life:

	Low QOL +	Low QOL -	Total
Twin	**13**	**98**	111
Single	**6**	**122**	128
Total	19	220	239

	Value	Lower 95% CI	Upper 95% CI
Odds rat	2.70	0.99	7.36

	Low QOL +	Low QOL -	Total
Triplet	**2**	**8**	10
Single	**6**	**122**	128
Total	8	130	138

	Value	Lower 95% CI	Upper 95% CI
Odds rat	5.08	0.88	29.34

3) Social stigma:

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

	Stigma +	Stigma -	Total
Twin	**20**	**91**	111
Single	**10**	**118**	128
Total	30	209	239

	Value	Lower 95% CI	Upper 95% CI
Odds rat	2.59	1.16	5.81

	Stigma +	Stigma -	Total
Triplet	**2**	**8**	10
Single	**10**	**118**	128
Total	12	126	138

	Value	Lower 95% CI	Upper 95% CI
Odds rat	2.95	0.55	15.81

4) Maternal depression:

	Depress +	Depress -	Total
Twin	**25**	**86**	111
Single	**20**	**108**	128
Total	45	194	239

	Value	Lower 95% CI	Upper 95% CI
Odds rat	1.57	0.82	3.02

	Depress +	Depress -	Total
Triplet	**4**	**6**	10
Single	**20**	**108**	128
Total	24	114	138

	Value	Lower 95% CI	Upper 95% CI
Odds rat	3.60	0.93	13.92

5) Maternal stress:

	Stress +	Stress -	Total
Twin	**8**	**103**	111
Single	**9**	**119**	128

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

Total	17	222	239

	Value	Lower 95% CI	Upper 95% CI
Odds rat	1.03	0.38	2.76

	Stress +	Stress -	Total
Triplet	**1**	**9**	10
Single	**9**	**119**	128
Total	10	128	138

	Value	Lower 95% CI	Upper 95% CI
Odds rat	1.47	0.17	12.92

6) Lower marital satisfaction

	Low mar satis +	Low mar satis -	Total
Twin	**13**	**98**	111
Single	**10**	**118**	128
Total	23	216	239

	Value	Lower 95% CI	Upper 95% CI
Odds rat	1.57	0.66	3.72

	Low mar satis +	Low mar satis -	Total
Triplet	**2**	**8**	10
Single	**10**	**118**	128
Total	12	126	138

	Value	Lower 95% CI	Upper 95% CI
Odds rat	2.95	0.55	15.81

Erez, Vardi, Hallak, et al., 2006 **#51770**	**Geographical location:** Beer Sheba, Israel **Study dates:** 1988-2002 **Size of population (no.**	**Age:** IVF: 31 Spontaneous: 29 **Race/ethnicity (n [%]):** NR	**Definition(s) of outcome(s):** Mild GH was defined as diastolic blood pressure 590 mmHg and 5110	1) IVF vs. none, mild and severe preeclampsia combined:	**Comments:** None **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: -

	Out +	Out -	Total
Exp +	**51**	**193**	244
Exp -	**241**	**2143**	2384

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	of patients): 2628 **Study type:** Case-control	**Diagnoses (n [%]):** NR **Inclusion criteria:** - Twin pregnancy - Delivered in hospital - > 22 weeks **Exclusion criteria:** < 3 prenatal visits	mmHg and systolic blood pressure 5140 mmHg and 5160 mmHg. Severe GH was defined as diastolic blood pressure 5110 mmHg and systolic blood pressure 5160 mmHg. Preeclampsia was defined as elevated blood pressure and proteinuria. The severity of preeclampsia was defined according to the severity of hypertension and any one of the following: proteinuria in nephritic range defined as þ3 proteinuria by dipstick or more than 3 g protein in the urine in 24 hours collection, thrombocytopenia 4100 000, elevated liver enzymes, persistent headache and blurred vision	Total 292 2336 2628 Value / Lower 95% CI / Upper 95% CI Odds rat 2.35 1.68 3.29 2) After adjusting for chronic HTN, diabetes, primiparity, twin discordance, and maternal age, OR for IVF 1.08 (0.74, 1.39)	Appropriateness of the control population: + Comparability of cases and controls with respect to potential confounders: + Appropriateness of statistical analyses: +
Ericson, Nygren, Olausson, et al., 2002 **#2440**	**Geographical location:** Sweden **Study dates:** Born 1984-1997 **Size of population (no.**	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR	**Definition(s) of outcome(s):** Hospitalization (any cause)	1) Odds ratios, any hospitalization: OR 95% CI All children Crude 1.74 1.67,1.82 Adjusted* 1.84 1.76,1.92 All term births	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	of patients): 1,417,166 **Study type:** Cohort	**Inclusion criteria:** Live birth in Sweden - Exposure: IVF (from registry) **Exclusion criteria:** NR		Crude 1.25 1.19,1.32 Adjusted* 1.34 1.27,1.41 Singleton Adjusted* 1.40 1.32,1.48 Twins Adjusted* 1.17 1.07,1.27 *Adjusted for maternal age, parity, smoking 2) Adjusted*odds ratios, specific diagnoses: OR 95% CI Cerebral palsy 1.69 1.06,2.68 Epilepsy 1.54 1.10,2.15 Mental retardation 0.94 0.39,2.27 Developmental issue 1.35 0.86,2.11 All neurologic dx 1.51 1.18,1.93 Accident 1.06 0.95,1.17 Tumors 1.57 1.16,2.13 Asthma (> age 1) 1.37 1.20,1.56 Any infection 1.36 1.29,1.44 Congenital malformation 1.84 1.67,2.03 *Adjusted for maternal age, parity, smoking, year of birth 3) ORs increase with duration of infertility, decrease with child age (but still significant through age 6) 4) Based on Cancer Registry, no increased cancer risk—RR 0.88, 95% CI 0.44,1.58	Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
Farr, Schieve, and Jamieson, 2007	**Geographical location:** US (SART registry) **Study dates:** 1999-2002	**Age:** Range: < 33 48,804 (32.9%) 33–34 22,887 (15.4%) 35–37 32,369 (21.8%)	**Definition(s) of outcome(s):** Loss of pregnancy	1) Loss after 7 weeks, single heart beat vs. 2 or more heart beats: Loss+ Loss - Total Two or **2176** **43015** 45191	**Comments:** None **Quality assessment:** Unbiased selection of the cohort

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results				Comments/Quality Scoring
#70990	**Size of population (no. of patients):** 148,494 **Study type:** Cohort All pregnancies in SART registry	38–40 24,284 (16.4%) 41–42 9,642 (6.5%) > 42 10,508 (7.1%) **Race/ethnicity (n [%]):** White 72,980 (49.15) Asian* 4,473 (3.01) White Hispanic 4,403 (2.97) African American* 3,509 (2.36) Other race 116 (0.08) Missing 63,013(42.43) **Diagnoses (n [%]):** Not reported in detail **Inclusion criteria:** NR **Exclusion criteria:** - Treatments canceled prior to egg retrieval, treatments with unsuccessful embryo transfers, and treatments using zygote intrafallopian transfer, gamete intrafallopian transfer , or zygote or gamete intrafallopian transfer in combination with IVF with transcervical embryo transfer, use of both donor and patient oocytes or embryos , both freshly fertilized and frozen embryos, a gestational carrier, or those missing data on whether the treatment resulted in pregnancy - Missing or conflicting values for dates of oocyte retrieval, embryo transfer, ultrasound observation of fetal heartbeat, or		more Single Total Rel risk	 **9875** 12051 Value 0.35	 **62664** 105679 Lower 95% CI 0.34	 72539 117730 Upper 95% CI 0.37	(prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		pregnancy outcome and pregnancies with missing data on potential confounders.			
Fisher, Ham-marberg, and Baker, 2005 **#40270**	**Geographical location:** Melbourne, Australia **Study dates:** Jul 2000-Aug 2002 **Size of population:** 745 **Study type:** Cohort (retrospective) Systematic audit of consecutive medical records of mother-infant dyads admitted to mother/baby unit. Mode of conception spontaneous, OI & AI (ovulation induction & artificial insemination), or IVF	**Age:** Mean (SD): Spontaneous: 33.09 (4.01) OI & AI: 33.45 (3.11) IVF: 35.88 (3.6) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Consecutive **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Edinburgh Postnatal Depression Scale (EPDS)	1) EPDS score > 12 on day 1: Day 1 > 12 / Day 1 ≤ 12 / Total OI/AI: **7** / **5** / 12 Spont: **322** / **356** / 678 Total: 329 / 361 / 690 Value / Lower 95% CI / Upper 95% CI Odds rat: 1.55 / 0.49 / 4.93 Day 1 > 12 / Day 1 ≤ 12 / Total IVF: **22** / **23** / 45 Spont: **322** / **356** / 678 Total: 344 / 379 / 723 Value / Lower 95% CI / Upper 95% CI Odds rat: 1.06 / 0.58 / 1.93 2) EPDS score > 12 on day 5: Day 5 > 12 / Day 5 ≤ 12 / Total OI/AI: **3** / **9** / 12 Spont: **102** / **551** / 653 Total: 105 / 560 / 665 Value / Lower 95% CI / Upper 95% CI Odds rat: 1.80 / 0.48 / 6.77 Day 5 > 12 / Day 5 ≤ 12 / Total IVF: **6** / **38** / 44 Spont: **102** / **551** / 653 Total: 108 / 589 / 697	**Comments:** No mention that abstractors were blinded to mode of conception **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: - Use of validated method for genomic test: Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Odds rat: Value 0.85; Lower 95% CI 0.35; Upper 95% CI 2.07	
Gauthier, Paoletti, Clavel-Chapelon, et al., 2004 **#11240**	**Geographical location:** France **Study dates:** Enrolled between June 1990-Nov 1991; follow-up through June 2000 **Size of population (no. of patients):** Infertile: 6602 No infertility: 85,948 **Study type:** Cohort	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** NR **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Breast cancer cases, validated through medical records when possible	1) Adjusted hazard ratios (proportional hazards models): Any treatment for infertility: 0.95 (0.82, 1.11) Treated with drugs/IVF: 0.94 (0.78, 1.12) No association with specific drugs, duration of treatment, or age at treatment	**Comments:** - Infertilty status, treatment by self-report - 9.7 years mean follow-up—longer than most cohorts in this population **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: - Use of validated method for ascertaining exposure: - Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
Geipel, Ludwig, Germer, et al., 2001 **#4920**	**Geographical location:** Lubeck, Germany **Study dates:** Jan 1995-Jul 1999 **Size of population:** ICSI: 114 singletons, 32 twins. Equal numbers of controls.	**Age:** Mean: ICSI: 32.6 Control: 32.5 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR	**Definition(s) of outcome(s):** "High-risk" = CHtn, DM, BMI > 27, nullipar ≥ 35yo, multipar with h/o FGR, preex, abruption, or IUFD Discordance > 20% SGA < 10%ile for German	1) C/S in singletons: ICSI: C/S+ **40**, C/S- **74**, Total 114 ctrl: C/S+ **35**, C/S- **79**, Total 114 Total: C/S+ 75, C/S- 153, Total 228 Value; Lower 95% CI; Upper 95% CI	**Comments:** - No mention of how controls conceived – IVF? OI? Spont? - All were di/di twins - Similar rates of nulliparity and AMA in both groups **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

<table>
<tr><th>Study</th><th>Study Design</th><th>Patients</th><th>Clinical Presentation</th><th>Results</th><th>Comments/Quality Scoring</th></tr>
<tr><td></td><td>Study type: Case-control</td><td>Inclusion criteria:
ICSI pregnancies that had 18-24 wk uterine artery Doppler studies. Controls selected from database, also only routine exams, matched for age, parity, plurality.

Exclusion criteria:
Fetuses with malformations or other indications besides screening (suspected anomaly, FGR)</td><td>population

Preex = repeated BP ≥ 140/90 + proteinuria > 500 mg/day</td><td>Odds rat 1.22 0.70 2.12

2) C/S in twins:

C/S+ C/S- Total
ICSI 25 7 32
ctrl 21 11 32
Total 46 18 64

Value Lower 95% CI Upper 95% CI
Odds rat 1.87 0.62 5.68

No difference in any other outcome: SGA, preex, abruption, PPROM, PTD.

No significant difference in any outcome by Doppler result, or among high-risk or low-risk patients.</td><td>Appropriateness of the control population: -
Verification that the control is free of cancer: NR
Comparability of cases and controls with respect to potential confounders: -
Validated dietary assessment method: NR
Appropriateness of statistical analyses: +</td></tr>
<tr><td>Glazebrook, Sheard, Cox, et al., 2004

#13650</td><td>Geographical location:
United Kingdom

Study dates: NR

Size of population:
260 (129 natural conceptions, 95 IVF singletons, 36 IVF multiples)

Study type: Cohort</td><td>Age:
Median (IQR):
Natural: 39 (27-31)
IVF single: 34 (31-37)
IVF multiple: 32 (29-35)

Race/ethnicity (n [%]):
NR

Diagnoses (n [%]): NR

Inclusion criteria:
IVF group:
- Residence in UK
- At least 18 wks pregnant

Natural conception group:
- Stable relationship
- Speak English
- Age ≥ 24 yrs
- At least 18 wks pregnant
- No med/surg treatment for infertility in current pregnancy</td><td>Definition(s) of outcome(s):

Birthweight

Days premature

Newborn length of hospitalization

NICU admission

Newborn medical complications

Psychiatric/emotional well-being @ 1 yr postpartum

Parenting stress index @ 1 yr postpartum</td><td>1) All data except for NICU admission & newborn complications are reported as continuous variables, therefore, unable to calculate RR from these data.

<table>
<tr><th></th><th>Natural concept single</th><th>IVF single</th><th>IVF multiple</th></tr>
<tr><td>Mean BWT (kg)</td><td>3.37</td><td>3.31</td><td>2.15</td></tr>
<tr><td>Median days preterm</td><td>1.0</td><td>3.0</td><td>22.5</td></tr>
<tr><td>Median days baby in hospital</td><td>3.5</td><td>4.0</td><td>7.0</td></tr>
<tr><td>Parent distress</td><td>24</td><td>24.83</td><td>28</td></tr>
<tr><td>Parent-child dysfunc-tional interaction</td><td>14</td><td>14</td><td>16</td></tr>
<tr><td>Difficult</td><td>0</td><td>9</td><td>24</td></tr>
</table></td><td>Comments:
None

Quality assessment:
Unbiased selection of the cohort (prospective recruitment of subjects): +
Large sample size: +/-
Adequate description of the cohort: +
Use of validated method for genomic test: NR
Use of validated method for ascertaining clinical outcomes: +
Adequate follow-up period: +
Completeness of follow-up: +
Analysis (multivariate adjustments) and reporting of results: +</td></tr>
</table>

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		- Nulliparous - Singleton pregnancy **Exclusion criteria:** NR		child Defensive respond-ing: 15 / 14 / 15 2) NICU admission for singletons only: Sing IVF: **6** / **89** / 95 Sing natural: **6** / **123** / 129 Total: 12 / 212 / 224 **Rel risk** (Value / Lower 95% CI / Upper 95% CI): 1.36 / 0.45 / 4.08 3) Newborn medical complications: Sing IVF: **26** / **69** / 95 Sing natural: **22** / **107** / 129 Total: 48 / 176 / 224 **Rel risk** (Value / Lower 95% CI / Upper 95% CI): 1.60 / 0.97 / 2.65	
Goody, Rice, Boivin, et al., 2005 **#40820**	**Geographical location:** Cardiff, UK **Study dates:** 1996 **Size of population:** 101 families with ART twins, 1,073 naturally conceived control DZ	**Age:** Mean (SD): NC 28.43, ART 29.61 **Race/ethnicity (n [%]):** 93% British in both grps Small numbers of Bangladeshi/Indian/Pakistani, African/Caribbean,	**Definition(s) of outcome(s):** Pregnancy risk score calculated based on # of cigarettes smoked during pregnancy, admission to hosp bc of Htn & edema, VB.	Data on C/S not presented. No n given, just % 1) Behind in reading: ART: **15** / **86** / 101 NC: **201** / **872** / 1073 Total: 216 / 958 / 1174	**Comment :** - Response rate 73% - 77% gave permission to contact teachers, 92% of teachers replied. - Relied on parental reporting, not record review or standardized tests. - No information of specific conception techniques. - NC families had more siblings,

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	twin pairs **Study type:** Cohort (retrospective) Questionnaire mailed to families of school-age twins	Jewish, Arab, SE Asian. **Diagnoses (n [%]):** NR **Inclusion criteria:** School-aged twins in 9 health districts in Greater Manchester and Lancashire, UK who completed & returned package of questionnaires. Only twins assessed to be dizygotic by questionnaire and 'an algorithm based on previous work' were included. **Exclusion criteria:** Failure to indicate whether or not ART had been used	Delivery risk included emergency C/S, operative vag del, labor <3h or >36h. Modified DuPaul ADHD rating scale used to assess parent & teacher-assessed child psychopathology. Internalizing Sx – Rutter scales Antisocial behavior – conduct difficulties subscale of Rutter scales Family Environment – maternal report of Family Environment Scale Educational difficulties – mothers report	<table><tr><th></th><th>Value</th><th>Lower 95% CI</th><th>Upper 95% CI</th></tr><tr><td>Odds rat</td><td>0.76</td><td>0.43</td><td>1.34</td></tr></table> 2) Learning difficulty: <table><tr><th></th><th>yes</th><th>no</th><th>Total</th></tr><tr><td>ART</td><td>12</td><td>89</td><td>101</td></tr><tr><td>NC</td><td>147</td><td>926</td><td>1073</td></tr><tr><td>Total</td><td>159</td><td>1015</td><td>1174</td></tr></table> <table><tr><th></th><th>Value</th><th>Lower 95% CI</th><th>Upper 95% CI</th></tr><tr><td>Odds rat</td><td>0.85</td><td>0.45</td><td>1.59</td></tr></table> No parent- or teacher-rated measure of child psychopathology differed between grps except teacher-rated ADHD (continuous variable, higher in NC grp). When maternal smoking & demographics were controlled for, no difference found.	were of lower social class, mothers more likely to have smoked during preg. **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: - Use of validated method for genomic test: NR Use of validated method for ascertaining clinical outcomes: - Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
Gray and Wu, 2000 **#7000**	**Geographical location:** Fishkill, NY and Burlington, VT **Study dates:** June 1989-July 1990 conducted study, reported pregnancies from 1980-1990	**Age:** ≤ 24 n=1001 25-29 n= 1277 30-34 n=573 ≥ 35 n=116 **Race/ethnicity (n [%]):** 92.8% white n = 1459	**Definition(s) of outcome(s):** Subfertility ≥ 1yr to conception Spontaneous abortion	1) SAb among those with and without subfertility: <table><tr><th></th><th>SAb +</th><th>SAb -</th><th>Total</th></tr><tr><td>Subfert +</td><td>67</td><td>225</td><td>292</td></tr><tr><td>Subfert -</td><td>375</td><td>2592</td><td>2967</td></tr><tr><td>Total</td><td>442</td><td>2817</td><td>3259</td></tr></table> <table><tr><th></th><th>Lower</th><th>Upper</th></tr></table>	**Comments:** Retrospective interviews, subject to significant recall bias, especially associated with poor outcome **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results				Comments/Quality Scoring
		Diagnoses (n [%]): NR			Value	95% CI	95% CI	Large sample size: +
	Size of population (no. of patients): 1572 women			Rel risk	1.82	1.44	2.29	Adequate description of the cohort: +
		Inclusion criteria: Women, 15-44 yr old, work in manufacturing or non-manufacturing jobs or wives of male employees						Use of validated method for ascertaining exposure: -
	Study type: Cohort study							Use of validated method for ascertaining clinical outcomes: +
								Adequate follow-up period: -
		Exclusion criteria: s/p sterilization, hysterectomy, or husband s/p vasectomy						Completeness of follow-up: +
								Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Hansen, Kurincsuk, Bower, et al., 2002 **#2520**	**Geographical location:** Perth, Australia **Study dates:** 1993 - 97 **Size of population:** 301 ICSI, 837 IVF, 4,000 naturally conceived **Study type:** Case-control All ICSI & IVF births in time period, compared to randomly selected naturally-conceived controls in same time period	**Age:** Mean (SD): ICSI 32.6 (4.0), IVF 34.1 (4.6), NC 28.2 (4.4) **Race/ethnicity (n [%]):** (ICSI IVF, NC): White 230 (96%), 639 (95%), 3,500 (88%) Aboriginal or Torres Strait Islander 1 (<1%), 3 (<1%), 280 (7%) Other 9 (4%), 34 (5%), 280 (7%) **Diagnoses (n [%]):** NR **Inclusion criteria:** Pregnancies >=20wks, terminations because of fetal anomalies (regardless of length of gestation) – included all those conceived by ICSI or IVF, and random sample of 4,000 non-ART controls. Data collected by Midwives' Notification System, which collects info on all infants delivered in western Australia **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Birth defect = abnormalities probably of prenatal origin Maj/minor by CDC method F/u period is 1yr	1) C/S, ICSI vs NC: C/S+ / C/S- / Total ICSI: **95** / **206** / 301 NC: **816** / **3184** / 4000 Total: 911 / 3390 / 4301 Value / Lower 95% CI / Upper 95% CI Odds rat: 1.80 / 1.39 / 2.32 2) C/S, IVF vs NC: C/S+ / C/S- / Total IVF: **365** / **472** / 837 NC: **816** / **3184** / 4000 Total: 1181 / 3656 / 4837 Value / Lower 95% CI / Upper 95% CI Odds rat: 3.02 / 2.58 / 3.53 3) C/S, ICSI vs NC, singletons only: C/S+ / C/S- / Total ICSI: **48** / **138** / 186 NC: **776** / **3130** / 3906 Total: 824 / 3268 / 4092 Value / Lower 95% CI / Upper 95% CI Odds rat: 1.40 / 1.00 / 1.97 4) C/S, IVF vs NC, singletons only: C/S+ / C/S- / Total IVF: **183** / **344** / 527 NC: **776** / **3130** / 3906 Total: 959 / 3474 / 4433 Value / Lower 95% CI / Upper 95% CI Odds rat: 2.15 / 1.76 / 2.61	**Comments:** - ICSI, IVF more likely married or cohabiting, nullip, white, metropolitan than NC grp - Same source of data and classification system for all grps. Data collected w/o reference to mode of conception - No effect on findings when pregnancies terminated for birth defects were added to analysis **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: - (not matched for mat age, gest age) Verification that the control is free of cancer: NR Comparability of cases and controls with respect to potential confounders: - (see above) Validated dietary assessment method: NR Appropriateness of statistical analyses: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

5) Birth defects overall, ICSI vs NC:

	Malf+	Malf-	Total
ICSI	**26**	**275**	301
NC	**168**	**3832**	4000
Total	194	4107	4301

	Value	Lower 95% CI	Upper 95% CI
Odds rat	2.16	1.40	3.32

6) Birth defects overall, IVF vs NC:

	Malf+	Malf-	Total
IVF	**75**	**762**	837
NC	**168**	**3832**	4000
Total	243	4594	4837

	Value	Lower 95% CI	Upper 95% CI
Odds rat	2.25	1.69	2.98

7) Birth defects, singletons only:

	Malf+	Malf-	Total
ICSI	**18**	**168**	186
NC	**164**	**3742**	3906
Total	182	3910	4092

	Value	Lower 95% CI	Upper 95% CI
Odds rat	2.44	1.47	4.07

8) Birth defects, singletons only:

	Malf+	Malf-	Total
IVF	**50**	**477**	527
NC	**164**	**3742**	3906
Total	214	4219	4433

	Value	Lower 95% CI	Upper 95% CI
Odds rat	2.39	1.72	3.33

Paper includes adjusted OR's for maternal

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				age, parity, infant sex, correlation btw siblings.	
Hashimoto, Lindsell, Brewer, et al., 2004 **#13870**	**Geographical location:** Cincinnati, Ohio **Study dates:** Jan 1996 – Dec 2000 **Size of population:** 382 infants (201 natural conception, 181 ART) **Study type:** Case-control	**Age:** NR **Race/ethnicity (n [%]):** For infants: 80.9% whites, 19.1% non-whites Natural conception: 68.2% white ART: 95% white **Diagnoses (n [%]):** NR **Inclusion criteria:** - All multiple live births during study dates with birthweight 401-1500 g, cared for in 1 of 3 Cincinnati NICUs, twins/triplets/quads **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Bronchopulmonary dysplasia (BPD) = supplemental oxygen at 36 wks postmenstrual age or discharge home on oxygen Death = death before NICU discharge or before 120 days of life Antenatal steroids = receipt with intent for pulmonary maturity	1) Risk of BPD: BPD: ART **33**, Natural **37**, Total 70 No BPD: ART **148**, Natural **164**, Total 312 Total: ART 181, Natural 201, Total 382 Odds ratio: Value 0.99, Lower 95% CI 0.59, Upper 95% CI 1.66 2) Risk of death: Death: ART **28**, Natural **38**, Total 66 No death: ART **153**, Natural **163**, Total 316 Total: ART 181, Natural 201, Total 382 Odds ratio: Value 0.79, Lower 95% CI 0.46, Upper 95% CI 1.34 3) Risk of death or BPD: Death or BPD: ART **61**, Natural **75**, Total 136 No death or BPD: ART **120**, Natural **126**, Total 246 Total: ART 181, Natural 201, Total 382 Odds ratio: Value 0.85, Lower 95% CI 0.56, Upper 95% CI 1.30	**Comments:** - Data on ART were available for 80% of the multiple births born to 75% of the mothers. - There is potential selection bias as the missing data points could differ significantly. **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: + Verification that the control is free of cancer: NR Comparability of cases and controls with respect to potential confounders: + Validated dietary assessment method: NR Appropriateness of statistical analyses: +
Hernandez-	**Geographical location:**	**Age:**	**Definition(s) of**	1) Gestational hypertension:	**Comments:**

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Diaz, Werler, and Mitchell, 2007 **#71320**	U.S. and Canada (general population) **Study dates:** 1998-206 **Size of population (no. of patients):** 5151 **Study type:** Cohort	< 25: 1162 25-30: 1400 31-35: 1761 > 35: 814 **Race/ethnicity (n [%]):** White: 3777 Black: 348 Other: 1025 **Diagnoses (n [%]):** NR **Inclusion criteria:** Mothers of malformed infants born during study period **Exclusion criteria:** NR	**outcome(s):** Self-report of physician diagnosis of high blood pressure, preeclampsia, or toxemia	Gest HTN + / Gest HTN - / Total Infertility treatment: **55** / **294** / 349 No infert treatment: **423** / **4339** / 4762 Total: 478 / 4633 / 5111 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.77 / 1.37 / 2.30 2) OR after adjustment for parity, prepregnancy BMI, number of fetuses 1.3 (1.0-1.9)	Exposure and outcome ascertainment based on subject self-report **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: - Use of validated method for ascertaining clinical outcomes: - Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
Hjelmstedt, Widstrom, Wramsby, et al., 2003 **#17130**	**Geographical location:** Stockholm, Sweden **Study dates:** Recruited May 1997-Jan 2000 **Size of population:** 57 women, 55 men who conceived after IVF; 43 women, 39 men who conceived naturally **Study type:** Case-control Compared women and men who conceived by IVF to those who conceived naturally regarding psychological variables	**Age:** Mean (SD): IVF women: 32.3 (2.1) Control women: 31.2 (1.8) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 26.3% Male factor: 26.3% Other: "Female" 36.8%, "combination of female and male" 10.5% **Inclusion criteria:** - Women 29-36 yo - Primiparous - In good health - Pregnant with singleton - Nonsmokers - Adequate Swedish language skills - Men with adequate	**Definition(s) of outcome(s):** Infertility Reaction Scale (IRS) used to assess recalled distress related to infertility Barnett scale to assess satisfaction with relationship with partner Karolinska Scales of Personality (KSP) used to measure personality traits Spielberger State and Trait Anxiety Inventory (STAI) Emotional Responses to Pregnancy Scale (ERPS)	Women in IVF group reported more muscular tension, irritability Men in IVF group reported more somatic anxiety, detachment, indirect aggression, guilt, psychic anxiety No difference between 2 groups for STAI	**Comments:** - 25% of eligible patients not approached because of busy recruiters' schedules - 25% of couples declined to participate - Authors state no significant difference between participants & nonparticipants with respect to cause of infertility, age, duration of infertility, # previous IVF treatments - Controls had cohabitated for fewer yrs than IVF **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: - Appropriateness of the control population: + Verification that the control is free of cancer: NR Comparability of cases and controls with respect to potential confounders: - Validated dietary assessment

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		Swedish language skills **Exclusion criteria:** NR			method: NR Appropriateness of statistical analyses: +
Hourvitz, Pri-Paz, Dor, et al., 2005 **#39160**	**Geographical location:** Tel Aviv, Israel **Study dates:** Jan 1995 - Dec 1997 **Size of population:** 322 ICSI, 201 IVF **Study type:** Cohort (retrospective) Retrospective comparison of outcomes of IVF vs ICSI pregnancies. Questionnaires mailed 1-3yr after delivery	**Age:** Mean (SD): IVF 31.8 (5.0), ICSI 30.6 (4.8) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Embryo transfers for IVF or ICSI during study period. **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Major malf = condition requiring surgical correction or causing functional impairment	No sig diff in mean birth wts by plurality in IVF vs ICSI. Only 2 major malformations, both in ICSI grp 1) Neonatal complications – singletons: neo comp+ / neo comp- / Total ICSI: **51** / **71** / 122 IVF: **58** / **140** / 198 Total: 109 / 211 / 320 Value / Lower 95% CI / Upper 95% CI Odds rat: 1.73 / 1.08 / 2.78 Twins neo comp+ / neo comp- / Total ICSI: **41** / **123** / 164 IVF: **22** / **75** / 97 Total: 63 / 198 / 261 Value / Lower 95% CI / Upper 95% CI Odds rat: 1.14 / 0.63 / 2.05 Triplets neo comp+ / neo comp- / Total ICSI: **12** / **14** / 26 IVF: **8** / **9** / 17 Total: 20 / 23 / 43 Value / Lower 95% CI / Upper 95% CI Odds rat: 0.96 / 0.28 / 3.28	**Comments:** - No mention made of response rate - No objective assessment of outcomes by record review or exams (relied on parental reports) **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: - Adequate description of the cohort: - Use of validated method for genomic test: NR Use of validated method for ascertaining clinical outcomes: - Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Huang, Au, Chien, et al., 2006 **#52630**	**Geographical location:** Taipei, Taiwan **Study dates:** 1992-2001 **Size of population (no. of patients):** 194 twin sets Spontaneous conception (SC) n = 50 IUI n = 63 IVF/ICSI n = 81 **Study type:** Cohort	**Age:** SC: 31.8 (3.7) IUI: 32.1 (3.0) IVF/ICSI: 33.7 (4.6) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Twin births **Exclusion criteria:** - Hypertension - Diabetes - < 24 wk gestation - Higher-order multiples - Incomplete data	**Definition(s) of outcome(s):** Preterm birth Low birthweight	1) Preterm birth, IUV vs. spontaneous conception: PTB + / PTB - / Total IUI: **23** / **40** / 63 Spontaneous: **20** / **30** / 50 Total: 43 / 70 / 113 Value: 0.91 (Lower 95% CI 0.57, Upper 95% CI 1.46) Rel risk 2) Low birthweight, IUI vs. spontaneous conception: LBWT + / LBWT - / Total IUI: **29** / **34** / 63 Spontaneous: **18.5** / **31.5** / 50 Total: 47.5 / 65.5 / 113 Value: 1.24 (Lower 95% CI 0.79, Upper 95% CI 1.95) Rel risk 3) Preterm birth, IVF/ICSI vs. spontaneous: PTB + / PTB - / Total IVF/ICSI: **35** / **46** / 81 Spontaneous: **20** / **30** / 50 Total: 55 / 76 / 131 Value: 1.08 (Lower 95% CI 0.71, Upper 95% CI 1.65) Rel risk 4) Low birthweight, IVF/ICSI vs. spontaneous: LBWT + / LBWT - / Total IVF/ICSI: **39** / **42** / 81	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: - Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

Spon-taneous	**19**	**31**	50
Total	58	73	131

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.27	0.83	1.93

Hui, Lam, Tang, et al., 2005

#41860

Geographical location: Hong Kong, China

Study dates: 1998-2002

Size of population (no. of patients):
234 ART
401 spontaneous conceptions

Study type: Cohort

Age:
Mean (SD):
Controls: 36 (4)
Fresh IVF: 36 (3)
Fresh ICSI: 34 (4)
Frozen IVF: 35 (4)
Frozen ICSI: 33 (3)

Race/ethnicity (n [%]): NR

Diagnoses (n [%]): NR

Inclusion criteria:
- IVF or ICSI with fresh (n = 149) or frozen embryos (n = 85), "known to have normal karyotype or babies did not show signs of chromosomal abnormalities at birth"
- Controls:

Exclusion criteria:
-> 1 gestational sac on ultrasound at 5-6 weeks

Definition(s) of outcome(s):

PAPP-A
Free β-hCG

Multiples of the median at 10-14 weeks, adjusted for maternal weight

1) Median PAPP-A multiples of median:

Group	N	Median
Controls	401	1.00
Fresh		
IVF	95	0.83
ICSI	57	0.70
Frozen		
IVF	54	0.95
ICSI	31	0.66

2) Median free ß-hCG multiples of median:

Group	N	Median
Controls	401	1.00
Fresh		
IVF	95	0.87
ICSI	57	0.82
Frozen		
IVF	54	1.21
ICSI	31	0.96

Comments:
- No adjustment for multiple comparisons
- Proportion of women who would have been referred for testing not reported
- Relevant obstetric outcomes (IUGR, etc.) not reported
- Rates of chromosomal abnormalities in ART pregnancies not reported

Quality assessment:
Unbiased selection of the cohort (prospective recruitment of subjects): +
Large sample size: -
Adequate description of the cohort: -
Use of validated method for ascertaining exposure: +
Use of validated method for ascertaining clinical outcomes: -
Adequate follow-up period: +
Completeness of follow-up: +
Analysis (multivariate adjustments) and reporting of results: -

Hui, Tang, Lam, et al.,

Geographical location: Hong Kong, China

Age:
Mean age (± SD) for

Definition(s) of outcome(s):

1) False positives based on 1:186 risk from general population:

Comments:
- Unclear if dating for ART

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

<table>
<tr><th>Study</th><th>Study Design</th><th>Patients</th><th>Clinical Presentation</th><th>Results</th><th>Comments/Quality Scoring</th></tr>
<tr><td>2005

#9670</td><td>Study dates: Jan 1997-Dec 2002

Size of population (no. of patients):
16,673 spontaneous pregnancies
119 Fresh IVF
62 Frozen IVF
81 Fresh ICSI
39 Frozen ICS

Study type: Cohort</td><td>controls (31.7 ± 3.7) significantly lower than for all ART groups (33.6-35.8)

Race/ethnicity (n [%]):
- Asian: 96.5% spontaneous, 98% ART
- No Caucasians in ART group, 127 (0.8%) in spontaneous group

Diagnoses (n [%]): NR

Inclusion criteria:
- Singleton pregnancy
- Known “normal outcomes”

Exclusion criteria:
Unknown or abnormal fetal outcome, including chromosomal abnormalities</td><td>Nuchal translucency measured by ultrasound at 10-14 weeks

Mean gestational age in days calculated on basis of ultrasound measurement (86.1 ± 7.1) significantly lower in spontaneous compared to ART pregnancy by approximately 2 days</td><td><table><tr><th>Group</th><th>N in group</th><th>N false +</th><th>%</th></tr><tr><td>Controls</td><td>16673</td><td>834</td><td>5%</td></tr><tr><td>Fresh</td><td></td><td></td><td></td></tr><tr><td>IVF</td><td>119</td><td>12</td><td>10.1%</td></tr><tr><td>ICSI</td><td>62</td><td>9</td><td>14.5%</td></tr><tr><td>Frozen</td><td></td><td></td><td></td></tr><tr><td>IVF</td><td>81</td><td>7</td><td>8.6%</td></tr><tr><td>ICSI</td><td>39</td><td>3</td><td>10.3%</td></tr></table>2) Relative risk of false positive:<table><tr><th></th><th>False +</th><th>-</th><th>Total</th></tr><tr><td>ART +</td><td>31</td><td>270</td><td>301</td></tr><tr><td>Spont</td><td>864</td><td>15909</td><td>16773</td></tr><tr><td>Total</td><td>895</td><td>16179</td><td>17074</td></tr></table><table><tr><th></th><th>Value</th><th>Lower 95% CI</th><th>Upper 95% CI</th></tr><tr><td>Rel risk</td><td>2.00</td><td>1.42</td><td>2.81</td></tr></table></td><td>pregnancies based on day of transfer or ultrasound measurement
- No adjustment for multiple comparisons
- Other relevant obstetric outcomes (IUGR, etc) not reported
Rates of chromosomal abnormalities in ART pregnancies not reported

Quality assessment:
Unbiased selection of the cohort (prospective recruitment of subjects): +
Large sample size: -
Adequate description of the cohort: -
Use of validated method for ascertaining exposure: +
Use of validated method for ascertaining clinical outcomes: +
Adequate follow-up period: +
Completeness of follow-up: +
Analysis (multivariate adjustments) and reporting of results: -</td></tr>
<tr><td>Hui, Tang, Ng, et al., 2006

#52670</td><td>Geographical location: Hong Kong, China

Study dates: 2001-2003

Size of population (no. of patients):
3317 spontaneous singletons
19 spontaneous dichorionic twins
27 ART dichorionic twins

Study type: Cohort</td><td>Age: NR

Race/ethnicity (n [%]):
Singletons: 95.5% Asian
Twins: 93.5% Asian

Diagnoses (n [%]): NR

Inclusion criteria:
- Dichorionic twins
- Known normal outcomes

Exclusion criteria:
Trisomy, fetal demise</td><td>Definition(s) of outcome(s):

Nuchal translucency at 10-14 weeks, multiples of median, adjusted for gestational age</td><td>1) Nuchal translucency, multiples of median (calculated as if each twin independent observation):
Singleton: 1.00 (range, 0.12-3.24)
Spontaneous twin: 1.07 (range, 0.64-1.94)
ART twin: 1.02 (range, 0.61-1.87)</td><td>Comments:
- No adjustment for multiple comparisons
- Each twin assumed to be independent—no control for
- Small sample size
- False positive rates not reported
- Other obstetric outcomes not reported

Quality assessment:
Unbiased selection of the cohort (prospective recruitment of subjects): +
Large sample size: -
Adequate description of the cohort: +
Use of validated method for ascertaining exposure: +
Use of validated method for</td></tr>
</table>

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

<table>
<tr><th>Study</th><th>Study Design</th><th>Patients</th><th>Clinical Presentation</th><th>Results</th><th>Comments/Quality Scoring</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>ascertaining clinical outcomes: +
Adequate follow-up period: +
Completeness of follow-up: +
Analysis (multivariate adjustments) and reporting of results: -</td></tr>
<tr><td>Hvidtjorn, Grove, Schendel, et al., 2005

#41270</td><td>Geographical location:
Aarhus, Denmark

Study dates:
Jan 1995 - Dec 2000

Size of population:
IVF/ICSI 9,444, non-IVF 395,025

Study type:
All liveborns in study period, analyzed retrospectively for cerebral palsy by mode of conception and number of embryos transferred – idea was to assess risk of CP in IVF/ICSI children, and in IVF/ICSI pregnancies affected by vanishing twin</td><td>Age: NR

Race/ethnicity (n [%]):
NR

Diagnoses (n [%]): NR

Inclusion criteria:
All liveborn children born in Denmark during study period

Exclusion criteria: NR</td><td>Definition(s) of outcome(s):

CP children identified through National Register of Hospital Discharges (mandatory reporting, recorded prospectively).

F/u period 1-7yr</td><td>1) CP by mode of conception:

<table>
<tr><th></th><th>CP+</th><th>CP-</th><th>Total</th></tr>
<tr><td>IVF/ICSI</td><td>41</td><td>9403</td><td>9444</td></tr>
<tr><td>not</td><td>1016</td><td>394009</td><td>395025</td></tr>
<tr><td>Total</td><td>1057</td><td>403412</td><td>404469</td></tr>
</table>

<table>
<tr><th></th><th>Value</th><th>Lower 95% CI</th><th>Upper 95% CI</th></tr>
<tr><td>Odds rat</td><td>1.69</td><td>1.24</td><td>2.31</td></tr>
</table>

Results of IVF/ICSI pregnancies by plurality and by presence or absence of vanishing twin (#embryos transferred >1 for singletons, >2 for twins):

2) Singletons < 32w:

<table>
<tr><th></th><th>CP+</th><th>CP-</th><th>Total</th></tr>
<tr><td>van</td><td>4</td><td>79</td><td>83</td></tr>
<tr><td>no van</td><td>0.5</td><td>5</td><td>5.5</td></tr>
<tr><td>Total</td><td>4.5</td><td>84</td><td>88.5</td></tr>
</table>

<table>
<tr><th></th><th>Value</th><th>Lower 95% CI</th><th>Upper 95% CI</th></tr>
<tr><td>Odds rat</td><td>0.51</td><td>0.02</td><td>10.97</td></tr>
</table>

3) Twins < 32w:

<table>
<tr><th></th><th>CP+</th><th>CP-</th><th>Total</th></tr>
<tr><td>van</td><td>4</td><td>56</td><td>60</td></tr>
<tr><td>no van</td><td>4</td><td>230</td><td>234</td></tr>
<tr><td>Total</td><td>8</td><td>286</td><td>294</td></tr>
</table>

<table>
<tr><th></th><th>Value</th><th>Lower 95% CI</th><th>Upper 95% CI</th></tr>
<tr><td>Odds rat</td><td>4.11</td><td>1.00</td><td>16.93</td></tr>
</table>
</td><td>Comments:
- May have underestimated CP rate bc of wide range of f/u (some children may have been Dx'd after 1yo)
- Disproportionate # of IVF children had shorter f/u time (bc number of IVF treatments increased over study period), so may have underestimated CP disproportionately in this grp
- Could not assess for vanishing twins in non-IVF/ICSI pregnancies

Quality assessment:
Valid ascertainment of cases: +
Unbiased selection of cases: -
Appropriateness of the control population: +
Verification that the control is free of cancer: -
Comparability of cases and controls with respect to potential confounders: ?not stated
Validated dietary assessment method: NR
Appropriateness of statistical analyses: +</td></tr>
</table>

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				4) Singletons ≥ 32w: CP+ CP- Total van **16** **5090** 5106 no van **0.5** **487** 487.5 Total 16.5 5577 5593.5 Value Lower 95% CI Upper 95% CI Odds rat 3.06 0.18 51.18 5) Twins ≥ 32w: CP+ CP- Total van **4** **775** 779 no van **8** **2487** 2495 Total 12 3262 3274 Value Lower 95% CI Upper 95% CI Odds rat 1.60 0.48 5.34 Cox regression analysis including plurality at delivery, GA, amt age, sex, parity, education – showed increased risk of CP in pregnancies where # of gestations at delivery < # gestations originally transferred (HRR 2.30 [0.99,5.32])	
Hvidtjorn, Grove, Schendel, et	**Geographical location:** Denmark	**Age:** 23% of IVF mothers <30, compared to 70% of non-	**Definition(s) of outcome(s):**	1) SGA—IVF singletons: Out + Out - Total	**Comments:** None

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
al., 2006 **#52710**	**Study dates:** Children born between January 1995-December 2000 **Size of population (no. of patients):** 403,968 singleton/twins (307,960 mothers). 9255 (2.3%) from IVF (7000 mothers) **Study type:** Cohort	IVF mothers **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** All liveborn singleton and twins in Denmark during study period **Exclusion criteria:** NR	Cerebral palsy diagnosis in medical records—diagnostic tests not described	IVF + **250** **5435** 5685 IVF - **12266** **371653** 383919 Total 12516 377088 389604 Value / Lower 95% CI / Upper 95% CI Rel risk 1.38 1.22 1.56 2) SGA—IVF twins: Out + / Out - / Total IVF + **548** **3022** 3570 IVF - **1623** **9141** 10764 Total 2171 12163 14334 Value / Lower 95% CI / Upper 95% CI Rel risk 1.02 0.93 1.11 3) CP: IVF singletons: Out + / Out - / Total IVF + **20** **5665** 5685 IVF - **947** **382972** 383919 Total 967 388637 389604 Value / Lower 95% CI / Upper 95% CI Rel risk 1.43 0.92 2.22 4) CP:IVF twins: Out + / Out - / Total Exp + **20** **3550** 3570 Exp - **61** **10733** 10794 Total 81 14283 14364 Value / Lower 95% CI / Upper 95% CI Rel risk 0.99 0.60 1.64 5) Risk associated with IVF decreased, CI's cross 1 after controlling for SGA, prematurity. Number of cases too small to draw conclusions about specific treatments or diagnoses	**Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: - (discharge summary/registry data) Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results:+

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Isaksson, Gissler, and Tiitinen, 2002 **#1670**	**Geographical location:** Helsinki, Finland **Study dates:** Jan 1993-Mar 1999 **Size of population:** Study patients: 107 women with unexplained infertility, with 118 pregnancies Spontaneous controls (Ctrl I): 445 women/545 children of spontaneous pregnancies; ART controls (Ctrl II): 2377 women/2853 children of all other ART pregnancies **Study type:** Case-control	**Age:** Age data reported only categorically **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Pregnancies after IVF or ICSI to women with unexplained infertility at one hospital during study period - Ctrl groups chosen from Finnish Medical Birth Registry: I = women with non-assisted pregnancy, matched by age, parity, yr of delivery, mother's residence, plurality II = all women delivering singletons or twins after IVF, ICSI, or FET in southern Finland during study period **Exclusion criteria:** One set of triplets	**Definition(s) of outcome(s):** Delivery = live or stillbirth > 22 wk or BW > 500 g SGA = BW < -2SD of Finnish population mean for sex Major anomaly = significant congenital structural anomaly, chromosomal defect, or congenital hypothyroidism PIH = BP ≥ 140/90 after 20 wk, or increase in SBP ≥ 30 or DBP ≥ 15 Unexplained infertility = comprehensive infertility evaluation failed to reveal any apparent cause	Note raw data not given, just %s 1) C/S in singletons, study group vs. spontaneously conceived ctrls: C/S + / C/S - / Total Study: **17** / **52** / 69 Ctrl I: **70** / **275** / 345 Total: 87 / 327 / 414 Value (Lower 95% CI, Upper 95% CI) Odds rat: 1.28 (0.70, 2.36) 2) LBW in singletons, study grp vs. spont ctrls: LBW + / LBW - / Total Study: **2** / **67** / 69 Ctrl I: **20** / **325** / 345 Total: 22 / 392 / 414 Value (Lower 95% CI, Upper 95% CI) Odds rat: 0.49 (0.11, 2.12) Similarly, no difference in twins 3) LBW in sing, study grp vs. all ART: LBW + / LBW - / Total Study: **2** / **67** / 69 Ctrl II: **95** / **1806** / 1901 Total: 97 / 1873 / 1970 Value (Lower 95% CI, Upper 95% CI) Odds rat: 0.57 (0.14, 2.35) Similarly, no difference in twins 4) Major congenital anomalies in singletons, study grp vs. spont ctrls:	**Comments:** - Unclear whether ctrl grp II contains pregnancies conceived by ART with unexplained infertility (study grp) - Those in study grp were more likely married or cohabiting, nonsmokers than spont grp **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: + for grp I, for grp II, unclear how they differed from study subjects Verification that the control is free of cancer: NR Comparability of cases and controls with respect to potential confounders: - (see above) Validated dietary assessment method: NR Appropriateness of statistical analyses: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Anom + / Anom - / Total Study: **5** / **64** / 69 Ctrl I: **12** / **333** / 345 Total: 17 / 397 / 414 Value (Odds rat): 2.17; Lower 95% CI: 0.74; Upper 95% CI: 6.37 Similarly, no difference in twins 5) Major congenital anomalies in singletons, study grp vs. all ART: Anom+ / Anom- / Total Study: **5** / **64** / 69 Ctrl II: **84** / **1817** / 1901 Total: 89 / 1881 / 1970 Value (Odds rat): 1.69; Lower 95% CI: 0.66; Upper 95% CI: 4.31 Similarly, no difference in twins	
Jensen, Sharif, Svare El, et al., 2007 **#71490**	**Geographical location:** Denmark **Study dates:** 1965-1998 **Size of population (no. of patients):** 54,362 **Study type:** Cohort	**Age:** Median: 30 for first evaluation, 40 for follow-up **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Referred to Danish hospital or clinic for evaluation of infertility **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Breast cancer in Danish cancer registry	1) Adjusted risks for use of infertility drugs (compared to diagnosis of infertility and no treatment, adjusted for age at follow-up, calendar year, gravidity, and paritiy) Gonadotropins 1.20 (0.82-1.78) Clompihene 1.08 (0.85-1.39) hCG 0.94 (0.73-1.21) GnRH 1.28 (0.75-2.19) Progesterone 3.36 (1.60-7.07)	**Comments:** - Not adjusted for multple drug usage - Progesterone used as part of IVF regimen **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes:+ Adequate follow-up period: + Completeness of follow-up: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
					Analysis (multivariate adjustments) and reporting of results: +
Jun and Milki, 2004 **#13000**	**Geographical location:** Stanford, CA **Study dates:** 1998 – 2003 **Size of population:** N = 623 (258 cases of IVF + assisted hatching, 365 controls IVF w/o assisted hatching) **Study type:** Cohort	**Age:** Mean (SD): 37.6 (4.1) for cases 37.8 (5.3) controls **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - All clinical pregnancies conceived after day 3 transfers **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Clinical pregnancy = gestational sac on ultrasound or ectopic pregnancy diagnosed by ultrasound, laparoscopy, or absence of gestational sac and increasing hcg after negative D&C	1) Ectopic pregnancy associated with assisted hatching (AH): Ect + / Ect - Assisted hatching: 14 / 244 (258) Control: 8 / 357 (365) 22 / 601 (623) Rel risk 2.48 (Lower 95% CI 1.05, Upper 95 % CI 5.82)	**Comments:** There was no difference in the incidence of tubal disease between cases vs. controls; however, there are no data describing why assisted hatching was chosen among cases and not among controls, which could cause some bias in this retrospective study. **Quality assessment:** Valid ascertainment of cases: Unbiased selection of cases: Appropriateness of the control population: Verification that the control is free of cancer: Comparability of cases and controls with respect to potential confounders: Validated dietary assessment method: Appropriateness of statistical analyses:
Jun and Milki, 2007 **#71540**	**Geographical location:** Palo Alto, CA **Study dates:** Jan 1998-Dec 2005	**Age:** NR **Race/ethnicity (n [%]):** NR	**Definition(s) of outcome(s):** Ectopic pregnancy	1) Ectopic pregnancy: Out + / Out - / Total Frozen: **5** / **175** (180)	**Comments:** Tubal disease more common in frozen group (32.4% vs. 18.3%) **Quality assessment:**

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Size of population (no. of patients): 744 **Study type:** Cohort	**Diagnoses (n [%]):** NR **Inclusion criteria:** Fresh or frozen thawed blastocyst (day 5) transfer **Exclusion criteria:** NR		Fresh **10** **554** 564 Total 15 729 744 Value / Lower 95% CI / Upper 95% CI Rel risk 1.57 0.54 4.52	Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: - Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes:+ Adequate follow-up period:+ Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -
Kallen, Finnstrom, Nygren, et al., 2005 **#42180**	**Geographical location:** Stockholm, Sweden **Study dates:** 1982 - April 2001 **Size of population:** 16,280 IVF children **Study type:** Cohort (retrospective) Infants conceived by IVF compared to all infants born in study period registered with Swedish medical Birth Register	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** All infants born in study period registered with Swedish medical Birth Register **Exclusion criteria:** Embryo transfers after April 1, 2001	**Definition(s) of outcome(s):** Congenital malformation info obtained from diagnostic codes in Swedish Medical Birth Register, Swedish Registry of Congenital Malformations, and Swedish Hospital Discharge Register For IVF vs all births analysis, only SMBR data used (except for some specific anomalies). Then "weeded out" common conditions, "which are variable in registration, and sometimes associated with preterm birth & LBW" (preauricular appendix, PDA, SUA, undescended test, hip subluxation, minor skin malf)	1) Congenital malformations, IVF vs all births in SMBR: Malf+ / Malf- / Total IVF **811** **15469** 16280 all **80881** **1959062** 2039943 Total 81692 1974531 2056223 Value / Lower 95% CI / Upper 95% CI Odds rat 1.27 1.18 1.36 "weeded": Malf+ / Malf- / Total IVF **535** **15745** 16280 all **45892** **1994051** 2039943 Total 46427 2009796 2056223 Value / Lower 95% CI / Upper 95% CI Odds rat 1.48 1.35 1.61 Significantly elevated OR for many specific anomalies, IVF vs all (obs vs expected based on actual numbers from all 3 sources), adjusted for yr of birth, and excluding those with chromosomal anomalies (see Table 4, too many to put in table)	**Comments:** I believe #1 comparisons included IVF children in both grps **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: (see above) Verification that the control is free of cancer: - (see above) Comparability of cases and controls with respect to potential confounders: Validated dietary assessment method: NR Appropriateness of statistical analyses: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Adjustment made for yr of birth, maternal age, parity, yrs of involuntary childlessness (20% missing data), maternal smoking. Found OR's decreased after adjustment (became NS when all adjustments applied) 2) Malformations, IVF grp only by IVF method: Malf+ / Malf- / Total ICSI: **428** / **4521** / 4949 IVF: **913** / **10370** / 11283 Total: 1341 / 14891 / 16232 Value (Lower 95% CI – Upper 95% CI) Odds rat: 1.08 (0.95 – 1.21) Also looked at fresh vs frozen sperm, ejaculated vs epidiymal vs testicular sperm, no signif diff in any comparison.	
Kallen and Robert-Gnansia, 2005 **#38960**	**Geographical location:** Lund, Sweden **Study dates:** July 1995 - 2002 **Size of population:** 398 cases, 728,822 controls **Study type:** Case-control Cases of craniosynostosis identified, then compared to all women who gave birth during study period	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Cases: infants with craniosynostosis born 1995 - 2002 identified through Medical Birth Registry, Registry of Congenital Malformations, and Hospital Discharge Registry. **Exclusion criteria:** Infants with known chromosomal anomalies	**Definition(s) of outcome(s):** Expected number of exposures calculated from population data	1) treatment for infertility as risk factor: cran+ / cran- / Total infert+: **14** / **22756** / 22770 infert-: **384** / **706066** / 706450 Total: 398 / 728822 / 729220 Value (Lower 95% CI – Upper 95% CI) Odds rat: 1.13 (0.66 – 1.93) Specific drugs analyzed by observed: expected numbers of exposed women with infants with craniosynostosis; significant RR for first-trimester exposure to anticonvulsants (RR 6.9 [2.3-16.2])	**Comment :** - Not known what type of craniosynostosis cases had; some may have been due to genetic causes, not drug exposures. - Drug usage based on prescription data **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: + Verification that the control is free of cancer: Comparability of cases and controls with respect to potential confounders: + (age and smoking only) Validated dietary assessment method: NR Appropriateness of statistical

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
					analyses: +
Kanyo and Konc, 2003 **#15580**	**Geographical location:** Budapest, Hungary **Study dates:** Dec 1998 – Dec 1999 **Size of population:** 134 children born after laser-assisted hatching (LAH) 894 children born during same period after spontaneous conception (used as control grp) **Study type:** Cohort Assessed prenatal karyotype if available, perinatal data, major/minor malformations, neonatal problems. Record review + phone interviews after delivery, at 12 wks, 6 mos, and 1 yr. Divided into Grp I (>35yo), II (>3 IVF cycles), III (both >35yo and >3 IVF cycles)	**Age:** Mean (range): Grp I: 37.0 (35-44) Grp II: 32.1 (25-35) Grp III: 38.5 (36-44) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Consecutive first 96 deliveries after laser-assisted hatching (LAH) **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Major malformation = causing functional impairment or requiring surgical correction.	No data on C/S rates, fetal reduction Authors report major malformation rate of 3% at their hospital. 1) Laser-assisted hatching as risk factor for major malformation: Maj malform + / Maj malform - / Total LAH +: **2** / **132** / 134 Risk -: **27** / **867** / 894 Total: 29 / 999 / 1028 Value (Lower 95% CI – Upper 95% CI) Rel risk: 0.49 (0.12 – 2.05) 2) Laser-assisted hatching as risk factor for minor malformation: Min malform + / Min malform - / Total LAH +: **14** / **120** / 134 Risk -: **99** / **795** / 894 Total: 113 / 915 / 1028 Value (Lower 95% CI – Upper 95% CI) Rel risk: 0.94 (0.56 – 1.60)	**Comments:** - No power analysis; small sample size makes conclusions regarding safety invalid. - No data presented re: completeness of f/u **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): not prospective, but included all cases of LAH Large sample size: - Adequate description of the cohort: - Use of validated method for genomic test: NR Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: no data presented Analysis (multivariate adjustments) and reporting of results: -
Katalinic, Rosch, Ludwig, et al., 2004	**Geographical location:** Germany **Study dates:** 1993 -	**Age:** Mean (SD): ICSI: 32.9 (3.9) Controls: 27.0 (4.7)	**Definition(s) of outcome(s):** Major malformations	1) Major malformations: Malform + / Malform - / Total	**Comments:** None **Quality assessment:**

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#13020	2001 **Size of population:** 3,372 ICSI, 8,016 natural conception **Study type:** Cohort study	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Cases recruited after the 16th wk and followed through the pregnancy, 1998 - 2000 - Control newborns from 1993-2001 according to the same protocol for the study cohort - No other criteria described **Exclusion criteria:** NR	Secondary outcomes = maternal complications PTB < 37wks Preeclampsia (Pre-X) > 140/90 BP + proteinuria > 300 mg	ICSI **298** **3074** 3372 Natural **488** **7528** 8016 Total 786 10602 11388 Value / Lower 95% CI / Upper 95% CI Rel risk 1.45 1.26 1.67 2) Preterm birth: PTB + / PTB - / Total ICSI **363** **2324** 2687 Natural **568** **7370** 7938 Total 931 9694 10625 Value / Lower 95% CI / Upper 95% CI Rel risk 1.89 1.67 2.14 3) Preeclampsia: Pre-X + / Pre-X - / Total ICSI **269** **2418** 2687 Natural **578** **7360** 7938 Total 847 9778 10625 Value / Lower 95% CI / Upper 95% CI Rel risk 1.37 1.20 1.58 4) Placental abruption: Abrupt + / Abrupt - / Total ICSI **62** **2625** 2687 Natural **89** **7849** 7938 Total 151 10474 10625 Value / Lower 95% CI / Upper 95% CI Rel risk 2.06 1.49 2.84 5) Placenta previa: Previa + / Previa - / Total ICSI **53** **2634** 2687	Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for genomic test: NA Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: n/a Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

Natural	**28**	**7910**	7938
Total	81	10544	10625

	Value	Lower 95% CI	Upper 95% CI
Rel risk	5.59	3.54	8.82

6) Placental insufficiency:

	Insuff +	Insuff -	Total
ICSI	**103**	**2584**	2687
Natural	**83**	**7855**	7938
Total	186	10439	10625

	Value	Lower 95% CI	Upper 95% CI
Rel risk	3.67	2.75	4.88

7) Oligohydramnios:

	Oligo +	Oligo-	Total
ICSI	**65**	**2622**	2687
Natural	**87**	**7851**	7938
Total	152	10473	10625

	Value	Lower 95% CI	Upper 95% CI
Rel risk	2.21	1.61	3.03

8) Cervical incompetence:

	Incomp +	Incomp -	Total
ICSI	**270**	**2417**	2687
Natural	**496**	**7442**	7938
Total	766	9859	10625

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.61	1.40	1.85

9) Cesarean delivery in singletons only:

	C/S +	C/S -	Total
ICSI	**689**	**1093**	1782

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Natural **1366** **6768** 8134 Total 2055 7861 9916 Value / Lower 95% CI / Upper 95% CI Rel risk 2.30 2.13 2.48	
Klemetti, Gissler, and Hemminki, 2002 **#1330**	**Geographical location:** Finland **Study dates:** 1991-1993; 1998-1999 **Size of population (no. of patients):** All births in each time period **Study type:** Cohort	**Age:** 1998-1999: IVF: 39.3% ≥ 35 Non-IVF: 17.3% ≥ 35 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** All births in Finland **Exclusion criteria:** None	**Definition(s) of outcome(s):** Single pregnancies Multiple gestations	1) Adjusted OR*, singleton pregnancies, ART vs non-ART, 1998-1999: OUTCOME / OR / 95% CI Maternal Antepartum hospitalization 2.23 2.03,2.46 >7 days in hospital 1.37 1.11,1.70 C-section 1.30 1.17,1.45 Neonatal Weigh < 2500 gm 1.70 1.39,2.09 Gest age <37 weeks 1.79 1.52,2.11 1 min Apgar 0-6 1.35 1.11,1.65 >7 days in hospital 1.86 1.60,2.16 Perinatal mortality 1.27 0.59,2.70 *Adjusted for county of residence, smoking, age, marital status, previous pregnancies, previous deliveries 2) Adjusted OR*, multiple gestations, ART vs non-ART, 1998-1999: OUTCOME / OR / 95% CI Maternal Antepartum hospitalization 1.66 1.31,2.10 >7 days in hospital 1.02 0.78,1.34 C-section 1.12 0.89,1.40 Neonatal Weigh < 2500 gm 1.12 0.96,1.31 Gest age <37 weeks 1.45 1.24,1.68 1 min Apgar 0-6 1.23 0.99,1.54 >7 days in hospital 1.24 1.04,1.44 Perinatal mortality 0.84 0.40,1.75	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: - Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period:+ Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				*Adjusted for county of residence, smoking, age, marital status, previous pregnancies, previous deliveries 3) Risks for all outcomes decreased from 1991-1993 to 1998-1999, largely due to decrease in higher-order multiples.	
Klemetti, Gissler, Sevon, et al. 2005 **#39840**	**Geographical location:** Oulu, Finland **Study dates:** ART 1996 - 1998 **Size of population:** IVF 4,559, other ART 4,467, controls 27,078 **Study type:** Case-control Register-based; identified cases (conceived by ART) then randomly selected controls (naturally-conceived) in 3:1 ratio	**Age:** Mean (SD): IVF 33.9 (4.5) Other ART 31.2 (4.6) Controls 29.8 (5.3) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Cases: Children born to women after ART 1996 - 1998 in Finland. Controls: naturally-conceived children randomly selected from Medical Birth Register **Exclusion criteria:** Controls excluded those conceived through IVF or other ART	**Definition(s) of outcome(s):** Cases & controls linked to Finnish Register of Congenital Malformations (collects info on all infants with congenital anomaly or birth defect through delivery info, neonatal, pedi, and path depts., and cytogenetic labs, and by linkage to other national registers. Congenital anomaly = major congenital structural anomaly, chromosomal defect, or congenital hypothyroidism. Physician reviewed Dx blinded to mode of conception.	1) Any congenital anomaly, IVF singletons: anom+ / anom- / Total IVF: **125** / **2805** / 2930 Ctrl: **756** / **25733** / 26489 Total: 881 / 28538 / 29419 Value / Lower 95% CI / Upper 95% CI Odds rat: 1.52 / 1.25 / 1.84 Other art singletons: anom+ / anom- / Total other: **138** / **3788** / 3926 Ctrl: **756** / **25733** / 26489 Total: 894 / 29521 / 30415 Value / Lower 95% CI / Upper 95% CI Odds rat: 1.24 / 1.03 / 1.49 IVF multiples: anom+ / anom- / Total IVF: **70** / **1559** / 1629 Ctrl: **31** / **558** / 589 Total: 101 / 2117 / 2218 Value / Lower 95% CI / Upper 95% CI Odds rat: 0.81 / 0.52 / 1.25 Other art multiples: anom+ / anom- / Total	**Comments:** - ART moms more often married, nulliparous, upper class. - More multiples in ART grps. **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: + Verification that the control is free of cancer: + Comparability of cases and controls with respect to potential confounders: - Validated dietary assessment method: NR Appropriateness of statistical analyses: - (not adjusted by potential confounders)

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Other **27** **514** 541 Ctrl **31** **558** 589 Total 58 1072 1130 Value / Lower 95% CI / Upper 95% CI Odds rat 0.95 0.56 1.61 Data given also by organ system, and by gender.	
Klip, Burger, de Kraker, et al., 2001 **#3670**	**Geographical location:** Amsterdam, Netherlands **Study dates:** Women in cohort diagnosed 1980 - 1995 **Size of population:** 9,479 cases, 7,521 controls **Study type:** Cohort of women with infertility in registry, mailed questionnaire to assess for cancer in offspring	**Age:** Mean (SD): given as categorical ranges **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Original cohort of women unable to achieve conception after >=1yr, >18yo at first visit to fertility clinic. Of these, women alive on 1/1/97 were mailed questionnaire. Eligible offspring were >=26wks or 1000g. Exposed = conceived by IVF, insemination, fertility drug use. Control = no IVF. **Exclusion criteria:** From questionnaire: Death, incomplete or foreign address, emigration, privacy reason Excluded from pregnancies: miscarriages, stillbirths, not yet born at time of	**Definition(s) of outcome(s):** CA in offspring of ART conceptions Average f/u was 6yr (4.6yr in exposed, 7.8yr in ctrl)	1) Any CA: CA+ / CA- / Total Observed **7** **9465** 9472 Expected **7.1** **9464.9** 9472 Total 14.1 18929.9 18944 Value / Lower 95% CI / Upper 95% CI Odds rat 0.99 0.35 2.80 2) Leukemia: leuk+ / leuk- / Total Observed **3** **9469** 9472 Expected **2.3** **9469.7** 9472 Total 5.3 18938.7 18944 Value / Lower 95% CI / Upper 95% CI Odds rat 1.30 0.23 7.27	**Comments:** - Response rate 66.9% - Open-ended questions, not specific to cancer **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: + Use of validated method for genomic test: NR Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: - Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		interview, unknown gender, unknown birthdate, unknown exposure status.			
Koivurova, Hartikainen, Gissler, et al. 2002 **#2150**	**Geographical location:** Oulu, Finland **Study dates:** 1990 - 95 **Size of population:** 304 IVF, 569 controls, 103 twin controls **Study type:** Cohort	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Register of IVF clinic at 2 centers which cover all IVF in northern Finland provided study grp. 2 control grps: I – chosen at random from Finnish Med Birth Register, matched for sex, yr of birth, area of residence, parity, mat age, social class II – multiples randomly chosen and matched as above **Exclusion criteria:** No triplets & quads for matching available; excluded for analysis stratified for plurality, but included in population-based analyses	**Definition(s) of outcome(s):** 3yr f/u of records Perinatal mortality rate includes stillbirths from >22wks or BW >=500g. Early neonatal mortality = neonatal deaths <7d from birth Late neonatal mort 7-27d Mortality rates compared with national figures from FMBR for northern Finland	1) Preterm birth <3 7wks: PTB+ / PTB- / Total IVF: **95** / **209** / 304 Ctrl I: **44** / **525** / 569 Total: 139 / 734 / 873 Value / Lower 95% CI / Upper 95% CI Odds rat: 5.42 / 3.67 / 8.02 But significance disappears when comparing singletons to sing & twins to twins 2) Major malformations: Malf+ / Malf- / Total IVF: **20** / **284** / 304 Ctrl I: **25** / **544** / 569 Total: 45 / 828 / 873 Value / Lower 95% CI / Upper 95% CI Odds rat: 1.53 / 0.84 / 2.81	**Comments:** Trips/quads not matched for but still included in population-based analyses **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: - Use of validated method for genomic test: NR Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
Koivurova, Hartihainen, Karinen, et al., 2002 **#770**	**Geographical location:** Oulu, Finland **Study dates:** 1990-95 **Size of population:** 305 IVF, 671 Controls	**Age:** Mean: IVF: 31.8 Controls: 31.8 Range: IVF: 23-40 Controls: 19-40	**Definition(s) of outcome(s):** Gestational HTN = BP 140/90 or 30/15 Preex > 300 mg prot/24h	1) Threatened PTB, singletons: Threat PTB + / Threat PTB - / Total IVF: **22** / **131** / 153 Ctrl: **47** / **533** / 580	**Comments:** Data obtained from same source for both groups (FMBR) **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Study type: Cohort	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 25% Male factor: 16% Tubal factor: 41% Endometriosis, mixed, hormonal: 17% **Inclusion criteria:** - IVF pregnancies from registers of 2 clinics covering all IVF pregnancies in northern Finland > 22 wk or ≥ 500 g - Controls chosen from FMBR as in previous study; I = general population, II = matched for plurality **Exclusion criteria:** - < 22 wk - < 500 g	Threatened preterm birth = ctxs w/ or w/o cvx change requiring hospitalization	Total 69 664 733 Value / Lower 95% CI / Upper 95% CI Odds rat 1.90 1.11 3.27 2) Threatened PTB, twins: Threat PTB + / Threat PTB - / Total IVF **23** **39** 62 Ctrl **36** **46** 82 Total 59 85 144 Value / Lower 95% CI / Upper 95% CI Odds rat 0.75 0.38 1.48 C/S rates 25% in both IVF and control groups for singletons For firstborn twins, 53% (IVF), 46% (controls)	subjects): - Large sample size: + Adequate description of the cohort: + Use of validated method for genomic test: NR Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: NR Completeness of follow-up: NR Analysis (multivariate adjustments) and reporting of results: +
Kolibianakis, Osmanagaoglu, De Catte, et al., 2003 **#17460**	**Geographical location:** Brussels, Belgium **Study dates:** 1992 - 2000 **Size of population:** 685 amnio, 143 CVSs	**Age:** Mean (SD): Amnio – 32.4 (0.2) CVS – 33.8 (0.4) Median: NR Range: Amnio – 20-47	**Definition(s) of outcome(s):** Preterm delivery (< 37w) Low birthwt (< 2500g) VLBW (< 1500g)	1) CVS vs amnio as risk for fetal loss in ICSO population: Fetal loss+ / Fetal loss - / Total CVS **5** **130** 135 Amnio **6** **674** 680	**Comments:** - Not possible to randomize choice of procedure. - Maternal age lower in amnio grp compared to CVS. CVS known to have higher loss rate than amnio. Would not expect difference in ICSI population.

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Study type: Case-control Compared outcomes of ICSI pregnancies in which amniocentesis was performed, to those in which CVS was performed.	CVS – 22-50 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** See study type **Exclusion criteria:** NR	Fetal loss	Total 11 804 815 Value / Lower 95% CI / Upper 95% CI Odds rat 4.32 1.30 14.37 No sig diff in PTD rate, LBW, or VLBW	- Even so, this loss rate is higher than other series (most report loss rate for CVS of 1%, compared to 3% in this series), for amnio of 0.5%, compared to 0.9% in this series. **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: - Appropriateness of the control population: + Verification that the control is free of cancer: n/a Comparability of cases and controls with respect to potential confounders: - Validated dietary assessment method: - Appropriateness of statistical analyses: +
Koudstaal, Braat, Bruinse, et al., 2000 **#7340**	**Geographical location:** Amsterdam, Netherlands **Study dates:** NR (care established before end of 1992; published 2000) **Size of population:** 307 IVF, 307 control pregnancies **Study type:** Cohort	**Age:** Mean (SD): IVF 32.8 (4.3) Control: 32.7 (4.4) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Pregnancies > 16 wk; IVF pregnancies established before end of 1992, with prenatal care at hospital that performed the procedure. - Controls from registry of same hospital, matched for LMP w/I 2 yr, parity, ethnic origin, del date w/I 2 yr of case, height (w/i 10 cm), weight (w/I 10 kg), smoking status, ob & med	**Definition(s) of outcome(s):** SGA = birthwt < 10%ile for national reference curve LBW < 2500 g Stillbirth ≥ 500 g Neonatal death 7 d Perinatal mortality = IUFD + neonatal deaths / Total live + stillbirths	No diff in PIH, hyperemesis, GDM, poly, abruption, PPROM, FGR, previa, malformations. Raw data not given, but VB more common in IVF grp: 1st trim 21.2% vs 13.7% 2nd trim 7.8% vs 2.0% 3rd trim 8.6% vs 3.9% IVF pts spent more days on admission in hosp than controls (4.6 ± 10.2 vs 2.5 ± 5.4) Raw data not given for these, only %: 1) Elective (non-labored) C/S: C/S + / C/S - / Lower / Upper IVF 27 280 307 Control 13 294 307 40 574 614	**Comments:** Similar weight, height, BMI, cigarette use, EtOH use, primiparity, h/o PTD, congenital malformations, IUFD, neonatal mortality, C/S, PIH, GDM between groups. **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): Large sample size: Adequate description of the cohort: Use of validated method for genomic test: NR Use of validated method for ascertaining clinical outcomes: Adequate follow-up period: NR Completeness of follow-up: NR Analysis (multivariate adjustments) and reporting of results:

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		hx for "factors that might influence outcome of subsequent pregnancy" **Exclusion criteria:** - FET, reductions, IVF pregnancies for whom no suitable control could be found - Did not exclude pregnancies w/vanishing twin		Rel risk 2.08 (95% CI 1.09, 95 % CI 3.95) 2) LBW: IVF: LBW + 42, LBW - 265, 307 Control: LBW + 21, LBW - 286, 307 63, 551, 614 Rel risk 2.00 (Lower 95% CI 1.21, Upper 95 % CI 3.30) 3) PTD: Study drug: Preg + 46, Preg - 261, 307 Control: Preg + 18, Preg - 289, 307 64, 550, 614 Rel risk 2.56 (Lower 95% CI 1.52, Upper 95 % CI 4.30)	
Koudstaal, Bruinse, Helmer-horst, et al. 2000 **#8180**	**Geographical location:** Amsterdam, Netherlands **Study dates:** IVF preg established before end of 1992 (published 2000) **Size of population:**	**Age:** Mean (SD): IVF 31.7 (3.6), ctrl 31.2 (3.4) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR	**Definition(s) of outcome(s):** PTD < 37wks SGA < 10%ile by national reference curve	No difference in PIH, GDM, previa, PPROM, ut ctxs, elective C/S, induction perinatal mortality, congenital malformations. Raw data not shown, but vaginal bleeding more common in IVF (32.3% vs 18.8%) 1) PTD:	**Comments:** - No mention of matching for ob/med hx as in singleton study from this grp. - Similar parity, h/o PTD, IUFD, PIH, C/S **Quality assessment:**

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	96 IVF, 96 ctrl **Study type:** Case-control	**Inclusion criteria:** Pregnancies >16wks; IVF pregnancies established before end of 1992, with prenatal care at hospital that performed the procedure. Ctrls from registry of same hospital as cases, matched for mat age, parity, ethnic origin, del dat w/I 3yr, ht, wt, smoking status, prenatal care site **Exclusion criteria:** FET, reductions	LBW > 500g and ≤ 2500g Stillbirth ≥ 500g Neonatal death = death of liveborn ≥ 500g within 1st wk after birth C/S elective if performed before labor	PTD+ / PTD- / Total IVF **49** / **47** / 96 Ctrl **40** / **56** / 96 Total 89 / 103 / 192 Value (Lower 95% CI – Upper 95% CI) Odds rat 1.46 (0.83 – 2.58) 2) C/S per child: PTD+ / PTD- / Total IVF **77** / **115** / 192 Ctrl **59** / **133** / 192 Total 136 / 248 / 384 Value (Lower 95% CI – Upper 95% CI) Odds rat 1.51 (0.99 – 2.30)	Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: + Verification that the control is free of cancer: NR Comparability of cases and controls with respect to potential confounders: + Validated dietary assessment method: NR Appropriateness of statistical analyses: +
Kozinszky, Zadori, Orvos, et al. 2003 **#15900**	**Geographical location:** Szeged, Hungary **Study dates:** Jan 1995 – Dec 2001 **Size of population:** 376 pregnancies after ART, 12,920 deliveries total **Study type:** Case-control Pregnancies conceived by ART, controls conceived spontaneously matched 1:1 by G/P, maternal age, previous obstetric outcome.	**Age:** Mean (SD): ART – 32.3 (4) Spont – 32.0 (4.1) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** All deliveries at one hospital during study period **Exclusion criteria:** Triplet pregnancies (IVF 12, OI 5) were analyzed w/o spontaneous controls. No other exclusions reported	**Definition(s) of outcome(s):** IUGR defined as birthwt <10th %ile for GA, according to Hungarian data	No diff in any outcome except slightly lower birthweight for spontaneous twins 1) Cesarean for singletons: C/S + / C/S - / Total ART **117** / **167** / 284 Spont **98** / **186** / 284 Total 215 / 353 / 568 Value (Lower 95% CI – Upper 95% CI) Odds rat 1.33 (0.95 – 1.87) 2) FGR for singletons: FGR+ / FGR - / Total ART **18** / **266** / 284 Spont **12** / **272** / 284 Total 30 / 538 / 568 Value (Lower 95% CI – Upper 95% CI)	**Comments:** None **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: + Verification that the control is free of cancer: NR Comparability of cases and controls with respect to potential confounders: + Validated dietary assessment method: NR Appropriateness of statistical analyses: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Odds rat 1.53 0.72 3.25 3) Major malformations for singletons: ART **9** **275** 284 Spont **5** **279** 284 Total 14 554 568 Odds rat 1.83 0.60 5.52	
Kozinszky, Zadori, Orvos, et al., 2003 **#16940**	**Geographical location:** Szeged, Hungary **Study dates:** Jan 1995-May 2001 **Size of population:** 259 ART, 518 controls **Study type:** Case-control ART pregnancies (ART = mix of IVF, OI, and IUI) identified, compared to matched controls, presumably during same study period	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Live, singleton pregnancies resulting from ART - Controls spontaneously conceived, matched for G, P, maternal age (2:1) **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Congenital malformations diagnosed by neonatologist Preeclampsia not defined	1) Cesarean section: ART **110** **149** 259 Ctrl **143** **375** 518 Total 253 524 777 Odds rat 1.94 1.42 2.65 2) Congenital malformations: ART **7** **252** 259 Ctrl **13** **505** 518 Total 20 757 777 Odds rat 1.08 0.43 2.74 3) Preeclampsia: ART **45** **214** 259 Ctrl **58** **460** 518 Total 103 674 777	**Comments:** - ART group more likely to have GDM than controls - No info regarding planned vs unplanned cesarean, or indications **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: + Verification that the control is free of cancer: + Comparability of cases and controls with respect to potential confounders: + Validated dietary assessment method: NR Appropriateness of statistical analyses: - (no multivariate adjustments)

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Odds rat: Value 1.67, Lower 95% CI 1.09, Upper 95% CI 2.54 4) Preterm birth: ART: PTB + **33**, PTB - **226**, Total 259 Ctrl: PTB + **57**, PTB - **461**, Total 518 Total: PTB + 90, PTB - 687, Total 777 Odds rat: Value 1.18, Lower 95% CI 0.75, Upper 95% CI 1.87	
Kristiansson, Bjor, and Wramsby, 2007 **#53260**	**Geographical location:** Sweden **Study dates:** Registered for 1st birth between Jan 1981-Dec 2001 **Size of population (no. of patients):** 647,704 **Study type:** Cohort	**Age:** Mean (SD) age at conception: IVF: 32.8 (3.7) Non-IVF: 26.7 (4.3) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Registered for 1st birth during study period - Exposure: Treated with IVF/ICSI **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Cancer cases from Swedish national registry	1) Adjusted* rate ratios, date of conception plus 3 years used as start of followup: CIS of cervix RR 0.86 (0.60-1.19) All non-invasive 0.87 (0.64-1.16) Breast 0.74 (0.40-1.26) All invasive 1.00 (0.71-1.36) *Adjusted for age at followup, age at first conception, calendar year at followup, number of parities and multiple births. 2) CIS of cervix significantly lower in IVF subjects when date of conception used as start of followup (0.7, 95% CI 0.52, 0.92).	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
Kuwata, Matsubara, Ohkuchi, et al., 2004 **#11910**	**Geographical location:** Tochigi, Japan **Study dates:** Jan 1990-July 2001 **Size of population (no.**	**Age:** Mean (SD): Median: 29.5 spontaneous, 30.5 ovulation induction, 31.5-34.5 ART Range:	**Definition(s) of outcome(s):** Congenital anomalies (ICD-10)	1) Adjusted odds ratios (adjusted for maternal age only): Spontaneous conception OR 1.00 (ref) Ovulation OR 2.3 (0.7,7.3	**Comments:** - Potential for referral bias—unclear what criterion were for referral **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results			Comments/Quality Scoring
	of patients): 406 (94 spontaneous) **Study type:** Cohort	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Dichorionic twin gestation followed at hospital - Delivery at ≥24 weeks **Exclusion criteria:** - Referred after 20 weeks or referred for malformation - Frozen embryo transfer		induction GIFT IVF ICSI	 3.7 3.5 6.7	 1.2,11.8 1.1,11.5 2.1,21.9	subjects): - Large sample size: - Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
La Sala, Nucera, Gallinelli et al., 2004 **#12490**	**Geographical location:** Reggio Emilia, Italy **Study dates:** Jan 1992-Dec 2002 **Size of population:** 1072 ART pregnancies (440 IVF, 567 ICSI) **Study type:** Cohort study	**Age:** Mean (SD): 34.2 (4.0) **Race/ethnicity (n [%]):** > 95% Italian **Diagnoses (n [%]):** NR **Inclusion criteria:** Day 2-3 transfer w/o hatching **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Embryo = presence of cardiac activity on US	1) Total pregnancy loss after 2 embryos on 1st trimester US, by age 35: SAb + / SAb - / Total ≥ 35: **19** / **89** / 108 < 35: **11** / **142** / 153 Total: 30 / 231 / 261 Value (Lower 95% CI, Upper 95% CI) Rel risk: 2.45 (1.21, 4.93) 2) Total pregnancy loss after 1 embryo on 1st trimester u/s, by age 35: SAb + / SAb - / Total ≥ 35: **75** / **196** / 271 < 35: **75** / **235** / 310 Total: 150 / 431 / 581 Value (Lower 95% CI, Upper 95% CI) Rel risk: 1.14 (0.87, 1.51)	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: + Use of validated method for genomic test: NA Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: NA Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
La Sala, Nucera, Gallinelli, et al., 2004 **#11720**	**Geographical location:** Reggio Emilia, Italy **Study dates:** Jan 1992-Dec 2002 **Size of population:** 962 **Study type:** Retrospective cohort study	**Age:** Mean (SD): 34.2 (4.0) **Race/ethnicity (n [%]):** > 95% Italian **Diagnoses (n [%]):** NR **Inclusion criteria:** Patients undergoing IVF or ICSI **Exclusion criteria:** Loss to f/u or incomplete or spurious entries	**Definition(s) of outcome(s):** Embryonic loss rate from 1st to 2nd trimester as # embryos on 1st trimester US compared to # embryos on 2nd trimester US	Total loss of all embryos 1) Starting 4 embryos 1st trimester: **< 35 yo**: total loss+ / total loss- / Total IVF: **1** / **12** / 13 ICSI: **1** / **10** / 11 Total: 2 / 22 / 24 Value (Lower 95% CI, Upper 95% CI) Rel risk: 0.85 (0.06, 12.01) **≥ 35 yo**: total loss+ / total loss- / Total IVF: **1** / **3** / 4 ICSI: **1** / **5** / 6	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: - Adequate description of the cohort: - Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

Total 2 8 10

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.50	0.13	17.67

2) Starting 3 embryos 1st trimester:

< 35 yo	total loss+	total loss-	Total
IVF	**2**	**26**	28
ICSI	**1**	**18**	19
Total	3	44	47

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.36	0.13	13.93

≥ 35 yo	total loss+	total loss-	Total
IVF	**2**	**20**	22
ICSI	**2**	**15**	17
Total	4	35	39

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.77	0.12	4.94

3) Starting 2 embryos 1st trimester:

< 35 yo	total loss+	total loss-	Total
IVF	**8**	**78**	86
ICSI	**3**	**64**	67
Total	11	142	153

	Value	Lower 95% CI	Upper 95% CI
Rel risk	2.08	0.57	7.53

≥ 35 yo	total loss+	total loss-	Total
IVF	**13**	**44**	57
ICSI	**6**	**45**	51
Total	19	89	108

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.94	0.80	4.72

4) Starting 1 embryo 1st trimester:

< 35 yo	total loss+	total loss-	Total
IVF	**40**	**120**	160
ICSI	**34**	**116**	150
Total	74	236	310

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.10	0.74	1.64

≥ 35 yo	total loss+	total loss-	Total
IVF	**51**	**122**	173
ICSI	**25**	**73**	98
Total	76	195	271

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.16	0.77	1.74

Lambert-Messerlian, Dugoff, Vidaver, et al., 2006

#53400

Geographical location: Boston, MA; New York, NY; Salt Lake City, Provo, and Ogden, UT; Seattle, WA; Royal Oak, MI; Chapel Hill, NC

Study dates: NR, but subset of larger trial with reference given

Size of population (no. of patients):
IVF with ovulation induction: 277
IUI with ovulation

Age: NR

Race/ethnicity (n [%]): NR (adjusted in analysis)

Diagnoses (n [%]): NR

Inclusion criteria: ART singleton pregnancies

Exclusion criteria: NR

Definition(s) of outcome(s):

1st and 2nd trimester serum marker multiple of median, adjusted for gestational age, maternal race, diabetes, weight

Screen positive rate calculated at risk of 1:150 for 1st trimester markers, 1:300 for 2nd trimester markers

Markers:

1) Observed vs expected screen positive rates, 1st trimester markers:

Group	Observed (95% CI)		Expected
IVF-OI	8.6	5.3,11.9	5.5
IUI-OI	3.4	1.4,5.4	4.2
IUI	6.1	3.1,9.1	4.2
IVF-OI-ED	3.4	0,8.0	2.5
IVF-ED	1.8	0,5.3	1.0

2) Observed vs expected screen positive rates, 2nd trimester markers:

Group	Observed (95%	Expected

Comments:
- Adjusted for multiple comparisons by using p<0.01 as level of significance
- Other OB outcomes not reported
- No sample size estimate—confidence intervals wide

Quality assessment:
Unbiased selection of the cohort (prospective recruitment of subjects): +
Large sample size: -
Adequate description of the cohort: +
Use of validated method for

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	induction: 323 IUI alone: 247 IVF-OI with embryo donation 59 IVF-ED 56 Non-ART: 37,070 **Study type:** Cohort		1st trimester: Nuchal translucency PAPP-A Free ß-hCG 2nd trimester: AFP uE3 hCG Inhibin A	<table><tr><td></td><td>CI)</td><td></td><td></td></tr><tr><td>IVF-OI</td><td>20.2</td><td>15.4,25.0</td><td>14.7*</td></tr><tr><td>IUI-OI</td><td>21.2</td><td>16.6,25.7</td><td>11.9*</td></tr><tr><td>IUI</td><td>19.1</td><td>14.1,24.0</td><td>12.3*</td></tr><tr><td>IVF-OI-ED</td><td>12.3</td><td>3.8,20.8</td><td>7.4</td></tr><tr><td>IVF-ED</td><td>7.4</td><td>0.4,14.4</td><td>3.9</td></tr></table> *p < 0.01	ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
Lerner-Geva, Geva, Lessing, et al., 2003 **#17260**	**Geographical location:** Tel Aviv, Israel **Study dates:** Treatment for infertility 1984-92; case ascertainment through Israel National Cancer Registry through Dec 1996 **Size of population (no. of patients):** 1082; Standardized Incidence Ratio calculated for Israeli population **Study type:** Cohort	**Age:** Mean (SD): At treatment: 32.7 (4.8) At follow-up: 38.7 (5.2) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 38 (3.5%) Male factor: 326 (30.1%) Other (specify): Mechanical: 456 (42.1%) **Inclusion criteria:** Treated with IVF at Tel Aviv Medical Center **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Cancer cases by site in Israel National Cancer Registry	1) Standardized incidence ratios: <table><tr><th>Site</th><th>SIR</th><th>95% CI</th></tr><tr><td>Breast</td><td>1.02</td><td>0.33-2.39</td></tr><tr><td>Ovary</td><td>5.0</td><td>1.02-14.6</td></tr><tr><td>Cervix</td><td>4.6</td><td>0.93-13.5</td></tr><tr><td>Other</td><td>2.05</td><td>0.98-3.78</td></tr></table> Other cancers: melanoma (2), Hodgkin's lymphoma (2), multiple myeloma, angiosarcoma, brain, sarcoma, rectum, vulva. SIRs decreased when cancers diagnosed within 1st year of treatment were excluded.	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: - Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
Lerner-Geva,	**Geographical location:** Israel	**Age:** NR	**Definition(s) of outcome(s):**	1) SIR 1.14 (0.95-1.40) — subjects vs. general population	**Comments:** Tubal disease more common in

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Keinan-Boker, Blumstein, et al., 2006 **#71800**	**Study dates:** 1964-1984 for treatment, follow-up completed through Dec 1996 **Size of population (no. of patients):** 5,788 **Study type:** Cohort	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Seen at one of 5 infertility clinics between 1964-1984 **Exclusion criteria:** Records unavailable	Breast cancer in national registry	2) Breast cancer incidence, treated infertility vs. untreated infertility: Treated infert: **73** / **3003** / 3076 No treatment: **58** / **2654** / 2712 Total: 131 / 5657 / 5788 Rel risk: 1.11 (0.79 – 1.56) 3) Risk increased for women treated with clomiphene compared to other infertile women (hazard ratio 1.45, 95 CI 1.10,1.89)	frozen group **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: - Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results:
Lidegaard, Pinborg, and Andersen, 2005 **#9350**	**Geographical location:** Copenhagen, Denmark **Study dates:** Jan 1995 – Dec 2001 **Size of population:** 442,349 non-IVF, 6,052 IVF **Study type:** Cohort study	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - All singletons born in Denmark - IVF pregnancies identified by IVF registry **Exclusion criteria:** Twins & other multiples Each child only allowed to be counted once with Dx in each of 5 main Dx grps	**Definition(s) of outcome(s):** Diagnosis codes for known imprinting diseases used, as well as codes for diseases that might have been used in children with symptoms but no diagnosis of specific disorder Mean f/u time 4.5 yr for non-IVF group, 4.1 yr for IVF	1) No difference in rates of childhood cancers, mental diseases, congenital syndromes, or developmental disturbances between grps (data not given). 2) Imprinting disorders: IVF: **0.5** / **6052** / 6052.5 non-IVF: **54** / **442295** / 442349 Total: 54.5 / 448347 / 448401.5 Rel risk: 0.68 (0.04 – 10.96) 3) CP: IVF: **20** / **6032** / 6052 Non-IVF: **819** / **441530** / 442349 Total: 839 / 447562 / 448401	**Comments:** - Limitations of using diagnosis codes to define outcome - Outcome considered is rare – even with large sample size did not have any cases in IVF grp - CP finding interesting, but no adjustment made for gestational age at delivery **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - not prospective, but unbiased Large sample size: + Adequate description of the cohort: + Use of validated method for genomic test: NA Use of validated method for ascertaining clinical outcomes: - Adequate follow-up period: ? Completeness of follow-up: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Value / Lower 95% CI / Upper 95% CI Rel risk 1.78 / 1.15 / 2.78	Analysis (multivariate adjustments) and reporting of results: -
Ludwig and Katalinic, 2002 **#540**	**Geographical location:** Lubeck and Mainz, Germany **Study dates:** Aug 1998-Aug 2000 for exposed, 1990-1998 for unexposed **Size of population (no. of patients):** ICSI:2687 pregnancies (3372 children), 30940 (unexposed) **Study type:** Cohort	**Age:** Mean (SD): ICSI 32.9 (3.9); spontaneous: 28.7 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Ongoing pregnancy 16 weeks after ICSI (exposed) - Published data from birth registry (unexposed) **Exclusion criteria:** - Frozen embryo transfer - IVF in same cycle	**Definition(s) of outcome(s):** Major malformations: structural defects of body and/or organs, affecting viability and quality of life and requiring medical intervention	1) Major malformation: Out + / Out - / Total ICSI + **291** / **3081** / 3372 ICSI - **2140** / **28800** / 30940 Total 2431 / 31881 / 34312 Value / Lower 95% CI / Upper 95% CI Rel risk 1.25 / 1.11 / 1.40 No patterns seen for specific organ systems, but overall number small	**Comments:** - Different birth years (differential ascertainment/classification), significantly older maternal age—no adjustment - Unblinded ascertainment **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period:+ Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -
Luke, Brown, Nugent, et	**Geographical location:** Baltimore, MD Miami, FL	**Age:** Mean (SD): Assisted 33.1 (4.9)	**Definition(s) of outcome(s):**	1) Preeclampsia by assisted vs. spontaneous conception of twins:	**Comments:** None

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
al. 2004 **#13930**	Ann Arbor, MI Charleston, SC **Study dates:** 1990 - 2002 **Size of population:** 1,436 **Study type:** Cohort, retrospective	Spontaneous 24.8 (6.1) **Race/ethnicity (n [%]):** Assisted n=352 White 81% Black 7% Hispanic 7% Spontaneous White 37% Black 36% Hispanic 23% **Diagnoses (n [%]):** NR **Inclusion criteria:** Both twins liveborn >=24wks gestation Documented sexes & bwts No major congenital anomalies Maternal height, pregravid weight, and at least 3 prenatal weights with 1st at or before 20wks and the last within 1wk delivery **Exclusion criteria:** NR	Preeclampsia- not defined PPROM – not defined LBWT < 2500gm VLBWT < 1500gm FGR < 10% at 20-28wks PTD < 32wks & < 30wks but individual #s not provided		**Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - retrospective chart review Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining clinical outcomes: +/- Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

	preecla mpsia +	preecla mpsia -	Total
assisted	**70**	**282**	352
spontaneous	**174**	**551**	725
Total	244	833	1077

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.83	0.65	1.06

2) PPROM:

	PPROM +	PPROM-	Total
assisted	**70**	**282**	352
spontaneous	**174**	**551**	725
Total	244	833	1077

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.83	0.65	1.06

3) LBWT:

	LBWT+	LBWT-	Total
assisted	**204**	**148**	352
spontaneous	**246**	**479**	725
Total	450	627	1077

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.71	1.49	1.95

4) VLBWT:

	VLBWT+	VLBWT-	Total
assisted	**39**	**313**	352
spontaneous	**109**	**616**	725
Total	148	929	1077

		Lower	Upper

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Value 95% CI 95% CI Rel risk 0.74 0.52 1.04 5) FGR midgestation: FGR+ FGR- Total assisted **53** **299** 352 spontaneous **181** **544** 725 Total 234 843 1077 Value Lower 95% CI Upper 95% CI Rel risk 0.60 0.46 0.80	
Lynch, McDuffie, Murphy, et al., 2002 **#2690**	**Geographical location:** Denver, CO **Study dates:** Jan 1994-Nov 2000 **Size of population:** 528 mothers who delivered multiple gestations during study period **Study type:** Cohort (retrospective)	**Age:** Mean (SD): ART 37(5.4) OI 31(4) Ctrl 28(5.5) **Race/ethnicity (n [%]):** ART 91% white, 5% Hispanic, 0 black OI 91% white, 5% Hispanic, 1.5% black Controls 69% white, 15% Hispanic, 13% black **Diagnoses (n [%]):** NR **Inclusion criteria:** Multiple births from women who delivered in study period at CO KP facilities **Exclusion criteria:** 2nd set of multiple births (2 mothers)	**Definition(s) of outcome(s):** Preexisting HTN = 140/90 before conception or < 20wks ART – procedures that involved handling of human oocytes or embryos Preeclampsia = 30/15 increase or 140/90 > 20 wk x 2 occasions ≥6 h apart + 1+ proteinuria or 300mg/24h + edema Severe preeclampsia = 160/110, 5 g prot/24 h or 3+, oliguria < 500 cc/24 h, elevated creat, thrombocytopenia, elevated liver enzymes, cerebral or visual disturbances, epigastric pain, pulmonary edema or cyanosis, FGR,	1) Preeclampsia: Preex + Preex - Total ART **27** **42** 69 Spont **40** **290** 330 Total 67 332 399 Value Lower 95% CI Upper 95% CI Odds rat 4.66 2.59 8.37 Preex + Preex - Total CC **18** **73** 91 spont **40** **290** 330 Total 58 363 421 Value Lower 95% CI Upper 95% CI Odds rat 1.79 0.97 3.30 Preex + Preex - Total HMG **9** **29** 38 spont **40** **290** 330 Total 49 319 368 Value Lower 95% CI Upper 95% CI Odds rat 2.25 0.99 5.10	**Comments:** ART/OI older, more often white, married, nulliparous – adjusted for nulliparity **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: + Use of validated method for genomic test: NR Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: n/a Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
			oligohydramnios	Performed 2 multivariate logistic regressions, full and backward. (?) ART was significantly associated with preeclampsia when adjusted for maternal age and nulliparity (AOR 2.8 [1.1, 7]) – CC, HMG were not.	
Lynch, McDuffie, Stephens, et al., 2003 **#16930**	**Geographical location:** Boulder, CO **Study dates:** Jan 1994 - Dec 2001 **Size of population:** 562 sets of twins **Study type:** Cohort (retrospective)	**Age:** Range: 75 (39%) ≥35yo in assisted grp 43 (12%) ≥35yo in unassisted grp **Race/ethnicity (n [%]):** N(%) refers to women. 432 (77%) White 62 (11%) Hispanic 50 (9%) Af Am 18 (3.3%) other **Diagnoses (n [%]):** NR **Inclusion criteria:** Twins delivered > 20wks **Exclusion criteria:** 2 women gave birth to 2 sets of twins; 2nd set for each excluded	**Definition(s) of outcome(s):** LBW < 2500g VLBW < 1500g	1) Selective fetal reduction: Sel red + / Sel red - / Total Asst: **18** / **175** / 193 Unasst: **0.5** / **369** / 369.5 Total: 18.5 / 544 / 562.5 Value / Lower 95% CI / Upper 95% CI Rel risk: 68.92 / 4.17 / 1138.74 2) LBW: LBW + / LBW - / Total Asst: **113** / **80** / 193 Unasst: **218** / **151** / 369 Total: 331 / 231 / 562 Value / Lower 95% CI / Upper 95% CI Rel risk: 0.99 / 0.86 / 1.15	**Comments:** Assisted grp older, less Af Am, more nullip, less single, fewer smokers, higher previous miscarriage rate, fewer monochorionic twins **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: + Use of validated method for genomic test: Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
Maimburg and Vaeth, 2007	**Geographical location:** Denmark (population-based)	**Age:** Mean (SD): Maternal: cases 29.1 (4.3) Controls 28.9 (5.2)	**Definition(s) of outcome(s):** Infantile autism, based on	1) Crude odds ratio, infertility treatment vs. spontaneous: Autism + / Autism - / Total	**Comments:** None **Quality assessment:**

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#71910	**Study dates:** Jan 1990-Dec 1999 **Size of population (no. of patients):** 473 cases, 473 controls **Study type:** Case-control	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Cases—all cases entered into national registry; controls—randomly selected from national registry, matched for gender, birth year, birth county **Exclusion criteria:** NR	ICD codes, from national registry	Infertilty **10** **23** 33 Spont **463** **450** 913 Total 473 473 946 Value / Lower 95% CI / Upper 95% CI Odds rat 0.42 0.20 0.90 Adjusted odds ratio (adjusted for mothers age, mothers' country of origin, parity, multiplicity, birth weight, gestational age and birth defect) 0.37 (0.14-0.98).	Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: + Comparability of cases and controls with respect to potential confounders: + Appropriateness of statistical analyses: +
Manoura, Korakaki, Hatzidaki, et al. 2004 **#12220**	**Geographical location:** Crete, Greece **Study dates:** July 1994 - July 2002 **Size of population:** 221 twin pregnancies (427 infants) 73 by IVF & 148 spontaneous **Study type:** Cohort, retrospective	**Age:** Mean (SD): IVF 32.3 (6.3) Spontaneous 27.9 (4.8) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Twin pregnancies **Exclusion criteria:** Higher order multiples, ovulation induction, reduction to singleton, 1st trimester loss of 1 twin, uncontrolled DM, SLE	**Definition(s) of outcome(s):** Preeclampsia ≥ 140/90 after 20wks and ≥ 300mg proteinuria/24hr or abnl hematological or biochem markers associated with symptomatology GDM +3hr GTT PPROM PTB < 37wks SGA < 10%ile LBWT < 2500gm Perinatal deaths = stillbirths ≥ 500gm through 7d of life Neonatal death = within 28d of life	1) Preeclampsia: preeclampsia+ / preeclampsia- / Total IVF **3** **70** 73 spontaneous **3** **145** 148 Total 6 215 221 Value / Lower 95% CI / Upper 95% CI Rel risk 2.03 0.42 9.80 2) GDM: GDM+ / GDM- / Total IVF **3** **70** 73 spontaneous **3** **145** 148 Total 6 215 221 Value / Lower 95% CI / Upper 95% CI Rel risk 2.03 0.42 9.80 3) PPROM:	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): +/- Large sample size: + Adequate description of the cohort: +: Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

	PPROM +	PPROM-	Total
IVF	**10**	**63**	73
spontaneous	**8**	**140**	148
Total	18	203	221

	Value	Lower 95% CI	Upper 95% CI
Rel risk	2.53	1.04	6.15

4) IUFD:

	IUFD+	IUFD-	Total
IVF	**7**	**66**	73
spontaneous	**8**	**140**	148
Total	15	206	221

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.77	0.67	4.70

5) C-section:

	C/S+	C/S-	Total
IVF	**67**	**7**	74
spontaneous	**102**	**46**	148
Total	169	53	222

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.31	1.15	1.50

6) PTB:

	PTB+	PTB-	Total
IVF	**55**	**18**	73
spontaneous	**91**	**57**	148
Total	146	75	221

	Value	Lower 95% CI	Upper 95% CI

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results				Comments/Quality Scoring
				Rel risk	1.23	1.02	1.47	

7) LBWT:

	LBWT+	LBWT-	Total
IVF	**90**	**49**	139
spontaneous	**170**	**118**	288
Total	260	167	427

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.10	0.94	1.28

8) SGA:

	SGA+	SGA-	Total
IVF	**35**	**104**	139
spontaneous	**67**	**221**	288
Total	102	325	427

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.08	0.76	1.54

9) Perinatal death:

	perinatal death+	perinatal death-	Total
IVF	**11**	**128**	139
spontaneous	**24**	**264**	288
Total	35	392	427

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.95	0.48	1.88

10) Neonatal death:

	neonatal death+	neonatal death-	Total
IVF	**10**	**129**	139
spontan	**18**	**270**	288

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				eous Total 28 399 427 Value / Lower 95% CI / Upper 95% CI Rel risk 1.15 0.55 2.43	
Matias, Oliveira, da Sliva, et al., 2007 **#54010**	**Geographical location:** Porto, Portugal **Study dates:** 1994-2004 **Size of population (no. of patients):** 861 = 189 IVF, 672 ICSI **Study type:** Cohort	**Age:** < 38 yrs n = 770, 89.4% **Race/ethnicity (n [%]):** > 95% Portuguese **Diagnoses (n [%]):** NR **Inclusion criteria:** IVF ± ICSI **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Spontaneous abortion = complete pregnancy loss	Data presented are for ALL pregnancies – data presented for singletons and twins in paper 1) SAb by IVF v ICSI: SAb + / Sab - / Total ICSI 112 560 672 IVF 18 171 189 130 731 861 Lower 95% CI / Upper 95 % CI Rel risk 1.75 1.09 2.80 2) SAb by age cutpoint 38 yrs: Preg + / Preg - / Total > 38 26 65 91 ≤ 38 104 666 770 130 731 861 Lower 95% CI / Upper 95 % CI Rel risk 2.12 1.46 3.06 3) SAb by embryo transfer day: Sab+ / Sab- / Total ET2-3 **78** **350** 428 ET4-5 **34** **190** 224 Total 112 540 652 Value / Lower 95% CI / Upper 95% CI Rel risk 1.20 0.83 1.74	**Comments:** No adjustment for multiple comparisons, no multivariate adjustment **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): Large sample size: Adequate description of the cohort: Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				4) Loss rate higher for singletons than for twin pregnancies, especially in ICSI pregnancies	
Maymon, Jauniaux, Holmes, et al., 2001 **#4260**	**Geographical location:** Zrifin, Israel & London, UK **Study dates:** June 1998 - Nov 1999 **Size of population:** Art 83 women Spontaneous 91 women **Study type:** Cohort	**Age:** ART 31 (4) Spontaneous 32 (4) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Twins **Exclusion criteria:** NR	**Definition(s) of outcome(s):** NR	1) Abnl NT screen for ART vs spontaneous: abnl NT / nl NT / Total ART: **3** / **80** / 83 spontaneous: **13** / **78** / 91 Total: 16 / 158 / 174 Value (Lower 95% CI, Upper 95% CI) Rel risk: 0.25 (0.07, 0.86) 2) Complicated pregnancy outcome by ART vs spontaneous: complicated / not complicated / Total ART: **4** / **79** / 83 spontaneous: **10** / **81** / 91 Total: 14 / 160 / 174 Value (Lower 95% CI, Upper 95% CI) Rel risk: 0.44 (0.14, 1.35)	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -
Maymon and Shulman, 2004 **#13890**	**Geographical location:** Tel Aviv, Israel **Study dates:** Jan 2000-Sept 2002	**Age:** Mean (SD): IVF: 32.2 (4) Spontaneous: 30.4 (4) **Race/ethnicity (n [%]):**	**Definition(s) of outcome(s):** False positive results, based on 1st trimester PAPP-A and nuchal	1) Relative risk of false positive: False + / Total IVF +: **6** / **93** / 99 Spont: **66** / **1715** / 1781 Total: 72 / 1808 / 1880	**Comments:** No adjustment for multiple comparisons **Quality assessment:** Unbiased selection of the cohort

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Size of population (no. of patients): 99 IVF 1781 spontaneous conceptions (lab reference values) **Study type:** Cohort	NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Selection criteria unclear - Singleton pregnancies **Exclusion criteria:** NR - referenced	translucency, 2nd trimrester AFP, uE3, hCG, and inhibin A	Lower Upper Value 95% CI 95% CI Rel risk 1.64 0.73 3.68 2) Nuchal translucency MOM significantly higher, PAPP-A significantly lower in IVF pregnancies. 2nd trimester markers not significantly different.	(prospective recruitment of subjects): + Large sample size: - Adequate description of the cohort: - Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -
Maymon and Shulman, 2002 **#2400**	**Geographical location:** Tel Aviv, Israel **Study dates:** Jan 1999 - Sept 2000 **Size of population:** IVF 71 Spontaneous 285 **Study type:** Cohort	**Age:** IVF 31.5 (5) Spontaneous 30 (4) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Singleton 10 – 14 wks **Exclusion criteria:** >1 fetus, chromosomal aneuploidy, <24wks pregnancy loss, congenital anomalies	**Definition(s) of outcome(s):** False positive rate for 1st and 2nd trimester screening tests	1) 1st trimester false-positive for IVF vs spontaneous: screen+ screen- Total IVF **5** **66** 71 spontaneous **26** **259** 285 Total 31 325 356 Lower Upper Value 95% CI 95% CI Rel risk 0.77 0.31 1.94 2) 2nd trimester false-positive for IVF vs spontaneous: screen+ screen- Total IVF **7** **64** 71 spontaneous **14** **271** 285 Total 21 335 356 Lower Upper Value 95% CI 95% CI Rel risk 2.01 0.84 4.79 3) 1st & 2nd trimester false positive for IVF vs spontaneous: screen+ screen- Total	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) - and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				IVF **1** **70** 71 spontaneous **4** **281** 285 Total 5 351 356 Value / Lower 95% CI / Upper 95% CI Rel risk 1.00 / 0.11 / 8.84	
McMahon and Gibson, 2002 **#530**	**Geographical location:** Sydney, Australia **Study dates:** NR **Size of population (no. of patients):** 70 IVF couples, 63 controls **Number of cycles per patient:** Mean 5.0 (3.8) , range 1-23 **Study type:** Cohort	**Age:** Mean (SD): IVF 34.5 (3.0) Control 31.9 (2.4) Paternal age also higher in IVF group **Race/ethnicity (n [%]):** NR College education: 40% IVF, 53% controls **Diagnoses (n [%]):** NR **Inclusion criteria:** IVF: - No donor - First singleton pregnancy - Mother living with father Controls: - First singleton pregnancy - Mother living with father **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Pregnancy 30 weeks: questionnaire/interviews; instruments not explicitly described/references Mother-infant relationship at 4 months: Still-Face Procedure (standardized, videotaped, maternal and infant behaviors coded by blinded scorers) 12 months: Strange Situation (standardized, videotaped, maternal and infant behaviors coded by blinded scorers) Both instruments involve separation of infant from mother, observation of behaviors after reunion	1) 30 weeks: IVF mothers: lower self-esteem, greater external locus of control; much higher anxiety about defects in baby, injury during birth; fathers: lower self-esteem, higher trait anxiety, lower marital satisfaction 2) 4 months: IVF infants with more fussing, but no significant difference in maternal behaviors (despite self-reported lower feelings of competence among IVF mothers) 3) 12 months: Questionnaires: no differences in mothers, infants; IVF fathers report lower self-esteem, less caring from spouses Mothers reported more difficult infants, but no differences in observed behaviors.	**Comments:** - Methodology for selecting subjects not described. - Instruments for 30 week questionnaires not described, but, given terminology, likely to be standard instruments such as State-Trait Anxiety Index (referenced in earlier paper) - Large (2-9 fold) differences in preterm, low birthweight, NICU admission—not adjusted in analyses **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - (NR) Large sample size: - Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
Meijer, de Jong-Van den Berg,	**Geographical location:** The Netherlands	**Age:** Mean (SD): Median:	**Definition(s) of outcome(s):**	1) Crude odds ratio, all hypospadias, exposure=clomiphene:	**Comments:** - Small numbers don't allow multivariate analysis

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Van den Berg, et al., 2006 **#54100**	**Study dates:** 1981-2003 **Size of population (no. of patients):** 392 cases, **Study type:** Case-control	Range: **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Cases—male infants with hypospadias Controls—male infants with malformations other than hypospadias **Exclusion criteria:** - Hypospadias as part of a syndrome - Epispadia		Out + / Out - / Total Clomiphene +: **7** / **64** / 71 Clomiphene -: **385** / **4474** / 4859 Total: 392 / 4538 / 4930 Value / Lower 95% CI / Upper 95% CI Odds ratio: 1.27 / 0.58 / 2.79 2) Odds ratio for penoscrotal hypospadias 6.08 (1.4, 26.3), but based on only 25 cases	- No adjustment for multiple comparisons **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: - Comparability of cases and controls with respect to potential confounders: - Appropriateness of statistical analyses: +
Merlob, Sapir, Sulkes, et al., 2005 **#8910**	**Geographical location:** Petah Tiqva, Israel **Study dates:** 1986 - 1994, and 1995 - 2002 **Size of population:** 1986 - 1994: 31,007 infants (278 IVF) 1995 - 2002: 53,208 infants (1,632 ART) **Study type:** Cohort study	**Age:** NR (infants) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - All infants (livebirths, stillbirths, terminations) delivered at one center > 20 wk and weighing ≥ 500 g - 1986 - 94, “standard IVF” - 1995 - 2002, ART compared with spontaneously conceived infants delivered in same time periods **Exclusion criteria:** < 20wks, < 500g	**Definition(s) of outcome(s):** Major malformations (structural and chromosomal) diagnosed pre- or postnatally Excluded minor malformations (listed)	1) Major malformations by IVF, 1986 - 1994: Major malform + / Major malform - / Total IVF +: **26** / **252** / 278 IVF -: **1248** / **29481** / 30729 Total: 1274 / 29733 / 31007 Value / Lower 95% CI / Upper 95% CI Rel risk: 2.30 / 1.59 / 3.33 2) Major malformation by ART, 1995 - 2002: Major malform + / Major malform - / Total ART +: **147** / **1485** / 1632 ART -: **2681** / **48895** / 51576 Total: 2828 / 50380 / 53208 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.73 / 1.48 / 2.03	**Comments:** - Included stillbirths & terminations – important in eliminating bias - ART grp significantly older than spontaneous conception grp and contained significant percentage of multiple births (known risk factors, not controlled for) - Dx included prenatal diagnosis + physical exam of newborn **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - not prospective, but minimally biased Large sample size: + Adequate description of the cohort: + (but would have liked to know what % liveborn, stillborn, terminated) Use of validated method for genomic test: NR Use of validated method for ascertaining clinical outcomes:+ Adequate follow-up period: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
					Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -
Muller, Dreux, Lemeur, et al., 2003 **#14500**	**Geographical location:** Paris, Lyon, Dijon, Lyon, Marseille, Amiens, and Nantes, France **Study dates:** 1996-2002 **Size of population (no. of patients):** 1515 ART pregnancies 21,014 spontaneous conceptions **Study type:** Cohort	**Age:** ART: 31.7% ≥ 35 Spontaneous: 18.5% ≥35 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** NR **Exclusion criteria:** Embryo reduction	**Definition(s) of outcome(s):** 2nd trimester screening using AFP (all pregnancies), hCG, free ß-hCG, and uE3	1) Relative risk for positive result (calculated risk > 1/250), all pregnancies: Out + / Out - / Total ART + **192** **1323** 1515 Spont **1849** **19165** 21014 Total 2041 20488 22529 Value (Lower 95% CI, Upper 95% CI) Rel risk 1.44 (1.25, 1.66) 2) Relative risk for positive result (calculated risk > 1/250), women < 30 years old: Out + / Out - / Total ART + **11** **330** 341 Spont **298** **9621** 9919 Total 309 9951 10260 Value (Lower 95% CI, Upper 95% CI) Rel risk 1.07 (0.59, 1.94) 3) Relative risk for positive result (calculated risk > 1/250), women 30-34 years old: Out + / Out - / Total Exp + **63** **631** 694 Exp - **569** **6638** 7207 Total 632 7269 7901 Value (Lower 95% CI, Upper 95% CI) Rel risk 1.15 (0.90, 1.47) 4) Relative risk for positive result (calculated risk > 1/250), women 35-37 years old: Out + / Out - / Total	**Comments:** - All subjects had AFP; additional markers varied—not adjusted for variation in tests used - OB outcomes not reported **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: - Use of validated method for ascertaining exposure: - Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

Exp +	**63**	**273**	336
Exp -	**461**	**2145**	2606
Total	524	2418	2942

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.06	0.84	1.34

5) Relative risk for positive result (calculated risk > 1/250), women ≥ 38 years old:

	Out +	Out -	Total
Exp +	**57**	**87**	144
Exp -	**515**	**767**	1282
Total	572	854	1426

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.99	0.80	1.22

Murphy, Neale, Hey, et al., 2006

#54340

Geographical location: United Kingdom

Study dates: 1973 - 1989

Size of population (no. of patients):

Age:
Ov induction 29 yrs
Spontaneous 27.8 yrs

Race/ethnicity (n [%]): NR

Diagnoses (n [%]): NR

Definition(s) of outcome(s):

Preterm birth < 37wks

Low birthweight < 2500gm

Perinatal mortality =

1) Preterm birth:

	ptb+	ptb-	Total
ov indx	**146**	**248**	394
spontaneous	**1243**	**2280**	3523
Total	1389	2528	3917

Comments:
None

Quality assessment:
Unbiased selection of the cohort (prospective recruitment of subjects): -
Large sample size: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	All twins N=199 ovulation induction N=1773 spontaneous **Study type:** Cohort	**Inclusion criteria:** All twins >=28 wks with subfertility treated by ovulation induction-only, controls spontaneous conception **Exclusion criteria:** Any ART more advanced than ovulation induction	stillbirth + neonatal death	<table><tr><th></th><th>Value</th><th>Lower 95% CI</th><th>Upper 95% CI</th></tr><tr><td>Rel risk</td><td>1.05</td><td>0.92</td><td>1.20</td></tr></table> 2) Low birthweight: <table><tr><th></th><th>lbwt+</th><th>lbwt-</th><th>Total</th></tr><tr><td>ov indx</td><td>**189**</td><td>**205**</td><td>394</td></tr><tr><td>spontaneous</td><td>**1650**</td><td>**1873**</td><td>3523</td></tr><tr><td>Total</td><td>1839</td><td>2078</td><td>3917</td></tr></table> <table><tr><th></th><th>Value</th><th>Lower 95% CI</th><th>Upper 95% CI</th></tr><tr><td>Rel risk</td><td>1.02</td><td>0.92</td><td>1.14</td></tr></table> 3) Perinatal mortality: <table><tr><th></th><th>perinatal mort+</th><th>perinatal mort-</th><th>Total</th></tr><tr><td>ov indx</td><td>**11**</td><td>**383**</td><td>394</td></tr><tr><td>spontaneous</td><td>**98**</td><td>**3425**</td><td>3523</td></tr><tr><td>Total</td><td>109</td><td>3808</td><td>3917</td></tr></table> <table><tr><th></th><th>Value</th><th>Lower 95% CI</th><th>Upper 95% CI</th></tr><tr><td>Rel risk</td><td>1.00</td><td>0.54</td><td>1.86</td></tr></table>	Adequate description of the cohort: + Use of validated method for ascertaining exposure: - Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Nassar, Usta, Rechdam, et al., 2003 **#15350**	**Geographical location:** Beirut, Lebanon **Study dates:** Jan 1995 - Dec 2000 **Size of population:** 56 IVF twin pregnancies 112 spont twin preg **Study type:** IVF twins matched by age & parity 1:2 to spontaneous twins, sequentially at time of delivery.	**Age:** Mean (SD): 31 (5) **Race/ethnicity (n [%]):** Middle eastern (all) **Diagnoses (n [%]):** NR **Inclusion criteria:** Twin pregnancies delivered >= 25 wks **Exclusion criteria:** Women who underwent ovulation induction only, multifetal pregnancy reduction, or with medical disease (CHtn, DM, renal disease)	**Definition(s) of outcome(s):** Hypertensive disorders of pregnancy = BP > 140/90 on ≥ 2 occasions > 20wks in previously normotensive woman PTD < 37wks, extremely premature ≤ 32wks IUGR = birthwt <10th %ile for singletons	1) Preterm delivery < 37wks: PTD + / PTD - / Total IVF: **38** / **18** / 56 spont: **46** / **66** / 112 Total: 84 / 84 / 168 Value (Lower 95% CI, Upper 95% CI) Odds rat: 3.03 (1.54, 5.95) 2) C/S (despite similar rates of elective C/S and malpresenting Twin A): CS + / CS - / Total IVF: **43** / **13** / 56 spont: **65** / **47** / 112 Total: 108 / 60 / 168 Value (Lower 95% CI, Upper 95% CI) Odds rat: 2.39 (1.16, 4.94) 3) RDS: RDS + / RDS - / Total IVF: **14** / **42** / 56 spont: **9** / **103** / 112 Total: 23 / 145 / 168 Value (Lower 95% CI, Upper 95% CI) Odds rat: 3.81 (1.53, 9.49)	**Comments:** - Excluded those who delivered <25wks - Racially homogeneous sample **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: + Verification that the control is free of cancer: NR Comparability of cases and controls with respect to potential confounders: + Validated dietary assessment method: NR Appropriateness of statistical analyses: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Ochsenkuhn, Strowitzki, Gurtner, et al., 2003 **#15450**	**Geographical location:** Munich, Germany **Study dates:** 1991-96 **Size of population:** 322 singleton, 78 twins conceived by IVF or GIFT **Study type:** Cohort IVF/GIFT conceptions identified retrospectively from database, then matched; next respective spontaneously-conceived singleton or twin pregnancy in database matched for maternal age, gestational age, and parity	**Age:** Mean: GIFT/IVF: 32.6 Controls: 32.2 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Singleton and twin pregnancies conceived by GIFT or IVF with liveborns ≥ 24 wk and/or > 499 g **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Vaginal bleeding = menstrual like or heavier VB at ≥ 1 occasions > 20 wk Pregnancy-induced HTN = BP > 140/90 on ≥ 2 occasions > 20 wk in previously normotensive woman	1) C/S in singletons: C/S + / C/S - / Total IVF/GIFT: **86** / **276** / 362 Spont: **73** / **249** / 322 Total: 159 / 525 / 684 Odds rat: Value 1.06; Lower 95% CI 0.74; Upper 95% CI 1.52 2) Vaginal bleeding in singletons: VB + / VB - / Total IVF/GIFT: **13** / **349** / 362 Spont: **3** / **319** / 322 Total: 16 / 668 / 684 Odds rat: Value 3.96; Lower 95% CI 1.12; Upper 95% CI 14.03 3) Pregnancy-induced HTN in singletons: PIH+ / PIH - / Total IVF/GIFT: **12** / **350** / 362 Spont: **3** / **319** / 322 Total: 15 / 669 / 684 Odds rat: Value 3.65; Lower 95% CI 1.02; Upper 95% CI 13.04 4) C/S in twins: C/S + / C/S - / Total IVF/GIFT: **54** / **24** / 78 Spont: **43** / **35** / 78 Total: 97 / 59 / 156	**Comments:** Matching performed retrospectively based in part on GA at delivery; thus not possible to compare GA or prematurity-related complications **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: - Appropriateness of the control population: + Verification that the control is free of cancer: NR Comparability of cases and controls with respect to potential confounders: - Validated dietary assessment method: NR Appropriateness of statistical analyses: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

	Value	Lower 95% CI	Upper 95% CI
Odds rat	1.83	0.95	3.53

Olson, Keppler-Noreuil, Romitti, et al, 2005

#39830

Geographical location: Iowa City, Iowa

Study dates: 1989 - 2002

Size of population:
children born
1,462 IVF
343 IUI
8,422 natural conceptions

Study type: Matched cohort

Age:
IVF 33.9 (4.6)
IUI 32.4 (4.3)
33.3 (4.3)

Race/ethnicity (n [%]):
Caucasian 97%
Black 0.2%
Hispanic 0.9%
Other 1.7%

Diagnoses (n [%]): NR

Inclusion criteria:
All IVF & IUI pts in time frame of study

Matched 5 controls per case from same geographic region within Iowa, not in infertility dbase

Exclusion criteria: NR

Definition(s) of outcome(s):

Major birth defect through 1 yr of age - cause functional impairment or require surgical correction

1) C-section for IVF vs spontaneous conception, singletons only:

	cs+	cs-	Total
IVF	**198**	**447**	645
spontaneous	**1086**	**3504**	4590
Total	1284	3951	5235

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.30	1.14	1.47

2) C-section for IUI vs spontaneous conception, singletons only:

	cs+	cs-	Total
IUI	**198**	**447**	645
spontaneous	**79**	**185**	264
Total	277	632	909

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.03	0.82	1.28

3) PTB for IVF vs spontaneous, singleton only:

	ptb+	ptb-	Total
IVF	**10**	**635**	645
spontaneous	**36**	**4554**	4590
Total	46	5189	5235

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.98	0.99	3.96

4) PTB for IUI vs spontaneous, singletons only:

Comments:
None

Quality assessment:
Unbiased selection of the cohort (prospective recruitment of subjects): +
Large sample size: +
Adequate description of the cohort: +
Use of validated method for ascertaining clinical outcomes: +
Adequate follow-up period: +
Completeness of follow-up: +
Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

	ptb+	ptb-	Total
IUI	**6**	**258**	264
spontaneous	**36**	**4554**	4590
Total	42	4812	4854

	Value	Lower 95% CI	Upper 95% CI
Rel risk	2.90	1.23	6.82

5) LBWT for IVF vs spontaneous, singletons only:

	lbwt+	lbwt-	Total
IVF	**44**	**601**	645
spontaneous	**195**	**4395**	4590
Total	239	4996	5235

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.61	1.17	2.20

6) LBWT for IUI vs spontaneous, singletons only:

	lbwt+	lbwt-	Total
IUI	**23**	**241**	264
spontaneous	**195**	**4395**	4590
Total	218	4636	4854

	Value	Lower 95% CI	Upper 95% CI
Rel risk	2.05	1.36	3.10

7) Major birth defect for IVF vs spontaneous, all infants:

	birth defect+	birth defect-	Total
IVF	**90**	**1372**	1462
spontaneous	**369**	**8053**	8422

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Total 459 9425 9884 Value / Lower 95% CI / Upper 95% CI Rel risk 1.41 1.12 1.76 8) Major birth defects for IUI vs spontaneous, all infants: birth defect+ / birth defect- / Total IUI **17** **326** 343 spontaneous **369** **8053** 8422 Total 386 8379 8765 Value / Lower 95% CI / Upper 95% CI Rel risk 1.13 0.70 1.82	
Ombelet, Martens, De Sutter, et al., 2006 **#54580**	**Geographical location:** Belgium **Study dates:** Jan 1993-Dec 2003 **Size of population (no. of patients):** Singletons ART n = 12,021 Matched controls n = 12,021 Twins ART n = 3108, matched controls n = 3108 **Study type:** Cohort	**Age:** ART 29.7 (4.1) Natural 29.6 (4.1) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Controlled ovarian stimulation with/without insemination - Controls matched for maternal age, parity, year of birth, infant sex **Exclusion criteria:** Higher order multiples > twins	**Definition(s) of outcome(s):** Preterm birth < 37 wk Low birthweight < 2500 g NICU admission Perinatal mortality = perinatal + stillbirth+ neonatal deaths Intracranial bleeding Respiratory distress syndrome (RDS)	1) Singletons, PTB: PTB + / PTB - / Total COH **938** **11083** 12021 Natural **514** **11507** 12021 Total 1452 22590 24042 Value / Lower 95% CI / Upper 95% CI Rel risk 1.82 1.64 2.03 2) Singletons, LBWT: LBWT + / LBWT - / Total COH **794** **11227** 12021 Natural **441** **11580** 12021 Total 1235 22807 24042 Value / Lower 95% CI / Upper 95% CI Rel risk 1.80 1.61 2.02 3) Singletons, NICU admissions:	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: - Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

	NICU +	NICU -	Total
COH	**2194**	**9827**	12021
Natural	**1536**	**10485**	12021
Total	3730	20312	24042

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.43	1.35	1.52

4) Singletons, perinatal mortality:

	Perinatal mortality +	Perinatal mortality -	Total
COH	**182**	**11839**	12021
Natural	**140**	**11881**	12021
Total	322	23720	24042

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.30	1.04	1.62

5) Singletons, intracranial bleed:

	IC bleed +	IC bleed -	Total
COH	**46**	**11975**	12021
Natural	**14**	**12007**	12021
Total	60	23982	24042

	Value	Lower 95% CI	Upper 95% CI
Rel risk	3.29	1.81	5.97

6) Singletons, RDS:

	RDS +	RDS -	Total
COH	**102**	**11919**	12021
Natural	**40**	**11981**	12021
Total	142	23900	24042

	Value	Lower 95% CI	Upper 95% CI
Rel risk	2.55	1.77	3.67

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

7) Twins, preterm birth:

	PTB +	PTB -	Total
COH	**1669**	**1439**	3108
Natural	**1602**	**1506**	3108
Total	3271	2945	6216

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.04	0.99	1.09

8) Twins, LBWT:

	LBWT +	LBWT -	Total
COH	**1762**	**1346**	3108
Natural	**1719**	**1389**	3108
Total	3481	2735	6216

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.03	0.98	1.07

9) Twins, NICU admission:

	NICU +	NICU -	Total
COH	**2111**	**997**	3108
Natural	**2119**	**989**	3108
Total	4230	1986	6216

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.00	0.96	1.03

10) Twins, perinatal mortality:

	Perinatal mort +	Perinatal mort -	Total
COH	**196**	**2912**	3108
Natural	**152**	**2956**	3108
Total	348	5868	6216

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.29	1.05	1.58

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				11) Twins, intracranial bleed: IC bleed + / IC bleed - / Total COH: **61** / **3047** / 3108 Natural: **46** / **3062** / 3108 Total: 107 / 6109 / 6216 Rel risk: Value 1.33, Lower 95% CI 0.91, Upper 95% CI 1.94 12) Twins, RDS: RDS + / RDS - / Total ART: **191** / **2917** / 3108 Natural: **155** / **2953** / 3108 Total: 346 / 5870 / 6216 Rel risk: Value 1.23, Lower 95% CI 1.00, Upper 95% CI 1.51	
Orlandi, Rossi, Allegra, et al., 2002 **#1080**	**Geographical location:** Italy **Study dates:** Sep 1995 - Dec 2000 **Size of population:** ART 74 singletons, 30 twins Spontaneous 370 singletons, 150 twins **Study type:** Cohort	**Age:** Controls, singleton 31.99 (4.45) ART singletons 32.47 (3.8) Controls twins 31.34 (3.72) ART twins 31.27 (4.07) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Matched 5 controls per ART subject based on gestational age, maternal age, & time of testing	**Definition(s) of outcome(s):** NR	1) False+ rate for Down syndrome screening for ART vs spontaneous: false+ / no false+ / Total ART+: **7** / **59** / 66 spontaneous: **22** / **341** / 363 Total: 29 / 400 / 429 Rel risk: Value 1.75, Lower 95% CI 0.78, Upper 95% CI 3.93	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining clinical outcomes: +/- Adequate follow-up period: +/- Completeness of follow-up: +/- Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		Exclusion criteria: NR			
Parazzini, Pelucchi, Negri, et al. 2001 **#4940**	**Geographical location:** Italy, multi-center **Study dates:** Jan 1992 - Sept 1999 **Size of population:** 1,031 cases epithelial ovarian CA 2,411 controls **Study type:** Case-control	**Age:** Cases median 56, range 18-79 Controls median 57, range 17-79 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Admissions with histologically confirmed epithelial ovarian cancer Controls from same geographical areas, hospitalized for acute, non-neoplastic conditions **Exclusion criteria:** Borderline tumors Hormonal or gyn diseases, bilateral oophorectomy	**Definition(s) of outcome(s):** Ovarian Cancer confirmed by histological test	1) Ovarian Cancer in fertility drug use vs no fertility drug use: Ov CA+ / Ov CA- / Total fertility drug use: **15** / **26** / 41 no fertility drug use: **1016** / **2385** / 3401 Total: 1031 / 2411 / 3442 Value (Lower 95% CI, Upper 95% CI) Odds rat: 1.35 (0.71, 2.57) 2) Ovarian Cancer for time since last use of fertility drugs: Ov CA+ / Ov CA- / Total ≥ 25 yrs: **7** / **12** / 19 < 25 yrs: **7** / **13** / 20 Total: 14 / 25 / 39 Value (Lower 95% CI, Upper 95% CI) Odds rat: 1.08 (0.29, 4.01)	**Comments:** None **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: + Verification that the control is free of cancer: - Comparability of cases and controls with respect to potential confounders: + Appropriateness of statistical analyses: +
Perri, Chen,	**Geographical location:**	**Age:**	**Definition(s) of**	1) PTB for ART vs. spontaneous conception in	**Comments:**

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Yoeli, et al., 2001 **#4680**	Tel Aviv, Israel **Study dates:** 1996 **Size of population:** 95 ART singleton pregnancies 190 matched spontaneous conceptions of total 2546 spontaneous conceptions for cohort analysis **Study type:** Cohort	ART: 32.15 (4.5) Matched spontaneous: 32.13 (4.5) **Race/ethnicity (n [%]):** ART 82 Jewish, 13 Arabic Matched spontaneous 164 Jewish, 26 Arabic **Diagnoses (n [%]):** Unexplained infertility: 28% Endometriosis: 5% Male factor: 19% Tubal factor: 14% PCOS: 8% Other (specify): 6% 21% had > 1 indication **Inclusion criteria:** - Singleton ART-derived pregnancies achieved by IVF - ICSI - Transferring both IVF- and ICSI-derived embryos **Exclusion criteria:** NR	**outcome(s):** PTB < 37wk	cohort analysis: PTB + / PTB - / Total ART: **19** / **76** / 95 Spont: **185** / **2361** / 2546 Total: 204 / 2437 / 2641 Value: 2.75 (Lower 95% CI: 1.80, Upper 95% CI: 4.21) 2) PTB for ART vs. spontaneous conception in matched cohort analysis: PTB + / PTB - / Total ART: **19** / **76** / 95 Spont: **8** / **182** / 190 Total: 27 / 258 / 285 Value: 4.75 (Lower 95% CI: 2.16, Upper 95% CI: 10.45) 3) Cesarean delivery for ART vs. spontaneous conception in matched cohort analysis: C/S + / C/S - / Total ART: **40** / **55** / 95 Spont: **39** / **151** / 190 Total: 79 / 206 / 285 Value: 2.05 (Lower 95% CI: 1.42, Upper 95% CI: 2.96)	None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: +/- Use of validated method for ascertaining clinical outcomes: +/- Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -
Pinborg,	**Geographical location:**	**Age:** NR	**Definition(s) of**	1) Small-for-gestational-age, survivor of	**Comments:**

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Lidegaard, Freiesleben, et al., 2007 **#72240**	Copenhagen, Denmark **Study dates:** January 1995-Dec 2001 **Size of population (no. of patients):** 9557 **Study type:** Cohort	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Pregnancy after ART in one of 11 Danish clinics, with ultrasound at 8 weeks showing (i) one viable fetus plus an empty gestational sac or a fetus with no fetal heart beat, (ii) one viable fetus or (ii) two viable fetuses - Vanished twin: any empty gestational sac or 1st, 2nd, or 3rd trimester loss **Exclusion criteria:** More than 2 heart beats or no viable fetuses	**outcome(s):** SGA: < 10th percentile for gestational age	vanishing twins vs. singletons: Out + / Out - / Total Survivor: **34** / **608** / 642 Singletons: **188** / **5049** / 5237 Total: 222 / 5657 / 5879 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.48 / 1.03 / 2.11 Adjusted OR similar; increasing age of loss also associated (OR 2.08, 95% CI 1.00-4.35 Risk for survivors substantially lower than for twins	Birth weight percentiles for twins apparently not adjusted **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
Pinborg, Lidegaard, la Cour Freiesleben, et al., 2005 **#39560**	**Geographical location:** Denmark **Study dates:** Jan 1995-Dec 2001 **Size of population (no. of patients):** 8251 **Study type:** Cohort	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - ART pregnancy - 8 week U/S with 1 viable fetus + 1 empty sac or fetus without heart beat; or 1 viable fetus; or 2 viable fetuses **Exclusion criteria:** - > 2 heart beats - No viable fetuses	**Definition(s) of outcome(s):** Birthweight Prematurity Perinatal mortality	1) Overall incidence of spontaneous reduction 10.4%. 2) Adjusted risks (95% CI) (adjusted for maternal age, parity, and mode of conception) for spontaneous reduction vs singleton pregnancies: Low birthweight (< 2500 gm): 2.0 (1.5, 2.6) VLBW (< 1500 gm): 3.0 (1.9, 4.7) Preterm delivery (< 37 weeks): 1.6 (1.2, 2.0) Very preterm (< 32 weeks): 3.0 (1.9, 4.8) Risk for neonatal death increased, but not significant after adjustment for gestational age. Trend towards increased risk for cerebral palsy.	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: - Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Increased risk as gestational age of loss increases.	
Pinborg, Loft, Rasmussen, et al., 2004 **#14030**	**Geographical location:** Denmark national registries **Study dates:** Jan 1995-Dec 2000 **Size of population:** IVF/ICSI twins 3,393 Control twins 10,239 **Study type:** Cohort	**Age:** Mean (SD): Maternal age Ivf/icsi twins 33.1 (3.7) Control twins 30.5 (4.5) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** IVF/ICSI twins Non-IVF/ICSI twins **Exclusion criteria:** Stillbirths excluded from analysis	**Definition(s) of outcome(s):** Delivery = liveborn or stillborn after 22wks PTB < 37wks LBW < 2500gm VLBW < 1500gm Neonatal mortality= # deaths < 28d per 1000 livebirths Infant mortality = # deaths < 1yr Major malformation = functional impairment or requires surgical correction; all else minor	1) LBWT: LBWT+ / LBWT- / Total ART twins: **1439** / **1954** / 3393 control twins: **4147** / **6092** / 10239 Total: 5586 / 8046 / 13632 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.05 / 1.00 / 1.10 2) VLBW: VLBWT+ / VLBWT- / Total ART twins: **255** / **3138** / 3393 control twins: **696** / **9543** / 10239 Total: 951 / 12681 / 13632 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.11 / 0.96 / 1.27 3) PTB: PTB+ / PTB- / Total ART twins: **1490** / **1903** / 3393 control twins: **4249** / **5990** / 10239 Total: 5739 / 7893 / 13632 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.06 / 1.01 / 1.11 4) Neo mortality:	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +/-

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

	neo death+	neo death-	Total
ART twins	**30**	**3363**	3393
control twins	**141**	**10098**	10239
Total	171	13461	13632

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.64	0.43	0.95

5) Infant mortality:

	infant death+	infant death-	Total
ART twins	**35**	**3358**	3393
control twins	**54**	**10185**	10239
Total	89	13543	13632

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.96	1.28	2.99

Pinborg,	**Geographical location:**	**Age:**	**Definition(s) of**	ART twins compared to control twins & ART	**Comments:**

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Loft, Rasmussen, et al., 2004 **#10840**	Denmark national registries **Study dates:** Jan 1995-Dec 2000 **Size of population:** IVF/ICSI twins 3,393 Control twins 10,239 IVF/ICSI singletons 5,130 **Study type:** Cohort	Maternal age Ivf/icsi twins 33.1 (3.7) Control twins 30.5 (4.5) Ivf/icsi singles 33.8 (3.7) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** NR **Exclusion criteria:** NR	**outcome(s):** Up to 7 yrs of age: - Child hospitalizations - Surgical procedures Term birth ≥ 37wk Neonatal admission within 1st 28d of life	singletons 1) Childhood hospitalizations: ART twins: hospitalized+ **2367**, hospitalized- **1026**, Total 3393 control twins: hospitalized+ **7122**, hospitalized- **3117**, Total 10239 Total: hospitalized+ 9489, hospitalized- 4143, Total 13632 Rel risk: Value 1.00, Lower 95% CI 0.98, Upper 95% CI 1.03 ART twins: hospitalized+ **2367**, hospitalized- **1026**, Total 3393 ART singles: hospitalized+ **2557**, hospitalized- **2573**, Total 5130 Total: hospitalized+ 4924, hospitalized- 3599, Total 8523 Rel risk: Value 1.40, Lower 95% CI 1.35, Upper 95% CI 1.45 2) Surgical procedures: ART twins: surgical intervention+ **361**, surgical intervention- **3032**, Total 3393 control twins: surgical intervention+ **1145**, surgical intervention- **9094**, Total 10239 Total: surgical intervention+ 1506, surgical intervention- 12126, Total 13632 Rel risk: Value 0.95, Lower 95% CI 0.85, Upper 95% CI 1.06	None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results:

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

	surgical interventi on+	surgical interventi on-	Total
ART twins	**361**	**3032**	3393
ART singles	**436**	**4694**	5130
Total	797	7726	8523

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.25	1.10	1.43

Pinborg, Loft, Schmidt, et al., 2003

#16610

Geographical location: Copenhagen, Denmark

Study dates: Jan-Dec 1997

Size of population: 1769 questionnaires mailed, 1436 returned 236 IVF/ICSI twins, 634 IVF/ICSI singletons, 566 non-IVF/ICSI twins

Study type: Case-control

Questionnaire sent to all twin mothers and IVF/ICSI singleton mothers who delivered in Denmark in 1997. Questions related to demographics, infertility hx, pregnancy outcomes, childhood morbidities, impact on mother's life

Age:
Mean (SD):
IVF/ICSI twin moms 33.1 (3.5)
IVF/ICSI singletons 34.1 (3.5)
Non-IVF/ICSI moms 30.5 (4.4)

Race/ethnicity (n [%]): NR

Diagnoses (n [%]): NR

Inclusion criteria:
Identified women who delivered twins in 1997 through Danish Medical Birth Registry, cross-referenced with IVF registry to separate into cases/controls. Also included IVF/ICSI singletons.

Exclusion criteria:
See above

Definition(s) of outcome(s):

NICU admission

"Special needs" = speech therapy, physiotherapy, occupational therapy, or educational support

Compared to IVF/ICSI twins, IVF/ICSI singletons had lower risk of special needs (OR 0.6 [0.4-0.9]), non-IVF/ICSI twins had higher (1.1 [0.8-1.6]).

Influence on marital relationship, etc; crude data NR; multiple logistic regression used. Twins were predictor of more marital stress, less marital benefit; but the only predictors of high risk of divorce/separation were "no IVF/ICSI" and age > 30 y. Twins, nulliparity, BW < 1500 g, age < 30 y were associated with infant having high impact on mother's personal & social life.

1) NICU admissions:

	NICU +	NICU -	Total
IVF twin	**181**	**273**	454
Spont twin	**421**	**697**	1118
Total	602	970	1572

	Value	Lower 95% CI	Upper 95% CI
Odds rat	1.10	0.88	1.37

2) Special needs:

	Special	Special	Total

Comments:
- Response rate 81%
- Analyzed non-responders – only important difference was in 2 control groups: higher mortality rate in singleton and twin control group non-respondents than respondents
- Included stillbirths, neonatal deaths
- IVF moms older, of lower parity

Quality assessment:
Valid ascertainment of cases: +
Unbiased selection of cases: +
Appropriateness of the control population: +
Verification that the control is free of cancer: NR
Comparability of cases and controls with respect to potential confounders: -
Validated dietary assessment method: NR
Appropriateness of statistical analyses: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

	needs +	needs -	
IVF twin	**45**	**409**	454
Spont twin	**120**	**998**	1118
Total	165	1407	1572

	Value	Lower 95% CI	Upper 95% CI
Odds rat	0.92	0.64	1.31

	Special needs +	Special needs -	Total
IVF twin	**45**	**409**	454
IVF singleton	**38**	**588**	626
Total	83	997	1080

	Value	Lower 95% CI	Upper 95% CI
Odds rat	1.70	1.09	2.67

Pinborg, Loft, Schmidt, et al., 2003

#17310

Geographical location: Copenhagen, Denmark

Study dates: 1995 - 2000

Size of population:
266 IVF/ICSI twin mothers
764 IVF/ICSI singleton mothers
739 non-IVF/ICSI twin mothers

Study type: Other

Questionnaire sent (in 2001) to all IVF/ICSI mothers who gave birth in 1997, to assess perceptions of singletons

Age:
Mean (SD):
IVF/ICSI twins 33.1 (3.5)
Singletons 34.1 (3.5)
Non-IVF/ICSI twins 30.5 (4.4)

Race/ethnicity (n [%]): NR

Diagnoses (n [%]): NR

Inclusion criteria:
Identified women who delivered twins in 1997 through Danish Medical Birth Registry, cross-referenced with IVF registry to separate into cases/ctrls. Also included IVF/ICSI singletons.

Definition(s) of outcome(s):

Questionnaire assessed perceptions toward twins and attitudes toward SET; were advised on risk that twin preg carries to mother & child, & nearly 40% of IVF children are twins.

Asked whether they found singleton or twins most desirable (before & after preg), and why.

Delivery of at least one child with VLBW was predictive of agreement to SET
>5yr of infertility was predictive of disagreement to SET.

1) Would prefer to have twins; IVF moms vs spont moms:

	Prefer twins	Not prefer twins	Total
IVF twin mom	**200**	**36**	236
Spont twin mom	**334**	**232**	566
Total	534	268	802

	Value	Lower 95% CI	Upper 95% CI
Odds rat	3.86	2.61	5.71

Comment:
- Response rate 81%
- Analyzed nonresponders – only important difference was in 2 control grps: higher mortality rate in singleton and twin control grp nonrespondents than respondents.
- Included stillbirths, neonatal deaths

Quality assessment:
Valid ascertainment of cases: +
Unbiased selection of cases: +
Appropriateness of the control population: +
Verification that the control is free of cancer: NR
Comparability of cases and controls with respect to potential confounders: -
Validated dietary assessment method: NR

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	vs twins, and single embryo transfer (SET)	**Exclusion criteria:** See above		2) Disagree with SET, vs agree or neither agree nor disagree: Disagree SET: IVF twin mom **157**; Other **79**; Total 236 IVF singleton **473**; **161**; 634 Total 630; 240; 870 Odds rat: Value 0.68; Lower 95% CI 0.49; Upper 95% CI 0.94	Appropriateness of statistical analyses: +
Pinborg, Loft, Schmidt, et al., 2004 **#14280**	**Geographical location:** Denmark **Study dates:** Jan-Dec 1997 **Size of population:** 1436/1769 questionnaires mailed (81% response rate) 236 ART twins 566 control twins 634 ART singletons Respondents + non-respondents 538 ART twins 1496 control twins **Study type:** Retrospective cohort via national survey questionnaire via mail and national birth registry	**Age:** Mean (SD): ART twins 33.1 (3.5) Control twins 30.5 (4.4) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Registry identification **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Preeclampsia & GDM based on physician diagnosis as recorded in registry PTB < 37 wk LBW < 2500 g	Odds ratios given for maternal conditions in ART vs. control twins, stratified by age & parity; no raw numbers given Preeclampsia 1.0 [0.5, 1.7] GDM 1.9 [0.9, 4.0] Results for respondents only BIRTH OUTCOMES OBTAINED FROM REGISTRY, SO RESPONDENTS + NONRESPONDENTS INCLUDED 1) LBW < 2500 g: LBW +; LBW -; Total ART twins **94**; **444**; 538 Control twins **215**; **1281**; 1496 Total 309; 1725; 2034 Rel risk: Value 1.22; Lower 95% CI 0.97; Upper 95% CI 1.52 2) PTB < 37 wk: PTB +; PTB -; Total	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: - Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

ART twins	**123**	**415**	538	
Control twins	**280**	**1216**	1496	
Total	403	1631	2034	

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.22	1.01	1.47

3) Neonatal mortality:

	Neo death +	Neo death -	Total
ART twins	**18**	**520**	538
Control twins	**33**	**1463**	1496
Total	51	1983	2034

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.52	0.86	2.67

Pinborg, Loft, Schmidt, et al., 2004

#10120

Geographical location: Denmark

Study dates: 1995 - 2000

Size of population: ART 3393 twins, 5130 singletons
Spontaneous twins 10239

Study type: Cohort

Age:
Mean (SD):
Art twins 33.1 (3.7)
Control twins 30.5 (4.5)
Art singletons 33.8 (3.7)

Race/ethnicity (n [%]): NR

Diagnoses (n [%]): NR

Inclusion criteria: Danish medical birth registry

Exclusion criteria: NR

Definition(s) of outcome(s):

ICD-10 codes for following disease outcomes – no further definitions given
Cerebral palsy (CP)

Mental retardation (MR)

Retarded psychomotor development

1) CP in twins only:

	CP+	CP-	Total
ART twins	**11**	**3382**	3393
control twins	**41**	**10198**	10239
Total	52	13580	13632

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.81	0.42	1.57

2) MR in twins only:

	MR+	MR-	Total
ART twins	**4**	**3389**	3393
control	**14**	**10225**	10239

Comments:
None

Quality assessment:
Unbiased selection of the cohort (prospective recruitment of subjects): -
Large sample size: +
Adequate description of the cohort: -
Use of validated method for ascertaining clinical outcomes: +/-
Adequate follow-up period: +/-
Completeness of follow-up: +/- from 2-7 years of age, 2 is probably too young to accurately eliminate abnl neuro condition
Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

twins
Total 18 13614 13632

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.86	0.28	2.62

3) Retarded psychomotor dev twins only:

	pmotor+	pmotor-	Total
ART twins	**12**	**3381**	3393
control twins	**32**	**10207**	10239
Total	44	13588	13632

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.13	0.58	2.19

4) OR neuro sequelae IVF vs ICSI twins + singletons (raw #s not provided)
0.9 [0.5, 1.7]

Place and Englert, 2003

#14630

Geographical location: Brussels, Belgium

Study dates: April 1998 - March 2000

Size of population:
ICSI = 66
IVF = 52
Spont = 59

Study type: Cohort

Compared ICSI-conceived children with children conceived by conventional IVF, and with spontaneously-conceived children wrt somatic, psychomotor,

Age: Mean (SD): 31.9 (3.78)

Race/ethnicity (n [%]): NR

Diagnoses (n [%]): NR

Inclusion criteria:
Spont – families who gave birth to fullterm singletons at Erasme Hosp were contacted.
ICST & IVF – head of fertility clinic wrote to families after birth, asked for consent.
At least one partner Belgian, other European & residing in Belgium >=3y

Definition(s) of outcome(s):

Major malformation = requiring surgical correction or causing functional impairment.
Brunet –Lezine scale used to assess developmental function; yields developmental quotient (DQ), with mean score of 100. Done at 9 & 18 mos.

Wechsler preschool & primary scales of intelligence (WPPSI-R) to assess intellect at 3 & 5y (IQ).

No difference in maj malform, need for NICU care, health problems at all ages, longterm hospitalization, DQ (and no child showed significant delay).

Mean IQ at 3&5y significantly lower for IVF & ICSI grps than spont, but this difference disappeared after adjustment for parental education level.

1) Cesarean; no diff btw any of 3 grps:

	C/S	No C/S	Total
ICSI	**13**	**53**	66
Spont	**7**	**52**	59
Total	20	105	125

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.66	0.71	3.88

Comments:
- Acceptance rate 70% for ICSI, 60% for IVF, 40% spont.
- F/u rate 91% for ICSI, 93% for IVF, 84% for spont
Parents of spont grp had higher levels of education.
- Data collected prospectively

Quality assessment:
Unbiased selection of the cohort (prospective recruitment of subjects): -
Large sample size: -
Adequate description of the cohort: +
Use of validated method for genomic test: NR
Use of validated method for ascertaining clinical outcomes: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	and intellectual development over preschool period. Controls matched for birthdate, age & sex of child, maternal age, social class, ethnic background, family size, and birth order of child. Children seen at 2 of these timepoints: 9 mos, 18 mos, 3y, and/or 5y. Assessments performed by same clinical psychologist, in homes. Questionnaire also filled out by child's pediatrician.	**Exclusion criteria:** Pregnancies after frozen or thawed ET's, children with birthwt <2500g		2) IQ at 3yo: IQ < 85 / IQ ≥ 85 / Total ICSI: **6** / **25** / 31 Spont: **2** / **25** / 27 Total: 8 / 50 / 58 Value / Lower 95% CI / Upper 95% CI Rel risk: 2.61 / 0.57 / 11.89 IQ < 85 / IQ ≥ 85 / Total IVF: **7** / **12** / 19 Spont: **2** / **25** / 27 Total: 9 / 37 / 46 Value / Lower 95% CI / Upper 95% CI Rel risk: 4.97 / 1.16 / 21.37	Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
Poikkeus, Gissler, Unkila-Kallio, et al., 2007 **#72250**	**Geographical location:** Helsinki, Finland **Study dates:** 1997-2003 **Size of population (no. of patients):** 499 ART, 15,037 **Study type:** Cohort Single embryo transfer vs. singleton after double embryo transfer vs. spontaneous singleton	**Age:** Mean (SD): SET 32.6 (3.9) DET 34.2 (3.8) Spont 30.3 (5.3) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Exposed: Singleton pregnancy after IVF/ICSI at clinic - Control: 10% sample of all births in Finland matched for year of delivery, maternal place of residence **Exclusion criteria:**	**Definition(s) of outcome(s):** Pregnancy complications Birth weight Preterm delivery Neonatal	1) Delivery prior to 37 weeks, single embryo transfer vs. spontaneous: < 37 weeks / ≥ 37 weeks / Total SET: **33** / **236** / 269 Spont-: **666** / **14371** / 15037 Total: 699 / 14607 / 15306 Value / Lower 95% CI / Upper 95% CI Rel risk: 2.77 / 2.00 / 3.85 2) Delivery prior to 37 weeks, singleton after double embryo transfer vs. spontaneous: < 37 weeks / ≥ 37 weeks / Total DET: **26** / **204** / 230 Spont-: **666** / **14371** / 15037 Total: 692 / 14575 / 15267	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: - Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		- PGD - Delivery outside of Finland			

	Value	Lower 95% CI	Upper 95% CI
Rel risk	2.55	1.76	3.69

3) SGA, single embryo transfer vs. spontaneous:

	SGA+	SGA -	Total
SET	**10**	**259**	269
Spont	**314**	**14723**	15037
Total	324	14982	15306

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.78	0.96	3.30

4) SGA, double embryo transfer vs. spontaneous:

	SGA+	SGA -	Total
DET	**10**	**220**	230
Spont	**314**	**14723**	15037
Total	324	14943	15267

	Value	Lower 95% CI	Upper 95% CI
Rel risk	2.08	1.12	3.85

5) Adjusted for maternal age, parity, socioeconomic status:

Preterm birth
SET versus spontaneous 2.85 (1.96–4.16)
DET versus spontaneous 2.63 (1.73–4.00)
SET versus DET 0.99 (0.56–1.75)

Low birthweight
SET versus spontaneous 2.01 (1.19–3.99)
DET versus spontaneous 3.46 (2.20–5.46)
SET versus DET 1.74 (0.87–3.48)

SGA
SET versus spontaneous 1.42 (0.74–2.71)
DET versus spontaneous 1.59 (0.83–3.08)
SET versus DET 1.07 (0.43–2.69)

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Low Apgar score SET versus spontaneous 1.96 (1.01–2.82) DET versus spontaneous 1.75 (1.01–3.04) SET versus DET 1.01 (0.47–2.17) *NICU admission* SET versus spontaneous 1.96 (0.96–4.01) DET versus spontaneous 2.23 (1.08–4.58) SET versus DET 1.46 (0.51–4.14)	
Poikkeus, Saisto, Unkila-Kallio, et al., 2006 **#54990**	**Geographical location:** Helsinki, Finland **Study dates:** 1999 **Size of population (no. of patients):** ART: 367, control: 379 **Study type:** Cohort	**Age:** Mean (SD): ART: 33.0 (4.2) Control: 33.3 (4.0) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 26% Male factor: 27% All female: 33% Mixed: 20% **Inclusion criteria:** Finnish speaking ART: - Volunteering Finnish-speaking - Confirmed viable singleton pregnancy after either fresh or frozen IVF or - ICSI with their own gametes **Exclusion criteria:** Controls: - Previous infertility - Previous infertility treatment - Maternal age < 25 years	**Definition(s) of outcome(s):** Anxiety regarding pregnancy/childbirth using two validated instruments: - Fear-of-Childbirth Questionnaire - Pregnancy Anxiety Score "Severe" defined as ≥ 90th percentile on each scale	1) Severe fear of childbirth: Severe Fear / < 90th %ile / Total IVF: **42** / **325** / 367 Spontaneous: **40** / **339** / 379 Total: 82 / 664 / 746 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.08 / 0.72 / 1.63 2) Severe Pregnancy-related anxiety: Severe Fear / < 90th %ile / Total IVF: **46** / **323** / 369 Spontaneous: **38** / **341** / 379 Total: 84 / 664 / 748 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.24 / 0.83 / 1.86 3) Results between IVF, control groups similar when stratified by parity. Prevalence of severe scores significantly higher in nulliparous controls compared to parous controls. 4) ART not significant predictor in multivariate analysis; risk of severe fear of pregnancy	**Comments:** Control selection well-described **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				increased with duration of infertility, decreased with number of ART cycles.	
Poikkeus, Unkila-Kallio, Vilska, et al., 2006 **#55000**	**Geographical location:** Finland **Study dates:** 1999 **Size of population (no. of patients):** All singletons ART N = 324 Controls N = 304 **Study type:** Cohort	**Age:** ART 33.0 (4.1) Controls 33.3 (3.0) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Male factor: 88 (27%) Female factor 107 (33%). Combined 61 (19%) Unexplained 68 (21'%) **Inclusion criteria:** - Finnish-speaking - Viable pregnancy after fresh/frozen IVF+/-ICSI with own gametes **Exclusion criteria:** Controls excluded if h/o infertility or < 25 yr old	**Definition(s) of outcome(s):** Preterm birth < 37wks Cesarean delivery	1) Preterm birth (spontaneous + medically induced): PTB + / PTB - / Total ART: **21** / **303** / 324 Natural: **9** / **295** / 304 Total: 30 / 598 / 628 Value (Lower 95% CI – Upper 95% CI) Rel risk: 2.19 (1.02 – 4.70) 2) Cesarean delivery C/S + / C/S - / Total ART: **85** / **239** / 324 Natural: **58** / **246** / 304 Total: 143 / 485 / 628 Value (Lower 95% CI – Upper 95% CI) Rel risk: 1.38 (1.02 – 1.85) 3) LBWT: LBWT + / LBWT - / Total ART: **14** / **310** / 324 Natural: **4** / **300** / 304 Total: 18 / 610 / 628 Value (Lower 95% CI – Upper 95% CI) Rel risk: 3.28 (1.09 – 9.87) 4) NICU admission: NICU + / NICU - / Total ART: **12** / **312** / 324 Natural: **5** / **299** / 304 Total: 17 / 611 / 628	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: - Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

	Value	Lower 95% CI	Upper 95% CI
Rel risk	2.25	0.80	6.32

Putterman, Figueroa, Garry, et al. 2003

#14420

Geographical location: Mineola, NY

Study dates: Jan 1999 – Dec 2000

Size of population: 195 twin pregnancies (60 IVF, 34 ov stim, 101 spont)

Study type: Cohort (retrospective)

Age: Mean (SD): IVF 34.6 (4.2), ov stim 31.3 (3), spont 30.9 (4.8)

Race/ethnicity (n [%]): IVF 100% white, ov stim 94.1%, spont 69.3%

Diagnoses (n [%]): NR

Inclusion criteria: Twin pregnancies where 2 live neonates delivered >20w

Exclusion criteria: Pregnancies reduced to twins, twin gestations that delivered single liveborn

Definition(s) of outcome(s):

LBW < 2500g

VLBW < 1500g

SGA < 10%ile based on twin norms

Growth discordance >20% in birthwt

No diff in C/S, antepartum complications, prematurity, LBW, VLBW, growth discordance, NICU admission

1) C/S:

	C/S	no C/S	Total
IVF	**35**	**25**	60
Spont	**60**	**41**	101
Total	95	66	161

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.98	0.75	1.28

	C/S	no C/S	Total
ov stim	**20**	**14**	34
Spont	**60**	**41**	101
Total	80	55	135

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.99	0.72	1.37

2) LBW:

	LBW	not LBW	Total
IVF	**35**	**25**	60
Spont	**83**	**18**	101
Total	118	43	161

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.71	0.56	0.90

	LBW	not LBW	Total
ov stim	**22**	**12**	34

Comments:
- Women in IVF grp older, more often primiparous.
- Those in ov stim grp more often had poor obstetric hx (previous preg loss or preterm delivery).
- More mono/di twins in spont grop.

Quality assessment:
Unbiased selection of the cohort (prospective recruitment of subjects): -
Large sample size: -
Adequate description of the cohort: +
Use of validated method for genomic test: NR
Use of validated method for ascertaining clinical outcomes: +
Adequate follow-up period: +
Completeness of follow-up: +
Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Spont **83** **18** 101 Total 105 30 135 Value / Lower 95% CI / Upper 95% CI Rel risk 0.79 0.60 1.03	
Puumala, Ross, Olshan, et al., 2007 **#72320**	**Geographical location:** US (multiple sites) **Study dates:** Jan 1997-Oct 2002 **Size of population (no. of patients):** 159 cases, 173 controls **Study type:** Case-control	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** *Cases:* Down's syndrome with a diagnosis of acute lymphocytic or myeloblastic leukemia ≤19 years at diagnosis - telephone in their residence, - biologic mother available who spoke English, -resided in the United State or Canada at diagnosis *Controls:* Down's syndrome without leukemia seen by same primary physicians as cases **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Acute myeloblastic or lymphocytic leukemia	1) Adjusted OR (maternal age, gender, race, education) for "Ever history of trying >12 months for conception" and AML: 2.22 (1.14-4.33) However, risk not significantly increased with index pregnancy: Not trying (reference) 1.00 Trying < 12 months 1.39 (0.72-2.69) Trying > 12 months 2.11 (0.73-6.14)	**Comments:** - 25% of identified cases (n = 210) did not participate - Unclear biological or clinical significance of discriminating between "not trying" and "trying < 12 months"; crude OR when both groups combined as reference 1.26 (0.49, 3.24) **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: + Comparability of cases and controls with respect to potential confounders: + Appropriateness of statistical analyses: +
Rajesh, Yap, and Wu, 2006	**Geographical location:** Singapore	**Age:** Mean: IVF: 33.4	**Definition(s) of outcome(s):**	1) Singletons, PTB: PTB + / PTB - / Total	**Comments:** None

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#55140	**Study dates:** 1999-2003 **Size of population (no. of patients):** IVF +/- ICSI n = 271 **Study type:** Cohort	ICSI: 33.7 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** IVF +/-r ICSI during study period **Exclusion criteria:** NR	Preterm birth < 37 wks Low BWT < 2500 g Cesarean not separated by plurality	IVF **3** **50** 53 IVF/ICSI **18** **85** 103 Total 21 135 156 Value / Lower 95% CI / Upper 95% CI Rel risk 0.32 0.10 1.05 2) Twins, PTB: PTB + / PTB - / Total IVF **40** **10** 50 IVF/ICSI **35** **12** 47 Total 75 22 97 Value / Lower 95% CI / Upper 95% CI Rel risk 1.07 0.86 1.34 3) Singletons, LBWT: LBWT + / LBWT - / Total IVF **3** **50** 53 IVF/ICSI **16** **87** 103 Total 19 137 156 Value / Lower 95% CI / Upper 95% CI Rel risk 0.36 0.11 1.20 4) Twins, LBWT: LBWT + / LBWT - / Total IVF **42** **8** 50 IVF/ICSI **34** **13** 47 Total 76 21 97 Value / Lower 95% CI / Upper 95% CI Rel risk 1.16 0.94 1.44	**Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: - Adequate description of the cohort: - Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: +/- Analysis (multivariate adjustments) and reporting of results: -
Raty, Virtanen, Koskinen, et al., 2000	**Geographical location:** Turku, Oulu, Tampere, and Helsinki, Finland	**Age:** NR **Race/ethnicity (n [%]):** NR	**Definition(s) of outcome(s):** Multiples of median for	1) Multiples of median, AFP (95% CIs): Singleton: 1.00 (0.57,1.79) Spontaneous twins: 2.18 (1.24, 3.84) IVF twins: 2.30 (1.29, 4.68)	**Comments:** Test positive rate not reported **Quality assessment:**

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#8300	**Study dates:** 1994-1996 **Size of population (no. of patients):** 6548 singleton pregnancies (unclear if all spontaneous or some ART) 145 spontaneous twins 30 IVF twins **Study type:** Cohort	**Diagnoses (n [%]):** NR **Inclusion criteria:** NR **Exclusion criteria:** NR	AFP (n < 100 for free ß-hCG) APF drawn 14-18 weeks		Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: - Adequate description of the cohort: - Use of validated method for ascertaining exposure: - Use of validated method for ascertaining clinical outcomes: - Adequate follow-up period: + Completeness of follow-up: - Analysis (multivariate adjustments) and reporting of results: -
Raziel, Friedler, Schachter, et al., 2002 **#3030**	**Geographical location:** Israel **Study dates:** Jan 1994-Dec 1999 **Size of population:** 104 **Study type:** Cohort	**Age:** Pregnant 28 (4.5) Non-pregnant 29.4 (4) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - IVF - Hospitalization for OHSS **Exclusion criteria:** No embryo transfer performed	**Definition(s) of outcome(s):** Outcomes not defined	1) Pregnancy rate in OHSS vs no OHSS: Preg + / Preg - / Total OHSS +: **60** / **44** / 104 OHSS -: **1138** / **3784** / 4922 Total: 1198 / 3828 / 5026 Value / Lower 95% CI / Upper 95% CI Rel risk: 2.50 / 2.10 / 2.96 2) SAb rate in OHSS vs. no OHSS: Sab + / Sab - / Total OHSS +: **23** / **37** / 60 OHSS -: **169** / **969** / 1138 Total: 192 / 1006 / 1198 Value / Lower 95% CI / Upper 95% CI Rel risk: 2.58 / 1.82 / 3.66	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: - Adequate description of the cohort: - Use of validated method for ascertaining clinical outcomes: - Adequate follow-up period: + Completeness of follow-up: +/- Analysis (multivariate adjustments) and reporting of results: -
Reefhuis, Honein, Shaw, et al., 2003	**Geographical location:** San Francisco, Santa Clara, CA Atlanta, GA	**Age:** Mean (SD): 28.3 cases, 28.2 controls	**Definition(s) of outcome(s):** Case records were	Crude data are below. Analyses on subgrps done for potential confounders (mat age, white mat race, singleton births, nonsmoking mothers), but	**Comments:** Relied on maternal reports of fertility assistance use

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#16850	Iowa **Study dates:** Infants born: Jan 1993 - Jul 1996 (CA) Jan 1993 - Aug 1997 (GA) Jan 1993 - Dec 1995 (IA) **Size of population:** 99 cases, 777controls **Study type:** Case-control Used telephone interview, standard interview instrument	**Race/ethnicity (n [%]):** Cases 88% white, ctrls 64% white **Diagnoses (n [%]):** NR **Inclusion criteria:** Database of birth defects reviewed for infants with craniosynostosis. Controls were liveborn infants with no major birth defects **Exclusion criteria:** Infants with chromosomal anomalies or recognized syndromes, mothers with first-degree family history of craniosynostosis, mothers who did not speak English or Spanish.	reviewed by clinical geneticist & classified as isolated or assoc w/1 or more other unrelated birth defects. Use of ovulation stimulation = reported use from 3 mos before until 3 mos after conception	data too sparse to allow for simultaneous adjustment. Stronger association between CC and craniosynostosis in younger mothers (OR 5.5 [1.1-23.5]) & nonsmokers (OR 4.5 [1.2-14.8]). 1) Use of any fertility assistance: cases: any fert assist **10**, none **31**; ctrls: **89**, **744**; Total: 99, 775; Total 41, 833, 874 Odds rat 2.70 (Lower 95% CI 1.28, Upper 95% CI 5.69) 2) Use of clomiphene citrate: cases: CC only **5**, none **14**; ctrls: **89**, **753**; Total: 94, 767; Total 19, 842, 861 Odds rat 3.02 (Lower 95% CI 1.06, Upper 95% CI 8.59) 3) Use of artificial insemination: cases: AI **3**, none **6**; ctrls: **89**, **753**; Total: 92, 759; Total 9, 842, 851 Odds rat 4.23 (Lower 95% CI 1.04, Upper 95% CI 17.21) These CI's are a little different from published 4) Use of ART: cases: ART **2**; ctrls: **89**; Total 91	**Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: + Verification that the control is free of cancer: NR Comparability of cases and controls with respect to potential confounders: + Validated dietary assessment method: NR Appropriateness of statistical analyses: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				none **4** **753** 757 Total 6 842 848 Value / Lower 95% CI / Upper 95% CI Odds rat 4.23 0.76 23.43 These CI's are a little different from published	
Repokari, Punamaki, Poikkeus, et al., 2006 **#55210**	**Geographical location:** Helsinki, Finland **Study dates:** Recruited during 1999 **Size of population (no. of patients):** ART: 367, control: 379 **Study type:** Cohort	**Age:** Mean (SD): ART: 33.0 (4.2) Control: 33.3 (4.0) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 26% Male factor: 27% All female: 33% Mixed: 20% **Inclusion criteria:** Finnish speaking ART: - Volunteering Finnish-speaking - Confirmed viable singleton pregnancy after either fresh or frozen IVF or - ICSI with their own gametes **Exclusion criteria:** Controls: - Previous infertility - Previous infertility treatment - Maternal age < 25 years	**Definition(s) of outcome(s):** Questionnaires filled out by both parents - 2nd trimester - child aged 2 months - child aged 12 months Instruments included: Parenting Stress Index (Abidin)	1) Mother: Scores for overall parenting higher for ART group; increased significantly from 2 months to 12 months for ART group but not for control. 2) Obstetric risk factors and problems, difficult child characteristics negatively associated with parenting in control group but not ART group.	**Comments:** Same population as Poikkeus, Saisto, Unkila-Kallio, et al., 2006 (#54990) **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Repokari, Punamaki, Unkila-Kallio, et al., 2007 **#72370**	**Geographical location:** Helsinki, Oulu, and Turu, Finland **Study dates:** NR **Size of population (no. of patients):** 367 singleton pregnancies after ART, 379 singleton pregnancies after spontaneous conception **Study type:** Cohort	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Finnish-speaking couples who had viable pregnancies after ART (fresh or frozen embryo transfer after IVF or ICSI treatment with their own gametes) during 1999 at five infertility clinics in Finland - Controls recruited from couples undergoing routine second trimester ultrasound at Helsinki hospital **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Dyadic adjustment scale Dyadic consensus (agreement on time, finances, etc) Dyadic cohesion (common interests, time together) Marital satisfaction (# quarrels, general happiness with each other) Sexual affection Measured during pregnancy, when child 2 months and 12 months	1) Dyadic cohesion decreased from 2 – 12 months for control women 2) Sexual satisfaction significantly lower at 2 months for control men, returned to same as ART men by 12 months	**Comments:** Dropout rate higher among controls (34% vs. 27%) **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: - Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: - Analysis (multivariate adjustments) and reporting of results: +
Rice, McIntosh, and Halstead, 2005 **#9050**	**Geographical location:** British Columbia **Study dates:** Jan 1999 - Dec 2002 **Size of population:** IVF 88 Natural 596 **Study type:** Cohort	**Age:** Mean 33-34 Range 21.05 – 44.93 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Matched controls for maternal age, gestational age at time of sampling, serum sampling date **Exclusion criteria:** If corrected for Insulin-dependent diabetes or ethnicity Multiple gestations, even if	**Definition(s) of outcome(s):** Down's Syndrome = serum analysis of screen positive 1/385 or greater	1) Analyte levels in Down's Syndrome false positive rate: screen+ / screen- / Total IVF: **15** / **73** / 88 spontaneous: **81** / **515** / 596 Total: 96 / 588 / 684 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.25 / 0.76 / 2.07	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: +/- Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: - Completeness of follow-up: - Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		>1 sac on early ultrasound			
Romundstad, Romundstad, Sunde, et al., 2006 **#55320**	**Geographical location:** Norway **Study dates:** 1988-2002 **Size of population (no. of patients):** 502, 840 pregnancies **Study type:** Cohort	**Age:** % < 30: ART: 18.6% (singletons), 21.6% (twins) Spontaneous: 59.7% (singletons), 50.4% (twins) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Norwegian Birth Registry **Exclusion criteria:** - Gestational age < 22 wk - Birthweight < 500 g - Mother < 20 - Parity ≥ 5	**Definition(s) of outcome(s):** Placenta previa, diagnosed on US at 18 and 32 wk, confirmed at birth	1) Placenta previa, ART singletons: PP + / PP - / Total ART + : **89** / **5492** / 5581 ART - : **1821** / **825088** / 826909 Total: 1910 / 830580 / 832490 Value (Lower 95% CI – Upper 95% CI) Rel risk: 7.24 (5.86 – 8.94) Odds ratio after adjustment for maternal age, parity, previous C-section, duration between births, year of birth: 5.6 (95% CI 4.4, 7.0) 2) Placenta previa, ART twins: PP + / PP - / Total ART + : **16** / **1971** / 1987 ART - : **23** / **10884** / 10907 Total: 39 / 12855 / 12894 Value (Lower 95% CI – Upper 95% CI) Rel risk: 3.82 (2.02 – 7.21) Odds ratio after adjustment for maternal age, parity, previous C-section, duration between births, year of birth: 2.9 (95% CI 1.5, 5.8) 3) In 1349 women with pregnancies after both spontaneous and assisted conception, odds ratio for placenta previa with assisted conception after adjustment for maternal age, parity, and previous C-section: 2.9 (1.4, 6.1)	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
Rossing, Tang, Flagg, et al., 2004 **#12060**	**Geographical location:** Atlanta, GA, Detroit, MI, Seattle, WA **Study dates:** 1994 -	**Age:** Range: 35-54 Age stratified into 5-yr blocks	**Definition(s) of outcome(s):** History of infertility and use of ovulation inducing	Results stratified by Nulliparous vs. parous 1) Nulliparous, history of infertility: Ov CA+ / Ov CA- / Total	**Comments:** None **Quality assessment:** Valid ascertainment of cases: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	1998 **Size of population:** 378 cases interviewed of 547 eligible, 1,637 controls of 2,228 available **Study type:** Case-control, in-person interviews, identified subjects through tumor registry	**Race/ethnicity (n [%]):** Cases 13.5% black Controls 27.1% black, all else white **Diagnoses (n):** Endometriosis: 23 Tubal factor: 52 ovarian: 34 Cervical: 7 Endocrine: 27 Uterine: 26 **Inclusion criteria:** English speaking, white or black women residents of specified cities, 35-54 yrs old when diagnosed with first ovarian cancer, telephone service **Exclusion criteria:** NR	drugs on risk of ovarian cancer	Infertility + **42** **66** 108 Infertility- **98** **245** 343 Total 140 311 451 Value Lower 95% CI Upper 95% CI Odds rat 1.59 1.01 2.50 2) Parous, history of infertility: Ov CA+ Ov CA- Total Infertility + **101** **169** 270 Infertility- **512** **779** 1291 Total 613 948 1561 Value Lower 95% CI Upper 95% CI Odds rat 0.91 0.69 1.19 3) Nulliparous, use of ovulation-inducing drugs: Ov CA+ Ov CA- Total ovulation induction + **5** **103** 108 ovulation induction - **18** **325** 343 Total 23 428 451 Value Lower 95% CI Upper 95% CI Odds rat 0.88 0.32 2.42 4) Parous, use of ovulation-inducing drugs: Ov CA+ Ov CA- Total ovulation indx+ **12** **258** 270 ovulation indx - **67** **1224** 1291 Total 79 1482 1561	Unbiased selection of cases: + Appropriateness of the control population: + Verification that the control is free of cancer: - Comparability of cases and controls with respect to potential confounders: + Validated dietary assessment method: n/a Appropriateness of statistical analyses: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results				Comments/Quality Scoring
					Value	Lower 95% CI	Upper 95% CI	
				Odds rat	0.85	0.45	1.59	

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Saygan-Karamursel, Tekam, Aksu, et al., 2006 **#55480**	**Geographical location:** Ankara, Turkey **Study dates:** 1999-2003 **Size of population (no. of patients):** All twins 274 ICSI (12 underwent fetal reduction from triplets to twins) 348 spontaneous conception **Study type:** Cohort	**Age:** Mean (SD): ICSI: 31.45 (4.42) Spontaneous: 28.94 (4.37) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** All twins delivered after 24wks **Exclusion criteria:** Any ovarian stimulation or insemination procedures in control group	**Definition(s) of outcome(s):** Preterm birth < 37 wk Low birthweight < 2500 g Respiratory distress syndrome Perinatal morbidity and mortality (> 22 wks gestation stillbirth + neonatal death to 7 days of life)	1) Preterm birth: PTB + / PTB - / Total ICSI: **210** / **64** / 274 Spontaneous: **223** / **125** / 348 Total: 433 / 189 / 622 Value: 1.20 (Lower 95% CI: 1.08, Upper 95% CI: 1.32) 2) Low birthweight: LBWT + / LBWT - / Total ICSI: **200** / **74** / 274 Spontaneous: **210** / **138** / 348 Total: 410 / 212 / 622 Value: 1.21 (Lower 95% CI: 1.08, Upper 95% CI: 1.35) 3) Gestational diabetes: GDM + / GDM - / Total ICSI: **22** / **252** / 274 Spontaneous: **10** / **338** / 348 Total: 32 / 590 / 622 Value: 2.79 (Lower 95% CI: 1.35, Upper 95% CI: 5.80) 4) Respiratory distress syndrome: RDS + / RDS - / Total ICSI: **15** / **259** / 274 Spontaneous: **5** / **343** / 348 Total: 20 / 602 / 622	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: - Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

	Value	Lower 95% CI	Upper 95% CI
Rel risk	3.81	1.40	10.35

5) Perinatal mortality:

	Perinatal mort +	Perinatal mort -	Total
ICSI	**22**	**252**	274
Spon-taneous	**9**	**339**	348
Total	31	591	622

	Value	Lower 95% CI	Upper 95% CI
Rel risk	3.10	1.45	6.63

6) Perinatal morbidity:

	Perinatal morbidity +	Perinatal morbidity -	Total
ICSI	**45**	**229**	274
Spon-taneous	**27**	**321**	348
Total	72	550	622

	Value	Lower 95% CI	Upper 95% CI
Rel risk	2.12	1.35	3.32

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Schachter, Raziel, Friedler, et al. 2001 **#5060**	**Geographical location:** Tel Aviv, Israel **Study dates:** 1997 - 99 **Size of population:** 731 **Study type:** Cohort (retrospective)	**Age:** Mean (SD): OI/COH 30.2 (6.7) IVF **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Pregnancy after ART (OI w/COH, IVF, or micromanipulation (ICSI or assisted hatching) **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Monozygotic twinning = chorionicity demonstrated by US up to 9wks	1) MZ twinning by method of conception: OI vs IVF: MZ+ / MZ- / Total OI: **2** / **127** / 129 IVF: **1** / **138** / 139 Total: 3 / 265 / 268 Value (Lower 95% CI, Upper 95% CI) Odds rat: 2.17 (0.19, 24.26) 2) MZ twinning by method of conception: IVF vs IVF w/micromanipulation: MZ+ / MZ- / Total IVF: **1** / **138** / 139 micro: **4** / **459** / 463 Total: 5 / 597 / 602 Value (Lower 95% CI, Upper 95% CI) Odds rat: 0.83 (0.09, 7.50) 3) MZ twinning by method of conception: OI vs IVF w/micromanipulation: MZ+ / MZ- / Total OI: **2** / **127** / 129 micro: **4** / **459** / 463 Total: 6 / 586 / 592 Value (Lower 95% CI, Upper 95% CI) Odds rat: 1.81 (0.33, 9.98)	**Comments:** - Micromanipulation grp is heterogeneous in indications as well as procedures. - Ultrasound may mistakenly characterize zygosity **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: - Use of validated method for genomic test: n/a Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Schieve, Meikle, Ferre, et al., 2002 **#2510**	**Geographical location:** U.S. national data **Study dates:** 1996-1997 **Size of population:** 42,463 infants (18,408 singletons) **Study type:** Cohort	**Age:** Range: 20-60 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 7.8% Female factor: 68.1% Male factor: 24.1% **Inclusion criteria:** - Infants born in 1996 and 1997 - Conceived with ART **Exclusion criteria:** - Stillbirths (n = 182) - Missing birthweight (n = 3241)	**Definition(s) of outcome(s):** Low birth weight ≤ 2500 g Very low birthweight < 1500 g	1) LBWT for ART vs. spontaneous: ART: **2423** / **15975** / 18398 Spontaneous: **1339.4** / **17058.6** / 18398 Total: 3762.4 / 33033.6 / 36796 Rel risk: 1.81 (1.70 – 1.93) 2) Very LBWT for ART vs. spontaneous: ART: **480** / **17918** / 18398 Spontaneous: **263.4** / **18134.6** / 18398 Total: 743.4 / 36052.6 / 36796 Rel risk: 1.82 (1.57 – 2.11)	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -
Schieve, Tatham, Peterson, et al., 2003 **#16730**	**Geographical location:** United States **Study dates:** 1996-98 **Size of population (no. of patients):** N = 62,228 ART pregnancies **Study type:** Cohort	**Age:** 20-20 n = 8143 30-34 n = 22,190 35-37 n = 14,128 38-40 n = 9948 41-43 n = 4899 44-47 n = 2372 48-55 n = 548 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 4886, 7.9% Endometriosis: 8531, 13.7%	**Definition(s) of outcome(s):** Spontaneous abortion = loss of entire pregnancy	1) Spontaneous abortion, singletons vs. triplets (derived from total number of pregnancies and reported rates by plurality): Twins: **1379** / **17012** / 18391 Singleton: **7118** / **27865** / 34983 Total: 8497 / 44877 / 53374 Rel risk: 0.37 (0.35 – 0.39)	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: - Adequate follow-up period: - Completeness of follow-up: - Analysis (multivariate adjustments)

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		Male factor: 15,350, 24.7% Tubal factor: 15,450, 24.8% PCOS:9716, 15.6% Other (specify): Uterine factor 1201, 1.9% Other causes 7089, 11.4% **Inclusion criteria:** Clinical pregnancy **Exclusion criteria:** - Ectopic pregnancy - Incomplete data - Stillbirths - Induced abortions			and reporting of results: +
Schimmel, Hammer-man, Lusky, et al., 2006 **#55510**	**Geographical location:** Israel **Study dates:** 1995-2002 **Size of population (no. of patients):** 8181 **Study type:** Cohort	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** LIveborn, <1500 grams **Exclusion criteria:** - < 24 weeks - Liveborns from pregnancies with selective reduction, stillbirth, or elective termination - Pregnancies from non-ART infertility treatment (e.g., ovulation induction) - Greater than 3 infants	**Definition(s) of outcome(s):** Mortality—death prior to discharge from hospital Necrotizing enterocolitis (NEC) Intraventricular hemorrhage (IVH) Respiratory distress syndrome (RDS) Bronchopulmonary dysplasia (BPD) Patent ductus arteriosis (PDA) Congenital malformations	1) Adjusted odds ratios, ART vs spontaneous singletons (adjusted for maternal age, gestational age, birth weight, SGA, ethnicity, antenatal steroid therapy, maternal hypertension, delivery mode, and resuscitation): Outcome / OR / 95%CI Mortality 1.06 0.72,1.53 RDS 0.87 0.65,1.17 PDA 1.04 0.76,1.41 NEC 0.75 0.41,1.27 IVH 1.35 0.82,2.13 BPD 0.91 0.58,1.39 Malformation 1.47 0.96,2.19 2) Adjusted odds ratios, ART vs spontaneous singletons (adjusted for maternal age, gestational age, birth weight, SGA, ethnicity, antenatal steroid therapy, maternal hypertension, delivery mode, and resuscitation): Outcome / OR / 95%CI Mortality 0.71 0.51,1.01 RDS 0.88 0.64,1.22 PDA 1.01 0.77,1.32	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes:+ Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

NEC	0.95	0.61,1.49
IVH	0.78	0.53,1.14
BPD	0.76	0.50,1.16
Malformation	0.84	0.52,1.37

3) Adjusted odds ratios, ART vs spontaneous triplets (adjusted for maternal age, gestational age, birth weight, SGA, ethnicity, antenatal steroid therapy, maternal hypertension, delivery mode, and resuscitation):

Outcome	OR	95%CI
Mortality	0.73	0.25,2.15
RDS	1.58	0.53,1.67
PDA	0.74	0.32,1.71
NEC	0.76	0.17,3.34
IVH	1.78	0.60,5.30
BPD	0.97	0.33,2.86
Malformation	4.31	0.63,29.4

Sheard, Cox, Oates, et al., 2007

#72500

Geographical location: Nottingham, UK

Study dates: NR

Size of population (no. of patients): 175

Study type: Cohort

Age:
Median:
Singletons 33
Multiples 34

Race/ethnicity (n [%]): NR

Diagnoses (n [%]): NR

Inclusion criteria:
- Known to have successfully conceived following treatment for infertility at a research and treatment unit in a UK hospital
- At least 18 weeks pregnant;
- Resident in the UK and English speaking
- First time mothers.

Definition(s) of outcome(s):

Depression at 6 weeks postpartum measured by Edinburgh Postnatal Depression Scale

1) Depression (EPDS > 12), multiples vs. singletons:

	EPDS >12	EPDS ≤12	Total
Multiples	**7**	**39**	46
Singletons	**6**	**99**	105
Total	13	138	151

	Value	Lower 95% CI	Upper 95% CI
Rel risk	2.66	0.95	7.49

2) Adjusted for maternal age, cesarean, weeks postpartum, and “unsettled baby” score, risk for EPDS > 12 for multiples 3.43 (1.01, 11.6)

Comments:
Only 38% acceptance rate

Quality assessment:
Unbiased selection of the cohort (prospective recruitment of subjects): +
Large sample size: -
Adequate description of the cohort: +
Use of validated method for ascertaining exposure: +
Use of validated method for ascertaining clinical outcomes: +
Adequate follow-up period: +
Completeness of follow-up: +
Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		Exclusion criteria: - Unable to be contacted at time point - Neonatal death - Not available for interview			
Sheiner, Shoham-Vardi, Hershkovitz, et al., 2001 **#3790**	**Geographical location:** Beer Sheva, Israel **Study dates:** 1990-98 **Size of population:** Infertility treatment n = 35 Spontaneous conception n = 80 **Study type:** Cohort (retrospective)	**Age:** Mean (SD): Infertility: 43.9 (9.3) Spontaneous: 43.9 (5.9) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** All singleton births to nulliparous women > 40 yo during study period **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Cesarean section	1) Infertility treatment as risk factor for C/S: C/S + / C/S - / Total Infert: **25** / **10** / 35 Spont: **33** / **47** / 80 Total: 58 / 57 / 115 Value (Lower 95% CI – Upper 95% CI) Odds rat: 3.56 (1.51 – 8.40) When adjusted for malpresentation, arrest of 1st/2nd stage, NRFHR, abruption, previa, cord prolapse, PROM, hydramnios, oligo, GDMA2, failed induction, severe PIH, IUGR – OR remained significantly elevated.	**Comments:** - Authors state this institution is regional teaching hospital at which virtually all births to women in southern Israel take place, so nonselective - Infertility grp included IVF & OI pts - Infertility grp gave birth to more infants with BW < 2500 g and > 4000 g - Comparable rates of PTD, medical problems, induction of labor, meconium-stained fluid, congenital malformations, placenta previa, abruption, malpresentation - No mention of maternal obesity **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: - Adequate description of the cohort: + Use of validated method for genomic test: n/a Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
Shevell, Malone,	**Geographical location:** U.S., multicenter	**Age:** Spontaneous 29.9 (5.7)	**Definition(s) of outcome(s):**	1) PTB for ovulation indx vs. spontaneous:	**Comments:** None

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Vidaver, et al., 2005 **#39410**	**Study dates:** 1999-2002 **Size of population:** 36,062 pregnancies-34,286 spontaneous, 1222 ovulation induction, 554 IVF **Study type:** Cohort	Ovulation indx 32.6 (5.1) IVF 34.5 (5.2) **Race/ethnicity (n [%]):** Spont / ov indx / IVF: African Am 5.3/ 1.6/ 2.7 Hispanic 23.3/ 4.5/ 4.5 White 66.6/ 88.6/ 86.3 Other 4.9/ 5.2/ 6.5 **Diagnoses (n [%]):** NR **Inclusion criteria:** - Singleton pregnancy - Enrolled 10-13.9 wk into FASTER trial for noninvasive Downs syndrome screening **Exclusion criteria:** Pts who elected pregnancy termination	FGR < 10th percentile LBWT < 2500 g Preeclampsia (gestational HTN + proteinuria) PTB < 37 wk PPROM < 37 wk Placental abruption – premature separation of placenta Placenta previa GDM Cesarean delivery Fetal aneuploidy Congenital anomalies – major or minor confirmed at birth		**Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

	PTB +	PTB -	Total
Ov indx	**8**	**114**	122
Spont	**1783**	**32503**	34286
Total	1791	32617	34408

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.26	0.64	2.47

2) PTB for IVF vs. spontaneous:

	PTB +	PTB -	Total
IVF	**38**	**516**	554
Spont	**1783**	**32503**	34286
Total	1821	33019	34840

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.32	0.97	1.80

3) FGR for ovulation indx vs. spontaneous:

	FGR +	FGR -	Total
Ov indx	**3**	**119**	122
Spont	**377**	**33909**	34286
Total	380	34028	34408

	Value	Lower 95% CI	Upper 95% CI
Rel risk	2.24	0.73	6.87

4) FGR for IVF vs. spontaneous:

	FGR +	FGR -	Total
IVF	**5**	**549**	554
Spont	**377**	**33909**	34286
Total	382	34458	34840

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.82	0.34	1.98

5) LBWT for ov indx vs. spontaneous:

	LBWT +	LBWT -	Total

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

Ov indx	**9**	**113**	122
Spont	**1749**	**32537**	34286
Total	1758	32650	34408

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.45	0.77	2.72

6) LBWT for IVF vs. spontaneous:

	LBWT +	LBWT -	Total
IVF	**33**	**521**	554
Spont	**1749**	**32537**	34286
Total	1782	33058	34840

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.17	0.84	1.63

7) Preeclampsia for ov indx vs. spontaneous:

	Preecl +	Preecl -	Total
Ov indx	**4**	**118**	122
Spont	**823**	**33463**	34286
Total	827	33581	34408

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.37	0.52	3.59

8) Preeclampsia for IVF vs. spontaneous:

	Preecl +	Preecl -	Total
IVF	**26**	**528**	554
Spont	**823**	**33463**	34286
Total	849	33991	34840

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.96	1.34	2.86

9) Gestational diabetes for ov indx vs. spontaneous:

	GDM +	GDM -	Total

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

Ov indx	**7**	**115**	122
Spont	**1166**	**33120**	34286
Total	1173	33235	34408

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.69	0.82	3.47

10) Gestational diabetes for IVF vs. spontaneous:

	GDM +	GDM -	Total
IVF	**15**	**539**	554
Spont	**1166**	**33120**	34286
Total	1181	33659	34840

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.80	0.48	1.32

11) Cesarean delivery for ov indx vs. spontaneous:

	Ces +	Ces -	Total
Ov indx	**32**	**90**	122
Spont	**8091**	**26195**	34286
Total	8123	26285	34408

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.11	0.82	1.50

12) Cesarean delivery for IVF vs. spontaneous:

	Ces +	Ces -	Total
IVF	**261**	**293**	554
Spont	**8091**	**26195**	34286
Total	8352	26488	34840

	Value	Lower 95% CI	Upper 95% CI
Rel risk	2.00	1.82	2.18

13) PPROM for ov indx vs. spontaneous:

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

	PPROM +	PPROM -	Total
Ov indx	**2**	**120**	122
Spont	**549**	**33737**	34286
Total	551	33857	34408

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.02	0.26	4.06

14) PPROM for IVF vs. spontaneous:

	PPROM +	PPROM -	Total
IVF	**12**	**542**	554
Spont	**549**	**33737**	34286
Total	561	34279	34840

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.35	0.77	2.38

15) Placental abruption for ov indx vs. spontaneous:

	Abrupt +	Abrupt -	Total
Ov indx	**2**	**120**	122
Spont	**240**	**34046**	34286
Total	242	34166	34408

	Value	Lower 95% CI	Upper 95% CI
Rel risk	2.34	0.59	9.31

16) Placental abruption for IVF vs. spontaneous:

	Abrupt +	Abrupt -	Total
IVF	**12**	**542**	554
Spont	**240**	**34046**	34286
Total	252	34588	34840

	Value	Lower 95% CI	Upper 95% CI

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

	Value	Lower 95% CI	Upper 95% CI
Rel risk	3.09	1.74	5.49

17) Placenta previa for ov indx vs. spontaneous:

	Previa +	Previa -	Total
Ov indx	**1**	**121**	122
Spont	**206**	**34080**	34286
Total	207	34201	34408

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.36	0.19	9.65

18) Placenta previa for IVF vs. spontaneous:

	Previa +	Previa -	Total
IVF	**12**	**542**	554
Spont	**206**	**34080**	34286
Total	218	34622	34840

	Value	Lower 95% CI	Upper 95% CI
Rel risk	3.61	2.03	6.41

19) Aneuploidy for ov indx vs. spontaneous:

	Aneupl +	Aneupl -	Total
Ov indx	**0.5**	**121.5**	122
Spont	**137**	**34149**	34286
Total	137.5	34270.5	34408

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.03	0.06	16.39

20) Aneuploidy for IVF vs. spontaneous:

	Aneupl +	Aneupl -	Total
IVF	**2**	**552**	554
Spont	**137**	**34149**	34286
Total	139	34701	34840

	Value	Lower 95% CI	Upper 95% CI

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

Rel risk 0.90 0.22 3.64

21) Congenital anomalies for ov indx vs. spontaneous:

	Anomaly +	Anomaly -	Total
Ov indx	**3**	**119**	122
Spont	**651**	**33635**	34286
Total	654	33754	34408

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.30	0.42	3.97

22) Congenital anomalies for IVF vs. spontaneous:

	Anomaly +	Anomaly -	Total
IVF	**19**	**535**	554
Spont	**651**	**33635**	34286
Total	670	34170	34840

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.81	1.15	2.83

Sillis, Moomjy, Zaninovic, et al. 2000	**Geographical location:** New York, New York **Study dates:** Jan 1995 - March 1998	**Age (mean [SD]):** 35 (4.0) **Race/ethnicity (n [%]):** NR	**Definition(s) of outcome(s):** NR	1) Monozygotic twin rate in assisted hatching vs. routine IVF:	**Comments:** None **Quality assessment:** Unbiased selection of the cohort

	MZ twins+	MZ twins-	Total

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#8190	**Size of population:** 1,911 patients with 23 monozygotic twins **Study type:** Cohort	**Diagnoses (n [%]):** All had male factor but female factors not described **Inclusion criteria:** IVF patients with documented pregnancy by u/s **Exclusion criteria:** NR		AH **9** **636** 645 IVF **3** **210** 213 Total 12 846 858 Value / Lower 95% CI / Upper 95% CI Rel risk 0.99 0.27 3.63 2) MZ twin rate in ICSI vs. routine IVF: MZ twins+ / MZ twins- / Total ICSI **2** **175** 177 IVF **3** **210** 213 Total 5 385 390 Value / Lower 95% CI / Upper 95% CI Rel risk 0.80 0.14 4.75 3) MZ twin rate for assisted hatching + icsi vs. routine IVF: MZ twins+ / MZ twins- / Total AH+ICSI **9** **868** 877 IVF **3** **210** 213 Total 12 1078 1090 Value / Lower 95% CI / Upper 95% CI Rel risk 0.73 0.20 2.67	(prospective recruitment of subjects): not stated Large sample size: + Adequate description of the cohort: - Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -
Soares, Troncoso, Bosch, et al., 2005	**Geographical location:** Valencia, Spain **Study dates:** 1999-2003	**Age:** Oocyte recipients 38.9 (5.2) **Race/ethnicity (n [%]):**	**Definition(s) of outcome(s):** PTB not defined	1) PTB by age of oocyte recipient: PTB + / PTB - / Total ≥ 45 yo **8** **4** 12 < 45 yo **18** **76** 94	**Comments:** None **Quality assessment:** Unbiased selection of the cohort

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
#8920	**Size of population (no. of patients):** 106 singleton births **Number of cycles analyzed:** 3089 oocyte donation cycles **Number of cycles per patient:** # oocyte recipients not reported **Study type:** Cohort	NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Oocyte recipient IVF **Exclusion criteria:** Severe male factor	Hypertension GDM PPROM Cesarean delivery	Total 26 80 106 Value / Lower 95% CI / Upper 95% CI Rel risk 3.48 1.96 6.20 2) Hypertension by age of oocyte recipient: HTN + / HTN - / Total ≥ 45 yo **4** **8** 12 < 45 yo **10** **84** 94 Total 14 92 106 Value / Lower 95% CI / Upper 95% CI Rel risk 3.13 1.16 8.45 3) GDM by age of oocyte recipient: GDM + / GDM - / Total ≥ 45 yo **3** **9** 12 < 45 yo **13** **81** 94 Total 16 90 106 Value / Lower 95% CI / Upper 95% CI Rel risk 1.81 0.60 5.44 4) PPROM by age of oocyte recipient: PPROM + / PPROM - / Total ≥ 45 yo **3** **9** 12 < 45 yo **4** **90** 94 Total 7 99 106 Value / Lower 95% CI / Upper 95% CI Rel risk 5.88 1.49 23.15 5) Cesarean delivery by age of oocyte recipient: C/S + / C/S - / Total ≥ 45 yo **12** **0** 12	(prospective recruitment of subjects): + Large sample size: - Adequate description of the cohort: - Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: - Adequate follow-up period: - Completeness of follow-up: - Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				< 45 yo: **78** / **16** / 94 Total: 90 / 16 / 106 Rel risk (Value / Lower 95% CI / Upper 95% CI): 1.16 / 1.01 / 1.34	
Spandorfer, Davis, Barmat, et al., 2004 **#13220**	**Geographical location:** New York, NY **Study dates:** 1991-96 **Size of population:** 2014 IVF pregnancies 233 spontaneous loss after cardiac activity 1781 deliveries **Study type:** Retrospective cohort	**Age:** Mean (SD): SAb: 37.3 (3.8) Normal: 35.1 (4.1) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** IVF with fresh embryo transfer **Exclusion criteria:** Selective reduction Elective termination due to chromosome abnl or congenital malformation	**Definition(s) of outcome(s):** Spontaneous abortion = fetal loss after documented fetal cardiac activity by 7-wk US	Overall 11.6% SAb incidence 1) SAb risk by age: SAb + / SAb - / Total Age ≥ 35: **171** / **940** / 1111 Age < 35: **62** / **841** / 903 Total: 233 / 1781 / 2014 Rel risk (Value / Lower 95% CI / Upper 95% CI): 2.24 / 1.70 / 2.96	**Comments:** Report aneuploidy/chromosome results from 71/233 SAbs, difficult to interpret results due to significant amount of missing data **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: - Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -
Stromberg, Dahlquist, Ericson, et al., 2002 **#2700**	**Geographical location:** Sweden **Study dates:** 1982 - 1995	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):**	**Definition(s) of outcome(s):** NR	1) Treatment at childhood disability center for IVF vs. spontaneous singletons: Treat + / Treat - / Total IVF: **45** / **3183** / 3228 spontan: **115** / **10955** / 11070	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Size of population: All plurality IVF 5,680 Spontaneous 11,360 Twins only IVF 2,060 Spontaneous 4,120 **Study type:** Cohort	NR **Inclusion criteria:** 2 population based controls per IVF case, matched for sex, yr of birth & hospital 18 mos or older at time of f/u in 1997 **Exclusion criteria:** NR		eous Total 160 14138 14298 Value / Lower 95% CI / Upper 95% CI Rel risk 1.34 0.95 1.89 2) Treatment at childhood disability center for IVF vs. spontaneous all plurality: Treat + / Treat - / Total IVF **101** **5579** 5680 spontaneous **119** **11241** 11360 Total 220 16820 17040 Value / Lower 95% CI / Upper 95% CI Rel risk 1.70 1.30 2.21 3) Cerebral palsy for IVF vs. spontaneous singletons: CP+ / CP- / Total IVF **12** **3216** 3228 spontaneous **15** **11055** 11070 Total 27 14271 14298 Value / Lower 95% CI / Upper 95% CI Rel risk 2.74 1.29 5.86 4) Cerebral palsy for IVF vs. spontaneous twins: CP+ / CP- / Total IVF **15** **2045** 2060 spontaneous **28** **4092** 4120 Total 43 6137 6180 Value / Lower 95% CI / Upper 95% CI Rel risk 1.07 0.57 2.00	subjects): - Large sample size: + Adequate description of the cohort: - Use of validated method for ascertaining clinical outcomes: +/- Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Sun, Verster-gaard, Christen-sen, et al., 2007 **#56000**	**Geographical location:** Denmark **Study dates:** Oct 1997-June 2003 **Size of population (no. of patients):** 83,194 **Study type:** Cohort	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Singleton pregnancy - Enrolled in Danish National Birth Cohort Study **Exclusion criteria:** - Incomplete data on time to pregnancy (n=3539) - Infertility treatment, but not for index pregnancy (n=76)	**Definition(s) of outcome(s):** Epilepsy—ICD-10 coding from Danish Hospital Registry Febrile seizures—ICD-10 coding, event between 3 months and 5 years, no history of epilepsy prior to event	1) Epilepsy: Group / Adjusted incidence rate ratio* / 95% CI Conceived 1-5 months / 1.00 (ref) / Untreated subfertility / 1.38 / 1.00,1.89 IVF/ICSI / 1.83 / 1.09,3.06 IUI/hormone / 1.73 / 1.06,2.71 *Adjusted for maternal age, social status, BMI, smoking, maternal and paternal history of epilepsy, year of birth 2) Febrile seizures: Group / Adjusted incidence rate ratio* / 95% CI Conceived 1-5 months / 1.00 (ref) / Untreated subfertility / 1.06 / 0.93,1.22 IVF/ICSI / 1.01 / 0.78,1.30 IUI/hormone / 1.37 / 1.14,1.66 *Adjusted for maternal age, social status, BMI, smoking, maternal and paternal history of epilepsy, year of birth	**Comments:** Time to pregnancy, infertility treatment self-reported (IVF validated with national registry) **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: - Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
Sutcliffe, Taylor, Saunders, et al., 2001 **#4740**	**Geographical location:** United Kingdom **Study dates:** Jan 1997-Jan 1999 **Size of population:**	**Age:** ICSI 33.56 (3.93) Natural 30.28 (3.95) **Race/ethnicity (n [%]):** NR	**Definition(s) of outcome(s):** PTB < 37wks C-section	1) PTB for IVF vs. spontaneous: ptb+ / ptb- / Total IVF: **18** / **190** / 208 spontaneous: **14** / **207** / 221 Total: 32 / 397 / 429	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects):

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	208 children born after ICSI 221 naturally conceived **Study type:** Cohort	**Diagnoses (n [%]):** All conceived through ICSI, no further info given **Inclusion criteria:** Singletons only Controls matched for age, sex, maternal education, social class, geographic region **Exclusion criteria:** NR		 Value / Lower 95% CI / Upper 95% CI Rel risk 1.37 / 0.70 / 2.68 2) C-section for IVF vs. spontaneous: C/S+ / C/S- / Total IVF: **73** / **135** / 208 spontaneous: **53** / **168** / 221 Total: 126 / 303 / 429 Value / Lower 95% CI / Upper 95% CI Rel risk 1.46 / 1.09 / 1.97 3) Neurodevelopmental scoring on Griffith's scale of mental development IVF 98.08 (10.93) vs. natural 98.69 (9.99)	Large sample size: Adequate description of the cohort: Use of validated method for genomic test: Use of validated method for ascertaining clinical outcomes: Adequate follow-up period: Completeness of follow-up: Analysis (multivariate adjustments) and reporting of results:
Sydsjo, Wadsby, Kjellberg, et al., 2002 **#450**	**Geographical location:** Linkoping, Sweden **Study dates:** Jan 1996-Dec 1997 **Size of population:** 108 Study Group 108 Controls **Study type:** Cohort	**Age:** *Study Population* Mean (SD): 31.8 ± 3.3 (women) 33.1 ± 3.3 (men) Range: 24-39 (women) 25-40 (men) *Controls* Mean (SD): Women = study grp 32.3 ± 5.8 (men) Range: Women = study grp 24-50 (men) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:**	**Definition(s) of outcome(s):** ENRICH marital inventory providing scores of each partner's evaluation of relationship in 10 categories (measured during pregnancy and postpartum): 1-Personality Issues 2-Communication 3-Conflict resolution 4-Financial management 5-Leisure activities 6-Sexual relationship 7-Children and parenting 8-Family and friends 9-Equalitarian roles 10-Conception of life PCA is measure of couples agreement on	Neither OR nor RR appropriate. ENRICH marital inventory: Both grps scored high but IVF grp scored significantly higher on six of 10 scales. At f/u there was a decline in control grp, with IVF grp scores remaining stable. PCA scores: IVF grp scored higher than control on five of 10 scales during pregnancy, and control grp scored higher on one of ten. No significant differences were detected regarding obstetrical outcomes (except higher incidence of twin gestation in IVF grp), neonatal data, or in outcome interviews between grps.	**Comments:** No power calculations **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: Adequate description of the cohort: - (no race, ethnicity, diagnosis; no psych issues identified in entire cohort) Use of validated method for genomic test: NA Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: - (but authors plan 4 yr f/u) Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results:

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		Study population – all couples pregnant through IVF at Linkoping University Hospital who agreed to participate and who did not have children Control population – participants in ongoing prospective longitudinal study at Linkoping and were pregnant for the first time matched by maternal age to study group **Exclusion criteria:** - Previous pregnancy - Refusal to participate	ENRICH Obstetrical data: - Complicated pregnancy - Twin pregnancy - GA - C-section (overall) - Normal delivery - Instrumental delivery - Ectopic Interview 12 mo PP Toddler behavior questionnaire		
Tabs, Vejnovic, Radunovic, et al., 2004 **#42230**	**Geographical location:** Novi Sad, Serbia **Study dates:** Jan 1996-Dec 2002 **Size of population:** IVF 144 Control group 39112 All singletons **Study type:** Cohort	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Singletons only **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Preeclampsia Eclampsia No definitions of outcomes given	1) Preeclampsia for IVF vs. spontaneous: Preecl + / Preecl - / Total IVF: **3** / **141** / 144 Spont: **158** / **38954** / 39112 Total: 161 / 39095 / 39256 Value / Lower 95% CI / Upper 95% CI Rel risk: 5.16 / 1.67 / 15.97 2) Eclampsia for IVF v. spontaneous: Eclamp + / Eclamp - / Total IVF: **1** / **143** / 144 Spont: **22** / **39090** / 39112 Total: 23 / 39233 / 39256 Value / Lower 95% CI / Upper 95% CI Rel risk: 12.35 / 1.68 / 90.98	**Comments:** Unadjusted for maternal age or parity **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: - Use of validated method for ascertaining clinical outcomes: - Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Terry, Willett, Rich-Edwards, et al., 2006 **#56150**	**Geographical location:** US (Nurses Health Study II) **Study dates:** Enrolled 1989, followup 1993-2001 **Size of population (no. of patients):** 116,741 **Study type:** Cohort	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Registered nurses - Age 25-42 at **Exclusion criteria:** - History of breast or other cancer - No height/weight recorded - Fertility-status unclear	**Definition(s) of outcome(s):** Breast cancer cases, confirmed by pathology report in 99% of cases	1) Adjusted* hazard ratios, by diagnosis: HR 95% CI No infertilty 1.00 (ref) Infertility due to ovulatory disorder: 0.75 0.59,0.96 Other cause infertility 1.05 0.76,1.45 *Adjusted for age, height, current body mass index, body mass index at age 18 years, family history of breast cancer, history of benign breast disease, age at menarche, parity, age at first birth, oral contraceptive use, alcohol use, and physical activity. 2) Adjusted* hazard ratios, by ovulation induction: HR 95% CI No infertilty 1.00 (ref) Ovulatory infertility no induction 1.37 0.94,1.99 Ovulatory infertility, ovulation induction 0.60 0.42,0.85 Other infertilty 0.67 0.35,1.25 *Adjusted for age, height, current body mass index, body mass index at age 18 years, family history of breast cancer, history of benign breast disease, age at menarche, parity, age at first birth, oral contraceptive use, alcohol use, and physical activity.	**Comments:** - Exposure by self-reported (confirmed in 95% of sample of 40 records) - Use of ovulatory drugs by non-ovulatory disorder subjects not assessed **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: - Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: - Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
Tul and Novak-Antolic, 2006 **#56290**	**Geographical location:** Ljubljana, Slovenia **Study dates:** Feb 1999-Aug 2001 **Size of population (no. of patients):**	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:**	**Definition(s) of outcome(s):** 1st and 2nd trimester test results (nuchal translucency, PAPP-A, inhibin A, free ß-hCG)	1) Relative risk for positive results (risk > 1/300), based on nuchal translucency + free ß-hCG + PAPP-A + maternal age, IVF: Out + Out - Total IVF + **12** **118** 130 Control **28** **886** 914	**Comments:** No adjustment for multiple comparisons **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	914 spontaneous 130 IVF 54 ICSI **Study type:** Cohort	- Known mode of conception - Undergoing screening **Exclusion criteria:** NR		Total 40 1004 1044 Value / Lower 95% CI / Upper 95% CI Rel risk 3.01 1.57 5.78 After adjustment for maternal age, relative risk = 1.67 (0.79, 3.54) 2) Relative risk for positive results (risk > 1/300), based on nuchal translucency + free ß-hCG + PAPP-A + maternal age, ICSI: Out + / Out - / Total Exp + **7** **47** 54 Exp - **28** **886** 914 Total 35 933 968 Value / Lower 95% CI / Upper 95% CI Rel risk 4.23 1.94 9.24 After adjustment for maternal age, relative risk = 2.78 (1.1, 7.0) 3) PAPP-A lower, inhibin significantly higher in ART groups compared to spontaneous.	Large sample size: - Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
Tulandi, Martin, Al-Fadhli, et al., 2006 **#56300**	**Geographical location:** Montreal, London, and Toronto, Canada **Study dates:** Jan 2001-Dec 2005	**Age:** Mean (SD): Letrozole: 33.1 (5.3); Letrozole + FSH 32.4 (5.4); Clomiphene 32.9 (4.5); Clompihene +FSH 33.9 (4.9)	**Definition(s) of outcome(s):** Major and minor malformations based on WHO criteria	1) Major malformations, letrozole vs clomiphene: Out + / Out - / Total Letrozole **6** **508** 514 Clomiphene **12** **385** 397 Total 18 893 911	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Size of population (no. of patients): 931 **Study type:** Cohort	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Ovulation induction or augmentation for timed intercourse or intrauterine insemination with either letrozole or CC administered orally for 5 days from day 3 to 7 of the cycle. **Exclusion criteria:** IVF		<table><tr><th></th><th>Value</th><th>Lower 95% CI</th><th>Upper 95% CI</th></tr><tr><td>Rel risk</td><td>0.39</td><td>0.15</td><td>1.02</td></tr></table> 2) Minor malformations, letrozole vs clomiphene: <table><tr><th></th><th>Out +</th><th>Out -</th><th>Total</th></tr><tr><td>Letrozole</td><td>8</td><td>506</td><td>514</td></tr><tr><td>Clomiphene</td><td>7</td><td>390</td><td>397</td></tr><tr><td>Total</td><td>15</td><td>896</td><td>911</td></tr></table> <table><tr><th></th><th>Value</th><th>Lower 95% CI</th><th>Upper 95% CI</th></tr><tr><td>Rel risk</td><td>0.88</td><td>0.32</td><td>2.41</td></tr></table> 3) Similar to population risk (2-3%)	Large sample size: - Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -
Tully, Moffitt, and Caspi, 2003 **#17200**	**Geographical location:** England, Wales **Study dates:** Jan 1994-Dec 1995 **Size of population:** 121 families of 5 yo IVF or ovulation induction (OI) twins 121 naturally conceived (NC) 5 yo same-sex twins **Study type:** Case-control Birth register of twins used to identify cases (twins conceived by IVF/OI), controls (NC). Matched for gender, zygosity, ethnicity, family income & occupation, parental relationship,	**Age:** (maternal) Mean (SD): Cases: 36.0 (4.95) Controls: 35.6 (4.65) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Subset of participants in Environmental Risk Longitudinal Twin Study, drawn from births 1994 & 1995 in England & Wales - "IVF" included IVF, IUI, and GIFT **Exclusion criteria:** - Not Living in England or Wales - Not English-speaking - Not being reared by at least 1 biological parent	**Definition(s) of outcome(s):** Researchers visited homes in teams of 2 for total of 2-3 hrs. Had degrees in behavioral science and experience in psychology, anthropology, or nursing. Blinded to method of conception. Also gave questionnaire to teachers (93% response rate) Assessed: - Parental adjustment (quality of parental relationship, quarrelling, abuse, support, social support, depression); - Parenting (consistency, physical discipline, warmth, negativity);	No significant difference in any variable by method of conception, except inconsistency in discipline: NC group mean 2.11 (SD 1.57), IVF/OI group mean 1.58 (1.26). No categorical variables to analyze with 2x2 tables	**Comments:** - 71% of twins born in 1994-5 joined register - Well-matched with respect to potential confounders - Trained researchers, blinded to method of conception **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: + Verification that the control is free of cancer: NR Comparability of cases and controls with respect to potential confounders: + Validated dietary assessment method: NR Appropriateness of statistical analyses: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	birth order, birthwt, mat age, # children in family	- Opposite sex twins	- Children's behavior (Achenbach Child Behavior Checklist, Rutter Child Scales, DSM-IV)		
Tummers, De Sutter, and Dhont, 2003 **#16040**	**Geographical location:** Ghent, Belgium **Study dates:** 1993-2000 **Size of population:** 1200 singletons, 397 twins **Study type:** Cohort Records of all IVF/ICSI pts treated in 1 center reviewed, SAb rates in singletons compared to twins	**Age:** Mean (SD): singletons 31.3 (0.7), twins 30.7 (0.6) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR, but "not signif diff between grps" **Inclusion criteria:** Pts followed until ≥ 12 wk with reliable outcome info **Exclusion criteria:** Followed until < 12 wk gestation, no outcome information available, biochemical & ectopic pregnancies, triplets	**Definition(s) of outcome(s):** SAb = blighted ovum or fetal demise Ongoing preg = delivery > 25 wk For twins, separate data given for partial SAb (vanishing twin) or complete; overall considered incidence of SAb for each sac separately	1) Overall risk for SAb: SAb + / SAb - / Total Twins: **88** / **706** / 794 Single: **262** / **938** / 1200 Total: 350 / 1644 / 1994 Value (Lower 95% CI, Upper 95% CI) Rel risk: 0.51 (0.41, 0.64) Data given for risk of SAb by gestational age in %, but not sure whether the denominator is total number or number remaining pregnancies at that gest age. Difference persisted until 13 wks, when singleton rate = twin rate. 2) Risk for SAb stratified by maternal age: SAb + / SAb - / Total Twins > 35: **17** / **73** / 90 Single > 35: **59** / **126** / 185 Total: 76 / 199 / 275 Value (Lower 95% CI, Upper 95% CI) Rel risk: 0.59 (0.37, 0.95) SAb + / SAb - / Total Twins ≤ 35: **67** / **637** / 704 Single ≤ 35: **201** / **814** / 1015 Total: 268 / 1451 / 1719 Value (Lower 95% CI, Upper 95% CI)	**Comments:** Only 64% had f/u & reliable outcome info; data on dropout pt's characteristics not shown. **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: - Use of validated method for genomic test: NR Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results				Comments/Quality Scoring
				Rel risk	0.48	0.37	0.62	
Tworoger, Fairfield, Colditz, et al., 2007 **#72700**	**Geographical location:** US (multiple sites) **Study dates:** 1980-May 2004 **Size of population (no. of patients):** 121,700 **Study type:** Cohort	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** NR **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Ovarian cancer (validated through medical records, death certificates)	1) Adjusted odds ratio (adjusted for Adjusted for age (continuous), body mass index (< 21, 21 to < 23, 23 to < 25, 25 to < 30, ≥ 30 kg/m_2), parity (continuous), history of tubal ligation (ever/never), smoking history (never, current, past), age at menarche (< 11, 11, 12, ≥ 13 years), age at menopause (premenopausal, < 45, 45–49, 50–52, 53–54, ≥ 55 years), duration of postmenopausal hormone use (continuous), and duration of oral contraceptive use (continuous) Female infertility: 1.36 (1.07, 1.75) Male infertility: 1.23 (0.68, 2.25)				**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size:+ Adequate description of the cohort: + Use of validated method for ascertaining exposure: - Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) +and reporting of results:

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Ulug, Jozwiak, Mesut, et al., 2004 **#14040**	**Geographical location:** Istanbul, Turkey **Study dates:** 1997-2002 **Size of population:** 1448 pregnancies from ICSI with multiple gestation by early u/s **Study type:** Retrospective cohort	**Age:** Mean (SD): 30.09 (4.4) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Pregnancy by u/s with ≥ 8 mm sac with yolk sac ≥ 2 mm **Exclusion criteria:** Outside f/u, monochorionic, frozen embryo transfer, quintuplets	**Definition(s) of outcome(s):** Gestational sac loss = resorption of a gestational sac and cessation or lack of detection of cardiac activity	Results stratified by age and described as % of multiples that had any loss in number of gestational sacs 1) Twins (2 gestational sacs): Loss of any gsacs + / Loss of any gsacs - / Total Age ≥ 35: **52** / **173** / 225 Age < 35: **106** / **533** / 639 Total: 158 / 706 / 864 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.39 / 1.04 / 1.87 2) Triplets (3 gestational sacs): Loss of any gsacs + / Loss of any gsacs - / Total Age ≥ 35: **16** / **76** / 92 Age < 35: **53** / **293** / 346 Total: 69 / 369 / 438 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.14 / 0.68 / 1.89 3) Quadruplets (4 gestational sacs): Loss of any gsacs + / Loss of any gsacs - / Total Age ≥ 35: **4** / **22** / 26 Age < 35: **17** / **103** / 120 Total: 21 / 125 / 146 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.09 / 0.40 / 2.96	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: - Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Venn, Hemminki, Watson, et al., 2001 **#3380**	**Geographical location:** Australia **Study dates:** Women from IVF clinics before January 1, 1994 **Size of population:** 29,700 women No IVF: 21,086 IVF: 8614 **Study type:** Cohort	**Age:** Median (range) at entry: IVF: 32 (18-54) No IVF: 30 (18-51) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Female death **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Death, by cause	1) All-cause deaths for IVF vs. spontaneous: Death + / Death - / Total IVF: **72** / **17040** / 17112 Spont: **51** / **7782** / 7833 Total: 123 / 24822 / 24945 Value / Lower 95% CI / Upper 95% CI Rel risk: 0.65 / 0.45 / 0.92 2) Cancer deaths for IVF vs. spontaneous: Death + / Death - / Total IVF: **51** / **21035** / 21086 Spont: **29** / **8585** / 8614 Total: 80 / 29620 / 29700 Value / Lower 95% CI / Upper 95% CI Rel risk: 0.72 / 0.46 / 1.13 3) Breast cancer deaths for IVF vs. spontaneous: Death + / Death - / Total IVF: **26** / **21060** / 21086 Spont: **9** / **8605** / 8614 Total: 35 / 29665 / 29700 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.18 / 0.55 / 2.52	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: - Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: +/- Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Vernaeve, Bonduelle, Tournaye, et al., 2003 **#15420**	**Geographical location:** Brussels, Belgium **Study dates:** Jan 1994-Dec 2000 **Size of population:** 274 pregnancies (70 NOA, 204 OA) **Study type:** Cohort 2 cohorts defined histologically as non-obstructive azoospermia (NOA) = complete or incomplete maturation arrest, complete or incomplete germ cell aplasia, and tubular sclerosis and atrophy; or obstructive azoospermia (OA)	**Age:** Mean (range): NOA 31.4 (29.7-33.0) OA 32.7 (31.8-33.6) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Pregnant pts whose male partner had testicular sperm recovery for ICSI **Exclusion criteria:** Klinefelter's syndrome males	**Definition(s) of outcome(s):** Abortion = loss < 20wk PTD = del < 37wk LBW < 2500 g IUFD ≥ 20 wk Neonatal death ≤ 1 wk Major malformation = causing death or functional impairment, or requiring surgical correction	No difference between groups in any outcome studied. 1) LBW: LBW + / LBW - / Total NOA: **20** / **39** / 59 OA: **59** / **133** / 192 Total: 79 / 172 / 251 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.10 / 0.73 / 1.67 2) Selective reduction: Sel red + / Sel red - / Total NOA: **0.5** / **70** / 70.5 OA: **1** / **203** / 204 Total: 1.5 / 273 / 274.5 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.45 / 0.05 / 42.66 3) IUFD: IUFD + / IUFD - / Total NOA: **3** / **58** / 61 OA: **3** / **193** / 196 Total: 6 / 251 / 257 Value / Lower 95% CI / Upper 95% CI Rel risk: 3.21 / 0.67 / 15.51	**Comments:** 8% lost to followup **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: - Use of validated method for genomic test: NR Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Verstraelen, Goetgeluk, Derom, et al., 2005 **#40620**	**Geographical location:** Belgium **Study dates:** 1976-2002 **Size of population (no. of patients):** 2915 spontaneous twins 1453 ART twins (710 ovarian stimulation, 743 IVF/ICSI) **Study type:** Cohort	**Age:** Natural conception 28.6 (4.5) Ovarian stim 28.7 (3.7) IVF/ICSI 31.5 (3.4) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** All twins **Exclusion criteria:** Missing data	**Definition(s) of outcome(s):** Preterm birth < 37 wks Low birthweight < 2500gm	1) Preterm birth ovarian stimulation: ptb+ / ptb- / Total ov stim: **385** / **325** / 710 spontaneous: **1314** / **1601** / 2915 Total: 1699 / 1926 / 3625 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.20 / 1.11 / 1.30 2) Low birthweight ovarian stimulation: lbwt+ / lbwt- / Total ov stim: **476** / **234** / 710 spontaneous: **1803** / **1112** / 2915 Total: 2279 / 1346 / 3625 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.08 / 1.02 / 1.15 3) Low birthweight IVF/ICSI: lbwt+ / lbwt- / Total IVF/ICSI: **515** / **228** / 743 spontaneous: **1803** / **1112** / 2915 Total: 2318 / 1340 / 3658 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.12 / 1.06 / 1.18 4) Preterm birth IVF/ICSI: ptb+ / ptb- / Total IVF/ICSI: **441** / **302** / 743 spontaneous: **1803** / **1112** / 2915 Total: 2244 / 1414 / 3658	**Comments:** None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

	Value	Lower 95% CI	Upper 95% CI
Rel risk	0.96	0.90	1.03

5) Preterm birth 2 ART methods compared:

	ptb+	ptb-	Total
IVF/ICSI	**441**	**302**	743
ov stim	**385**	**325**	710
Total	826	627	1453

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.09	1.00	1.20

6) Low birthweight 2 ART methods compared:

	lbwt+	lbwt-	Total
IVF/ICSI	**515**	**228**	743
ov stim	**476**	**234**	710
Total	991	462	1453

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.03	0.96	1.11

Vollenhoven, Clark, Kovacs, et al., 2000

#7640

Geographical location: Australia

Study dates: 1990-97

Size of population: 60 PCOS patients 60 spontaneous

Study type: Cohort

Age: NR

Race/ethnicity (n [%]): NR

Diagnoses (n [%]): Unexplained infertility: 14% PCOS: 67% Other: Hypogonadotrophic hypogonadism: 12% Eugonadotrophic hypogonadism: 7%

Inclusion criteria: Controls matched for age,

Definition(s) of outcome(s):

Gestational diabetes based on 75 g glucose challenge, confirmed by 75 g fasting & 2 hr glucose tolerance test

1) Gestational diabetes in PCOS vs. spontaneous conception:

	GDM +	GDM -	Total
PCOS	**13.2**	**46.8**	60
Spont	**10.2**	**49.8**	60
Total	23.4	96.6	120

	Value	Lower 95% CI	Upper 95% CI
Rel risk	1.29	0.62	2.70

Comments: None

Quality assessment: Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: - Adequate description of the cohort: - Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		BMI, ethnicity; induction after gonadotropins for PCOS patients **Exclusion criteria:** NR			
Wang, Davies, and Norman, 2001 **#3420**	**Geographical location:** Woodville, Australia **Study dates:** 1987-99 **Size of population:** 1018 pregnancies **Study type:** Cohort (retrospective)	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 16% Endometriosis: 9% Male factor: 35% Tubal factor: 34% PCOS: 37% Other: 6% **Inclusion criteria:** Treated in Repro Med Unit (with IVF, GIFT, or ICSI) **Exclusion criteria:** PCOS status or BMI not assessed	**Definition(s) of outcome(s):** Pregnancy = embryonic sac by US at 4-6 wk after transfer SAb = pregnancy failing to reach 20 wk, excluding ectopics or induced Ab	1) SAb by mode of conception – conventional IVF versus ICSI for male factor only: SAb + / SAb - / Total ICSI: 43 / 289 / 332 IVF: 117 / 335 / 452 160 / 624 / 784 Rel risk 0.50 (Lower 95% CI 0.36, Upper 95 % CI 0.69) 2) SAb by mode of conception – conventional IVF versus ICSI for other etiology : SAb + / SAb - / Total Study drug: 9 / 47 / 56 Control: 117 / 335 / 452 126 / 382 / 508 Rel risk 0.62 (Lower 95% CI 0.33, Upper 95 % CI 1.15) 3) SAb by mode of conception – ICSI for male factor only versus for other etiology: SAb + / SAb - / Total ICSI-male: **43** / **289** / 332 ICSI-other: **9** / **47** / 56 Total: 52 / 336 / 388 Value / Lower 95% CI / Upper 95% CI Rel risk 0.81 (0.42, 1.56)	**Comments:** Confounders explored only by PCOS vs non-PCOS (which was objective of study), not by mode of conception **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: - Use of validated method for genomic test: n/a Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Wang, Norman, and Kristians-son, 2002 **#2420**	**Geographical location:** Uppsala, Sweden **Study dates:** 1986 - 1998 **Size of population:** 1,015 births by "low technology treatment" - IUI - donor insemination 1,019 by "high technology treatment" - IVF - ICSI - GIFT 1,019 births by natural conception **Study type:** Cohort (retrospective)	**Age:** Mean (SD): Ctrls 31.9 4.1) Low tech 30.9 (4.1) High tech 32.5 (4.1) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Infertile pts treated in this Unit; births defined as delivery >20wks or fetus >=400g **Exclusion criteria:** Multiple births	**Definition(s) of outcome(s):** "Definitions of threatened miscarriage, antepartum hemorrhage and congenital malformations based on recommendations of the WHO" Very preterm birth < 32wks Preterm < 37wks Elective / emergent C/S not defined	1) Threatened AB by mode of conception: low technology versus naturally-conceived: ThrAB+ / ThrAB- / Total Low: **56** / **959** / 1015 NC: **34** / **985** / 1019 Total: 90 / 1944 / 2034 Value / Lower 95% CI / Upper 95% CI Odds rat: 1.69 / 1.09 / 2.61 2) Threatened AB by mode of conception: high technology versus naturally-conceived: ThrAB+ / ThrAB- / Total High: **90** / **929** / 1019 NC: **34** / **985** / 1019 Total: 124 / 1914 / 2038 Value / Lower 95% CI / Upper 95% CI Odds rat: 2.81 / 1.87 / 4.21 3) Threatened AB by mode of conception: high technology versus low: ThrAB+ / ThrAB- / Total High: **90** / **929** / 1019 Low: **56** / **959** / 1015 Total: 146 / 1888 / 2034 Value / Lower 95% CI / Upper 95% CI Odds rat: 1.66 / 1.17 / 2.34 4) Congenital malformation by mode of conception: low technology versus naturally-conceived: Malf+ / Malf- / Total Low: **49** / **966** / 1015 NC: **46** / **973** / 1019 Total: 95 / 1939 / 2034	**Comments:** - Data on some confounders (previous preterm birth, previous SAB, race, socio-economic factors, smoking status) not available for control grp. - "High tech" women older, longer infertile period Did not differentiate ICSI from IVF **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: - Use of validated method for genomic test: n/a Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: - (no mention of when/how congenital malformations dx'd) Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

	Value	Lower 95% CI	Upper 95% CI
Odds rat	1.07	0.71	1.62

5) Congenital malformation by mode of conception: high technology versus naturally-conceived:

	Malf+	Malf-	Total
High	**44**	**975**	1019
NC	**46**	**973**	1019
Total	90	1948	2038

	Value	Lower 95% CI	Upper 95% CI
Odds rat	0.95	0.63	1.46

6) Congenital malformation by mode of conception: high technology versus low:

	Malf+	Malf-	Total
High	**44**	**975**	1019
Low	**49**	**966**	1015
Total	93	1941	2034

	Value	Lower 95% CI	Upper 95% CI
Odds rat	0.89	0.59	1.35

7) Preterm birth via elective C/S by mode of conception: low technology versus naturally-conceived:

	CS+	CS-	Total
Low	**3**	**109**	112
NC	**2**	**93**	95
Total	5	202	207

	Value	Lower 95% CI	Upper 95% CI
Odds rat	1.28	0.21	7.82

8) Preterm birth via elective C/S by mode of conception: high technology versus naturally-

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

conceived:

	CS+	CS-	Total
High	**6**	**148**	154
NC	**2**	**93**	95
Total	8	241	249

	Value	Lower 95% CI	Upper 95% CI
Odds rat	1.89	0.37	9.54

9) Preterm birth via elective C/S by mode of conception: high technology versus low:

	CS+	CS-	Total
High	**6**	**148**	154
Low	**3**	**109**	112
Total	9	257	266

	Value	Lower 95% CI	Upper 95% CI
Odds rat	1.47	0.36	6.02

10) Preterm birth via emergent C/S by mode of conception: low technology versus naturally-conceived:

	CS+	CS-	Total
Low	**26**	**13**	39
NC	**6**	**15**	21
Total	32	28	60

	Value	Lower 95% CI	Upper 95% CI
Odds rat	5.00	1.57	15.91

11) Preterm birth via emergent C/S by mode of conception: high technology versus naturally-conceived:

	CS+	CS-	Total
High	**32**	**17**	49
NC	**6**	**15**	21
Total	38	32	70

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

	Value	Lower 95% CI	Upper 95% CI
Odds rat	4.71	1.54	14.35

12) Preterm birth via emergent C/S by mode of conception: high technology versus low:

	CS+	CS-	Total
High	**32**	**17**	49
Low	**26**	**13**	39
Total	58	30	88

	Value	Lower 95% CI	Upper 95% CI
Odds rat	0.94	0.39	2.29

13) Spontaneous preterm birth by mode of conception: low technology versus naturally-conceived:

	PTB+	PTB-	Total
Low	**40**	**527**	567
NC	**38**	**622**	660
Total	78	1149	1227

	Value	Lower 95% CI	Upper 95% CI
Odds rat	1.24	0.79	1.97

14) Spontaneous preterm birth by mode of conception: high technology versus naturally-conceived:

	PTB+	PTB-	Total
High	**71**	**498**	569
NC	**38**	**622**	660
Total	109	1120	1229

	Value	Lower 95% CI	Upper 95% CI
Odds rat	2.33	1.55	3.52

15) Spontaneous preterm birth by mode of conception: high technology versus low:

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				PTB+ PTB- Total High **71** **498** 569 Low **40** **527** 567 Total 111 1025 1136 Value Lower 95% CI Upper 95% CI Odds rat 1.88 1.25 2.82	
Whiteman, Murphy, Hey, et al. 2000 **#6510**	**Geographical location:** Oxford, UK **Study dates:** 1970 - 1987 **Size of population:** 694 index pregnancies 694 ctrls **Study type:** Case-control NTD cases identified from 3 main sources: Oxford Record Linkage Study, Local AFP screening program, Abortions/congenital malformations data set. Also from pds surgery unit records, perinatal path reports, regional genetics unit, home birth & delivery suite registers. For each case, randomly selected ctrl from Oxford Record Linkage Study database, matched for maternal age and yr of NTD event. In every instance in which case's	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Women whose pregnancies affected by NTD alone or in combination with other defects in liveborn or stillborn child, late miscarriage, or terminated pregnancy and were dx'd in Oxfordshire or West Berkshire, England **Exclusion criteria:** Women whose pregnancies had terminated were excluded from control grp	**Definition(s) of outcome(s):** NTD = anencephaly, encephalocele, spina bifida aperta, or spina bifida occulta	No signif difference btw cases & ctrls for h/o subfertility, treatment for subfertility, clomid treatment 1) Treatment for subfertility this preg: Cases Ctrls Total Yes **14** **15** 29 No **680** **679** 1359 Total 694 694 1388 Value Lower 95% CI Upper 95% CI Odds rat 0.93 0.45 1.95 2) Clomid treatment this pregnancy: Cases Ctrls Total Yes **13** **13** 26 No **681** **681** 1362 Total 694 694 1388 Value Lower 95% CI Upper 95% CI Odds rat 1.00 0.46 2.17	**Comment :** - Estimate >90% completeness - Data abstracter not blinded - Terminations excluded from control grp, but if anything this would increase chance of finding a difference between grps - No mention of DM status **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: - Verification that the control is free of cancer: + Comparability of cases and controls with respect to potential confounders: - Validated dietary assessment method: n/a Appropriateness of statistical analyses: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	pregnancy was terminated following NTD dx, ctrl fetus had to be at least of same GA				
Winter, Wang, Davies, et al., 2002 **#460**	**Geographical location:** Woodville, Australia **Study dates:** 1994-99 **Size of population:** 1196 pregnancies **Study type:** Cohort (retrospective)	**Age:** Mean (SD): 32.7 (4.7) Range: 19.2-47.1 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 12% Endometriosis: 9% Male factor: 50% Tubal factor: 23% PCOS: 10% Other: 15% **Inclusion criteria:** Those embryo transfer cycles who had at least one hCG measurement done on day 16 (+/- 1 day) **Exclusion criteria:** Cycles in which menstruation occurred before day 16, no hCG measurement	**Definition(s) of outcome(s):** Early pregnancy loss (EPL) = pregnancy loss that occurred before 6-7 weeks gestation	1) EPL by mode of conception – ICSI vs IVF: EPL + / EPL - / Total ICSI: 88 / 510 / 598 IVF: 96 / 405 / 501 184 / 915 / 1099 Rel risk: 0.77 (Lower 95% CI 0.59; Upper 95 % CI 1.00) 2) EPL by mode of conception – ICSI vs GIFT: EPL+ / EPL- / Total ICSI: **88** / **510** / 598 GIFT: **11** / **86** / 97 Total: 99 / 596 / 695 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.30 / 0.72 / 2.34 3) EPL by mode of conception – IVF vs GIFT: EPL+ / EPL - GIFT: 11 / 86 / 97 IVF: 96 / 405 / 501 107 / 491 / 598 Rel risk: 0.59 (Lower 95% CI 0.33; Upper 95 % CI 1.06)	**Comments:** No mention of number of embryos transferred **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: - Use of validated method for genomic test: n/a Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Wojdemann, Larsen Shalmi, et al., 2001 **#4440**	**Geographical location:** Copenhagen, Denmark **Study dates:** Mar 1998 – Oct 1999 **Size of population:** 3026 spontaneously conceived 47 IVF 63 OI **Study type:** Cohort	**Age:** Mean (SD): Ctrls 29.1 IVF 34.4 OI 30.3 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Singletons from ongoing prospective study **Exclusion criteria:** Known chromosomal disorders, malformations	**Definition(s) of outcome(s):** PAPP-A, free-beta hCG, NT transformed into gestational age-independent MoM values	No differences between marker MoM's in IVF and OI grps compared with spontaneously conceived Screen positive (1:400) rates were 4.7% in IVF grp, 4.9% in spontaneous, 5.1% in OI grp (no diff)	**Comment :** - Small numbers in ART grps - No postnatal f/u to determine actual performance of test **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for genomic test: n/a Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
Woldringh, Frunt, Kremer, et al., 2005 **#56680**	**Geographical location:** Nijmegen, The Netherlands **Study dates:** Oct 1994-Apr 2004 **Size of population (no. of patients):** 123 **Study type:** Case-control	**Age:** Mean (SD): 33.6 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Unexplained infertility: 18% Endometriosis: 10% Male factor: 60% Tubal factor: 8% Cervical: 3% **Inclusion criteria:** - IVF or ICSI with resulting pregnancy - Preeclampsia reported by patient, verified by records - Controls matched for number of fetuses, parity, maternal age at the	**Definition(s) of outcome(s):** Preeclampsia: gestational hypertension (repeated blood pressure measurements of > 140 mm Hg systolic or > 90 mm Hg diastolic) and proteinuria (urine protein creatinine ratio of ≥ 0.3 g/10 mmol or dipstick test ≥ 1+ for protein) after 20 weeks of gestation	1) FSH requirements significantly higher, response significantly worse in cases than in controls.	**Comments:** None **Quality assessment:** Valid ascertainment of cases:+ Unbiased selection of cases: - Appropriateness of the control population: + Comparability of cases and controls with respect to potential confounders: + Appropriateness of statistical analyses: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		time of delivery, pre-pregnant BMI (kg/m^2), race and smoking. **Exclusion criteria:** - Frozen embryos - No live birth			
Wright, Schieve, Vahratian, et al. 2004 **#11600**	**Geographical location:** U.S. population-based sample/registry **Study dates:** 1999 – 2000 **Size of population:** 39,198 ART pregnancies 226 monozygotic (MZ) pregnancies 23,880 singletons 15,092 multiples **Study type:** Case-control	**Age:** Range: 20-44 Stratified **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Cases (MZ twins) = #fetal hearts on u/s > # embryos transferred Controls other singletons & multiples **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Exposure of interest = day of embryo transfer (ET) Outcome = monozygotic (MZ) twinning	Reference grp = day 3 ET 1) Day 2 ET: MZ+ cases / singleton ctrls / Total DAY 2 ET: **4** / **1345** / 1349 DAY 3 ET: **98** / **16774** / 16872 Total: 102 / 18119 / 18221 Value / Lower 95% CI / Upper 95% CI Odds rat: 0.51 / 0.19 / 1.39 MZ+ cases / other multiples ctrls / Total DAY 2 ET: **4** / **859** / 863 DAY 3 ET: **98** / **10590** / 10688 Total: 102 / 11449 / 11551 Value / Lower 95% CI / Upper 95% CI Odds rat: 0.50 / 0.18 / 1.37 2) Day 4 ET: MZ+ cases / singleton ctrls / Total DAY 4 ET: **4** / **595** / 599	**Comments:** None **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: + Comparability of cases and controls with respect to potential confounders: +/- Appropriateness of statistical analyses: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results				Comments/Quality Scoring
				DAY 3				
				ET	**98**	**16774**	16872	
				Total	102	17369	17471	
					Value	Lower 95% CI	Upper 95% CI	
				Odds rat	1.15	0.42	3.14	
					MZ+ cases	other multiples ctrls	Total	
				DAY 4				
				ET	**4**	**347**	351	
				DAY 3				
				ET	**98**	**10590**	10688	
				Total	102	10937	11039	
					Value	Lower 95% CI	Upper 95% CI	
				Odds rat	1.25	0.46	3.40	
				3) Day 5 ET:				
					MZ+ cases	singleton ctrls	Total	
				DAY 5				
				ET	**110**	**4451**	4561	
				DAY 3				
				ET	**98**	**16774**	16872	
				Total	208	21225	21433	
					Value	Lower 95% CI	Upper 95% CI	
				Odds rat	4.23	3.22	5.56	
					MZ+ cases	other multiples ctrls	Total	
				DAY 5				
				ET	**110**	**2972**	3082	
				DAY 3				
				ET	**98**	**10590**	10688	
				Total	208	13562	13770	

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

	Value	Lower 95% CI	Upper 95% CI
Odds rat	4.00	3.04	5.27

4) Day 6 ET:

	MZ+ cases	singleton ctrls	Total
DAY 6 ET	**10**	**715**	725
DAY 3 ET	**98**	**16774**	16872
Total	108	17489	17597

	Value	Lower 95% CI	Upper 95% CI
Odds rat	2.39	1.24	4.61

	MZ+ cases	other multiples ctrls	Total
DAY 6 ET	**10**	**324**	334
DAY 3 ET	**98**	**10590**	10688
Total	108	10914	11022

	Value	Lower 95% CI	Upper 95% CI
Odds rat	3.34	1.72	6.45

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Wu, Croen, Henning, et al., 2006 **#56750**	**Geographical location:** Northern California **Study dates:** Jan 1994-Dec 1997 **Size of population (no. of patients):** 18 cases, 1608 controls **Study type:** Case-control	**Age:** Mean (SD): Median: Range: Cases: 78% <35; controls: 16% < 35 **Race/ethnicity (n [%]):** Cases 67% white vs 53% controls **Diagnoses (n [%]):** NR **Inclusion criteria:** Cases: - Singleton - ≥36 weeks - Physician-confirmed diagnosis Controls: - Same criteria, except no diagnosis of spinal cord abnormalities, cerebral palsy (ICD9-CM, 1999; 343.0–343.9, 342.1, 342.8, 342.9, 344.0, 344.1, 344.30–344.32, and 344.5), genetic disease (ICD9-CM 237.7x, 277.2, 277.5, 333.6, 755.55, 759.5, 759.81), chromosomal abnormalities (ICD9-CM 758.x), arthrogryposis (ICD9-CM 754.59), ormuscle disease (ICD9-CM 335.x, 358.x, 359.x). **Exclusion criteria:** physician diagnosis of cerebral palsy (ICD9-CM, 1999; 343.0–343.9, 342.1, 342.8,	**Definition(s) of outcome(s):** Spinal neural tube defect, defined as spinal anomaly resulting from a defect in neurulation including spina bifida cystica (myelomeningocele or meningocele) and spina bifida occulta (intraspinal lipoma with tethered cord or dermal sinus tract)	1) History of infertility: |	Out +	Out -	Total
---	---	---	---
Infertility	**4**	**14**	18
No infertility	**96**	**1512**	1608
Total	100	1526	1626 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Odds rat	4.50	1.45	13.93 | 2) Infertility treatment: |	Out +	Out -	Total
---	---	---	---
Infert Rx	**4**	**14**	18
No Rx	**48**	**1560**	1608
Total	52	1574	1626 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Odds rat	9.29	2.95	29.26 | 3) Periconceptional clomiphene: |	Out +	Out -	Total
---	---	---	---
Clomiphene	**3**	**15**	18
No CC	**32**	**1576**	1608
Total	35	1591	1626 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Odds rat	9.85	2.72	35.71		**Comments:** - No multivariate analysis due to small # of cases - Maternal BMI not analyzed - 3/4 case mothers with dx of ovulatory infertility—prevalence in controls not reported **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: + Comparability of cases and controls with respect to potential confounders: - Appropriateness of statistical analyses: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
		342.9, 344.0, 344.1, 344.30–344.32, and 344.5), genetic disease (ICD9-CM 237.7x, 277.2, 277.5, 333.6, 755.55, 759.5, 759.81), chromosomal abnormalities (ICD9-CM 758.x), arthrogryposis (ICD9-CM 754.59), or muscle disease (ICD9-CM 335.x, 358.x, 359.x).			
Yokoyama, 2003 **#16870**	**Geographical location:** Kyoto, Japan **Study dates:** June 1998-Dec 1999 **Size of population (no. of patients):** 990 (359 infertility patients (76 ART, rest superovulation / AIH / Other), 631 spontaneous **Study type:** Cohort	**Age:** Mean (SD): Infertility: 32.7 (3.8) Control: 31.3 (4.0) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Mothers of multiples, identified through registry, newspaper advertisements, clinical practices **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Mailed questionnaire for symptoms; pregnancy/birth/pediatric data from medical records Lack of sleep: 5-point Likert scale Fatigue: Previously published fatigue scale Depressive symptoms: Yes/no response to DSM-III symptoms	1) Presence of depressive symptoms: Depress Sx + / Depress Sx - / Total Infertility: **56** / **303** / 359 Spontaneous: **66** / **565** / 631 Total: 122 / 868 / 990 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.49 / 1.07 / 2.08 2) In multivariate analysis, at least one disabled child (OR 2.27 [95% CI 1.05, 5.04]) and lack of method for alleviating stress (OR 2.4 (1.3, 4.6) only significant predictors of depressive symptoms.	**Comments:** - Questionnaire completed approximately 2 years after delivery - Higher order multiples significantly more common in infertility group (37.3% vs 4.4%) - Infants with disability more common in infertility group (at least one: 15.7% vs 8.4%) - Unclear extent of potential bias in recruitment **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
Zadori,	**Geographical location:**	**Age:** NR	**Definition(s) of**	No significant difference for most outcomes.	**Comments:**

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Kozinszky, Orvos, et al., 2003 **#16020**	Szeged, Hungary **Study dates:** Jan 1995-Feb 2002 **Size of population:** 230 IVF pregnancies, 185 singletons and 36 twins **Study type:** Case-control IVF pregnancies matched to spontaneous controls for age, parity, gravidity, previous obstetric outcome	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** All deliveries at university hospital in study period; cases were 230 IVF pregnancies **Exclusion criteria:** NR	**outcome(s):** Examined GDM, preeclampsia, myoma, previa, malpresentation, abruption, PROM, intrauterine infection, oligohydramnios, polyhydramnios (none defined). Intrapartum: C/S, fetal distress, CPD, retained placenta, pp hemorrhage, prolonged labor, prolonged 2nd stage Macrosomia = birthwt ≥ 4000 g, SGA < 10%ile for Hungarian data	More macrosomia & its effects (CPD, prolonged labor) in control singletons (but still more C/S in IVF, although not significant) 1) Premature birth (not defined) in singletons: PTB + / PTB - / Total IVF sing: **29** / **156** / 185 Ctrl sing: **14** / **171** / 185 Total: 43 / 327 / 370 Value (Lower 95% CI, Upper 95% CI) Odds rat: 2.27 (1.16, 4.45) 2) Premature birth (not defined) in twins: PTB + / PTB - / Total IVF twins: **50** / **22** / 72 Ctrl twins: **46** / **26** / 72 Total: 96 / 48 / 144 Value (Lower 95% CI, Upper 95% CI) Odds rat: 1.28 (0.64, 2.57) 3) C/S in singletons: C/S + / C/S - / Total IVF sing: **78** / **107** / 185 Ctrl sing: **69** / **116** / 185 Total: 147 / 223 / 370 Value (Lower 95% CI, Upper 95% CI) Odds rat: 1.23 (0.81, 1.86) 4) Threatened preterm delivery (not defined) in singletons: Threat PTB + / Threat PTB - / Total IVF sing: **52** / **133** / 185	- Poorly characterized cohort & matching process. - Groups similar for education, BMI, G/P **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: + Verification that the control is free of cancer: NR Comparability of cases and controls with respect to potential confounders: + Validated dietary assessment method: NR Appropriateness of statistical analyses: +

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Ctrl sing **21** **164** 185 Total 73 297 370 Value / Lower 95% CI / Upper 95% CI Odds rat 3.05 1.75 5.32	
Zadori, Kozinszky, Orvos, et al. 2003 **#16810**	**Geographical location:** Szeged, Hungary **Study dates:** 1/1/95 – 12/31/01 **Size of population:** 188 singletons, 74 twins, 39 from triplet pregnancies **Study type:** Other IVF-ET births matched to controls for maternal age, parity, gravidity	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** NR **Exclusion criteria:** NR	**Definition(s) of outcome(s):** Congenital malformations dx'd by same neonatologist according to ICD criteria. Dx'd 4 wks after delivery National average of major birth defects in Hungary 2.2%	1) Major malformations in singletons: Maj malform / Maj malform - / Total IVF sing **4** **184** 188 Ctrl sing **1** **187** 188 Total 5 371 376 Value / Lower 95% CI / Upper 95% CI Odds rat 4.07 0.45 36.72 2) Major malformations in twins: Maj malf + / Maj malf - / Total IVF twin **1** **73** 74 Ctrl twin **2** **72** 74 Total 3 145 148 Value / Lower 95% CI / Upper 95% CI Odds rat 0.49 0.04 5.56	**Comments:** - Short followup - Did not include pregnancies terminated bc of anomalies, but authors state this would not have changed results. - Unclear where this population comes from, or where controls drawn from. - "Short communication" **Quality assessment:** Valid ascertainment of cases: + Unbiased selection of cases: - Appropriateness of the control population: - Verification that the control is free of cancer: NR Comparability of cases and controls with respect to potential confounders: - Validated dietary assessment method: NR Appropriateness of statistical analyses: +
Zadori,	**Geographical location:**	**Age:** NR	**Definition(s) of**	1) Preterm birth:	**Comments:**

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Kozinszky, Orvos, et al., 2004 **#42250**	Hungary **Study dates:** 1995-2001 **Size of population (no. of patients):** N=75 ART twins N=94 spontaneous twins **Study type:** Cohort	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Twins born during study period **Exclusion criteria:** NR	**outcome(s):** Birthweight discordance >=20% difference between twins NICU admission Preterm birth not defined Birthweight given as continuous means only	ptb+ / ptb- / Total ART: **88** / **62** / 150 spontaneous: **106** / **82** / 188 Total: 194 / 144 / 338 Value (Lower 95% CI – Upper 95% CI) Rel risk: 1.04 (0.87 – 1.25) 2) NICU admission: NICU+ / NICU- / Total ART: **62** / **88** / 150 spontaneous: **100** / **88** / 188 Total: 162 / 176 / 338 Value (Lower 95% CI – Upper 95% CI) Rel risk: 0.78 (0.62 – 0.98) 3) Discordant birthweight between twins: discordant+ / discordant- / Total ART: **34** / **116** / 150 spontaneous: **30** / **158** / 188 Total: 64 / 274 / 338 Value (Lower 95% CI – Upper 95% CI) Rel risk: 1.42 (0.91 – 2.21)	None **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: - Adequate description of the cohort: - Use of validated method for ascertaining exposure: - Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: - Analysis (multivariate adjustments) and reporting of results: -
Zaib-un-	**Geographical location:**	**Age:**	**Definition(s) of**	No diff in PIH/preex, GDM, birthwt, NICU	**Comments:**

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Nisa, Ghazal-Aswad, and Badrinath, 2003 **#16420**	Al-Ain, UAE **Study dates:** 1/97 – 12/01 **Size of population:** 132 twin pregnancies (36 ART, 96 spontaneous) **Study type:** Cohort Retrospectively reviewed all twins born in one institution during study period, analyzed by ART vs spont.	Mean (SD): spont 29.2, ART 30.2 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** All twin deliveries **Exclusion criteria:** Deliveries < 23wks	**outcome(s):** Compared mean mat age, parity, number of antenatal clinic visits, highest recorded BP, impaired glucose tolerance, threatened premature labor, GA at birth, birthweight, discordant growth, mode of delivery, perinatal M&M (none defined)	admissions, stillbirth, neonatal death 1) Preterm delivery: yes / no / Total ART: **15** / **21** / 36 Spont: **49** / **47** / 96 Total: 64 / 68 / 132 Value / Lower 95% CI / Upper 95% CI Rel risk: 0.82 / 0.53 / 1.26 2) Nonelective C/S: yes / no / Total ART: **12** / **24** / 36 Spont: **27** / **69** / 96 Total: 39 / 93 / 132 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.19 / 0.68 / 2.08 3) Discordant growth: yes / no / Total ART: **6** / **30** / 36 Spont: **14** / **82** / 96 Total: 20 / 112 / 132 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.14 / 0.48 / 2.75 4) Antenatal admission: yes / no / Total ART: **15** / **21** / 36 Spont: **23** / **73** / 96 Total: 38 / 94 / 132 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.74 / 1.03 / 2.94	Retrospective collection of data, no outcomes defined. **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: - Adequate description of the cohort: - Use of validated method for genomic test: n/a Use of validated method for ascertaining clinical outcomes: - Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Zhu, Basso, Obel, et al., 2006 **#56870**	**Geographical location:** Denmark **Study dates:** June 1997-Feb 2008 **Size of population (no. of patients):** 85,381 **Study type:** Cohort	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR: **Inclusion criteria:** NR **Exclusion criteria:** - Spontaneous abortion - Gestational trophoblastic disease - Ectopic - Unknown pregnancy outcome - Stillbirth - Triplets	**Definition(s) of outcome(s):** Congenital malformations from ICD-10 in national registry	1) Significantly increased hazard ratios for all congenital anomalies among both infertile couples conceiving spontaneously and those receiving treatment. Only genital anomalies increased when comparing infertile couples conceiving spontaneously compared to those receiving treatment (HR for treatment 2.32, 95% CI 1.24. 4.35) 2) Hazard ratio* by time to conception: Spontaneous conception Time (months) HR 95% CI 0-2 1.00 (ref) 3-5 1.16 1.06, 1.27 6-12 1.17 1.06,1.30 >12 1.29 1.14,1.45 Infertility treatment 6-12 1.00 (ref) >12 1.34 0.94,1.92 *adjusted for maternal age at conception, pre-pregnancy body mass index, smoking, alcohol intake, coffee consumption, and occupational status.	**Comments:** Exposure ascertained by questionnaire, outcome by national registry **Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for ascertaining exposure: - Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period:+ Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
Zhu, Obel, Hammer	**Geographical location:** Denmark	**Age:** % < 30:	**Definition(s) of outcome(s):**	1) SGA, infertility with spontaneous conception (> 12 months to conception) vs. no	**Comments:** Exposure by self-report

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Bech, et al., 2007 **#72960**	**Study dates:** 1997-2003 **Size of population (no. of patients):** 61,145 **Study type:** Cohort	Fertile: 57.8% Infertile, spontaneous conception: 46.1% Infertile, treatment: 34.9% **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** - Participation in Danish National Birth Cohort - Singleton pregnancy **Exclusion criteria:** - Not pregnant at time of interview - Unplanned pregnancy - Infertility treatment not associated with this pregnancy - Treatment other than ICSI, IUI, IVF, hormones - Spontaneous or elective abortion, mole, ectopic - Unknown outcome	SGA <5th percentile	infertility: Out + / Out - / Total >12 months: **345** / **5377** / 5722 < 12 months: **2200** / **48414** / 50614 Total: 2545 / 53791 / 56336 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.39 / 1.24 / 1.55 2) SGA, infertility with treatment vs. < 12 months to conception: Out + / Out - / Total Exp +: **304** / **3967** / 4271 Exp -: **2200** / **48414** / 50614 Total: 2504 / 52381 / 54885 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.64 / 1.46 / 1.84 3) Adjusted for maternal age, smoking, parity: > 12 months duration: 1.24 (1.10, 1.40) Infertility treatment: 1.40 (1.23, 1.60) Results similar for all types of treatment	**Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort:+ Use of validated method for ascertaining exposure: - Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: +
Zuppa, Maragliano,	**Geographical location:** Rome, Italy	**Age:** NR	**Definition(s) of outcome(s):**	1) Preterm birth:	**Comments:** None

Evidence Table 3. Question 4 – Longer-Term Outcomes (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Scapillati, et al., 2001 **#5590**	**Study dates:** 1988-1997 **Size of population (no. of patients):** N = 228 spontaneous twins N = 32 ART twins **Study type:** Cohort	**Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Twin births **Exclusion criteria:** NR	Preterm birth < 37wks Low birthweight < 2500gm Respiratory distress syndrome Hyaline membrane disease (HMD) (diagnosed by clinical course, chest xray, blood gas and acid-base values), chronic lung disease (oxygen dependency at 28th day of life)	ptb+ / ptb- / Total ART: **24** / **8** / 32 spontaneous: **120** / **108** / 228 Total: 144 / 116 / 260 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.43 / 1.13 / 1.80 2) Low birthweight: lbwt+ / lbwt- / Total ART: **24** / **8** / 32 spontaneous: **123** / **105** / 228 Total: 147 / 113 / 260 Value / Lower 95% CI / Upper 95% CI Rel risk: 1.39 / 1.10 / 1.76 3) Respiratory distress syndrome: RDS+ / RDS- / Total ART: **11** / **21** / 32 spontaneous: **27** / **201** / 228 Total: 38 / 222 / 260 Value / Lower 95% CI / Upper 95% CI Rel risk: 2.90 / 1.60 / 5.27	**Quality assessment:** Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: - Adequate description of the cohort: - Use of validated method for ascertaining exposure: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: -

Appendix E: Peer Reviewers

The Duke Evidence-based Practice Center is grateful to the following peer reviewers who read and commented on a draft version of this report:

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