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Therapeutic Management, Delivery, and Postpartum Risk Assessment and Screening in Gestational Diabetes

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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 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 focused on four questions: (1) What are the risks and benefits of an oral diabetes agent (i.e., glyburide), as compared to all types of insulin, for gestational diabetes? (2) What is the evidence that elective labor induction, cesarean delivery, or timing of induction is associated with benefits or harm to the mother and neonate? (3) What risk factors are associated with the development of type 2 diabetes after gestational diabetes? (4) What are the performance characteristics of diagnostic tests for type 2 diabetes in women with gestational diabetes?

Data Sources: We searched electronic databases for studies published through January 2007. Additional articles were identified by searching the table of contents of 13 journals for relevant citations from August 2006 to January 2007 and reviewing the references in eligible articles and selected review articles.

Review Methods: Paired investigators reviewed abstracts and full articles. We included studies that were written in English, reported on human subjects, contained original data, and evaluated women with appropriately diagnosed gestational diabetes. Paired reviewers performed serial abstraction of data from each eligible study. Study quality was assessed independently by each reviewer.

Main Results: The search identified 45 relevant articles. The evidence indicated that (1) maternal glucose levels do not differ substantially in those treated with insulin versus insulin analogues or oral agents; (2) average infant birth weight may be lower in mothers treated with insulin than with glyburide; (3) induction at 38 weeks may reduce the macrosomia rate, with no increase in cesarean delivery rates; (4) anthropometric measures, fasting blood glucose (FBG), and 2-hour glucose value are the strongest risk factors associated with development of type 2 diabetes; (5) FBG had high specificity, but variable sensitivity, when compared to the 75-gm oral glucose tolerance test (OGTT) in the diagnosis of type 2 diabetes after delivery.

Conclusions: The evidence suggests that benefits and a low likelihood of harm are associated with the treatment of gestational diabetes with an oral diabetes agent or insulin. The effect of induction or elective cesarean on outcomes is unclear. The evidence is consistent that anthropometry identifies women at risk of developing subsequent type 2 diabetes; however, no evidence suggested the FBG out-performs the 75-gm OGTT in diagnosing type 2 diabetes after delivery.

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Appendixes and Evidence Tables for this report are provided electronically at http://www.ahrq.gov/clinic/tp/gdmparttp.htm**.**

Executive Summary

Introduction

Gestational diabetes mellitus (gestational diabetes), one of the most common medical complications of pregnancy, is defined as carbohydrate intolerance of variable degree, with an onset or first recognition occurring during pregnancy. Of the estimated 4 million births annually in the United States, gestational diabetes affects approximately 200,000 (7 percent), depending on the criteria (diagnostic test and threshold values) chosen for diagnosis. Initial diagnostic criteria for gestational diabetes were based on the ability to identify women at risk of developing type 2 diabetes, since 15 to 60 percent of women with gestational diabetes develop type 2 diabetes mellitus within 5 to 15 years of delivery. Therefore, the diagnosis and subsequent management of gestational diabetes after delivery has important implications for the prevention of type 2 diabetes. Questions remain, however, about the optimal ways to assess the postpartum risk of diabetes and to screen women for diabetes after a diagnosis of gestational diabetes has been made.

Equally important, gestational diabetes is associated with both maternal and infant complications, including maternal and neonatal hypoglycemia and complications of macrosomia, such as birth trauma and cesarean delivery. Treatment recommendations for gestational diabetes are based primarily on evidence from early trials suggesting that insulin treatment can reduce the incidence of macrosomia. To date, relatively little work has been done to synthesize more recent evidence regarding the management of maternal glucose or physicians' decisions to recommend elective labor induction or cesarean delivery in women with gestational diabetes.

Furthermore, while there is substantial literature regarding risk factors for type 2 diabetes, there has been no comprehensive review of these risk factors or the relative magnitude of their associations with type 2 diabetes. Finally, little work has been done to investigate the performance of postpartum glucose testing in women with gestational diabetes or to analyze the effect of performing the tests at different time intervals following delivery on the relative performance of current screening modalities.

Because of the broad clinical and public health policy implications of the management of women with gestational diabetes, the American College of Obstetricians and Gynecologists (ACOG) requested an evidence report from the Agency for Healthcare Research and Quality (AHRQ) through the Evidence-based Practice Center program (EPC) to systematically and critically examine the literature on specific aspects of the management of gestational diabetes. We were guided in our key questions and outcomes of interest by the ACOG, the AHRQ, and our panel of technical experts.

Our key questions were:

1. What is the evidence for the risks and benefits of oral diabetes agents (e.g., second-generation sulfonylureas and metformin), as compared to all types of insulin, for both the mother and neonate in the treatment of women with gestational diabetes?
   a. How does maternal outcome vary based on the level of glucose at the initiation of a medication?

b. How does neonatal outcome vary based on the level of glucose at the initiation of a medication?

Maternal outcomes

- cesarean delivery
- glycemic control (fasting blood glucose [FBG], 1-hour [hr] and 2-hr postprandial glucose [PPG])
- hemorrhage
- hypoglycemia
- operative vaginal delivery
- perineal tears
- pre-eclampsia
- weight

Neonatal outcomes

- anoxia
- birth trauma
- birth weight
- congenital malformations
- hyperbilirubinemia
- hypoglycemia
- large for gestational age (LGA)
- macrosomia
- mortality
- neonatal intensive care admissions
- respiratory distress syndrome
- shoulder dystocia
- small for gestational age (SGA)

2. What is the evidence that elective cesarean delivery or the choice of timing of induction in women with gestational diabetes results in beneficial or harmful maternal and neonatal outcomes?
   a. What is the evidence for elective cesarean delivery at term, as compared to an attempt at vaginal delivery (spontaneous or induced) at term, with regard to beneficial or harmful maternal and neonatal outcomes in gestational diabetes?
      i. cesarean versus spontaneous labor and vaginal delivery
      ii. cesarean versus induced labor and vaginal delivery
      iii. cesarean versus any attempt at vaginal delivery at term
   b. What is the evidence for labor induction at 40 weeks, as compared to labor induction at an earlier gestational age (less than 40 weeks) or spontaneous labor, with regard to beneficial or harmful maternal and neonatal outcomes in gestational diabetes?
      i. labor induction at less than 40 weeks versus labor induction at 40 weeks
      ii. labor induction at 40 weeks versus spontaneous labor
      iii. labor induction at less than 40 weeks versus spontaneous labor
   c. How is the estimated fetal weight (EFW) related to outcomes of management of gestational diabetes with elective cesarean delivery or the timing (i.e., gestational age range) of labor induction?
   d. How is gestational age related to outcomes of management of gestational diabetes with elective cesarean delivery or the choice of timing (i.e., gestational age range) of labor induction?

Maternal outcomes

- cesarean delivery
- hemorrhage
- infection
- operative vaginal delivery
- perineal tears

Neonatal outcomes

- same as Key Question 1

3. What risk factors, including but not limited to family history, physical activity, pre-pregnancy weight, and gestational weight gain, are associated with short-term and long-term development of type 2 diabetes following a pregnancy with gestational diabetes?

4. What are the performance characteristics (sensitivity, specificity, and reproducibility) of tests for diagnosing type 2 diabetes after pregnancy in patients with a history of gestational diabetes? Are there differences in the performance characteristics of the test results based on subgroup analysis?

Methods

Approach to Evaluating the Literature

We identified the primary literature on labor and postpartum management of gestational diabetes and the association with maternal and neonatal outcomes through a comprehensive search plan that included electronic and hand searching. We ran searches of the following databases for the specified periods of time: MEDLINE® (1950 through January 2007), EMBASE® (1974 through January 2007), The Cochrane Central Register of Controlled Trials (CENTRAL; Issue 1, 2007), and the Cumulative Index to Nursing & Allied Health Literature (CINAHL®; 1982 through January 2007). Hand searching for relevant citations took several forms. From our electronic search, we identified the 13 journals (see Appendix B[a]) that were most likely to publish articles on this topic. We scanned the table of contents of each issue of these journals for relevant articles from August 2006 through January 2007. For the second form of hand searching, reviewers received eligible articles and flagged references of interest for the team to compare to the existing database.

Two independent reviewers conducted title scans in a parallel fashion. If either reviewer thought that a title was potentially eligible, its abstract was reviewed. If the abstract was deemed to meet the inclusion criteria by two reviewers, the abstract was included in our article review. Any differences of opinion were resolved by the two primary reviewers or by a third independent reviewer.

Each eligible article underwent double review by study investigators. A primary reviewer completed all data abstraction forms, and a second reviewer confirmed the first reviewer's data abstraction forms for completeness and accuracy. The reviewers assessed study quality independently. Reviewer pairs were formed to include personnel with both clinical and methodological expertise. A third reviewer re-reviewed a random sample of articles by the first two reviewers to ensure consistency in the abstraction of the articles.

Quality Assessment

We used several study quality assessment tools, based on the study design of the articles included in the review. Our dual, independent review of article quality judged articles on several aspects of each study type's internal validity. Quality assessment of trials for Key Questions 1 and 2 was based on the Jadad criteria and included: (1) whether the study was randomized, (2) the appropriateness of the randomization scheme, (3) whether the study was blinded, (4) the appropriateness of the blinding, and (5) the description of withdrawals and drop-outs. For each

trial, we created a score between 5 (high quality) and 0 (low quality). Quality assessment of observational studies for Key Questions 1, 2, and 3 was designed by selecting key elements from the Standards for Reporting of Observational Studies (STROBE) checklist for reporting observational studies. The STROBE checklist is based on the consensus of 27 participants of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group and includes recommendations for standards for individual studies with regard to the presentation of the study hypotheses, eligibility criteria, study population, power and sample size calculations, definitions of outcomes, and description of loss to followup and missing data. Quality assessment of the diagnostic test studies for Key Question 4 was designed by selecting key elements from the Standards for Reporting of Diagnostic Accuracy (STARD) Initiative and included items about reporting the sampling design, describing the lost-to-followup, reporting diagnostic accuracy, verifying positive and negative tests equally, interpreting the tests independently, reporting reproducibility, and reporting subgroup analyses.

Based on the quantity, quality, and consistency of the studies, we graded the overall body of evidence for each of the key questions using the evidence-grading scheme recommended by the GRADE Working Group.

Analysis

We conducted meta-analyses when there were sufficient data (three or more studies) and the studies were homogeneous with respect to key variables (population characteristics, study duration, intervention/exposure/comparison tests, and length of followup). When the data were not sufficient to allow us combine the studies in a meta-analysis, we prepared a qualitative summary of the results.

Results

Search Results

We retrieved 11,400 unique citations from our original search. After reviewing the titles and abstracts, 552 were deemed eligible for further review, and the full articles were retrieved. A total of 45 articles were ultimately included in this review.

Key Question 1

What is the evidence for the risks and benefits of oral diabetes agents (e.g., second-generation sulfonylureas and metformin), as compared to all types of insulin, for both the mother and neonate in the treatment of women with gestational diabetes?

a. How does maternal outcome vary based on the level of glucose at the initiation of a medication?
b. How does neonatal outcome vary based on the level of glucose at the initiation of a medication?

- We identified eight randomized controlled trials (RCTs) with a total of 845 participants that met our inclusion criteria for review: Three trials compared insulin to glyburide; two trials compared insulin to insulin lispro; one trial compared long-acting to short-acting insulin; one trial compared four-times-daily insulin to two-times daily insulin; and one trial compared diet to insulin.
- Two small trials and one large trial (404 women) reported no significant difference in maternal glucose control or rates of cesarean delivery between the insulin and glyburide groups.
- A meta-analysis of the three RCTs comparing insulin and glyburide showed that treatment with insulin was associated with a lower mean infant birth weight when compared to glyburide (weighted mean difference: -93 grams [gm]) (95 percent confidence interval [CI]: -191 to 5 gm), but the difference was small and not statistically significant.
- The largest trial reported no difference in the proportion of infants with hypoglycemia (9 percent with glyburide as compared to 6 percent with insulin therapy [$p = 0.25$]). A smaller trial reported a significantly higher percentage of infants with hypoglycemia in the glyburide group than in the insulin or acarbose groups (33 percent compared to 4 percent and 5 percent, respectively; $p = 0.006$).
- Four observational studies (N = 911 women) compared the effects of insulin and glyburide on maternal and neonatal outcomes.
- Due to potential selection bias, loss to followup, and the lack of any power analysis to estimate detectable effect sizes, none of the observational studies was deemed strong enough to justify a modification of the conclusions drawn from the RCTs.
- We graded the overall evidence comparing insulin and glyburide as very low.
- We identified two RCTs that compared insulin lispro to insulin. It appeared that insulin lispro might be associated with tighter maternal glucose control than regular insulin, but there were only limited data to support this conclusion.
- Both RCTs reported similar rates of cesarean delivery among women in the insulin lispro group, as compared to the insulin group.
- No evidence existed to suggest that neonatal outcomes differ between women treated with insulin lispro and those treated with regular insulin.
- We graded the strength of the evidence comparing insulin to insulin lispro as very low.
- One RCT (N = 23 women) reported that long-acting insulin was associated with a higher proportion of infants with macrosomia when compared to short-acting insulin. No

difference in birth trauma or metabolic abnormalities was found, but this study was not adequately powered to detect differences in these outcomes.

- There was insufficient evidence to allow us to draw any conclusions regarding maternal outcomes.
- One RCT (N = 274 women) reported that twice-daily insulin was associated with a higher proportion of hypoglycemia (6 percent versus 1 percent; p = 0.002) and hyperbilirubinemia (21 percent versus 11 percent; p = 0.002) when compared to four-times-daily insulin. No evidence existed to suggest a difference in maternal glucose levels or cesarean delivery between twice-daily and four-times-daily use of insulin.
- We identified only one RCT (N = 95 women) that reported lower rates of macrosomia (5.9 percent versus 26.5 percent, respectively; p = 0.005) and lower infant birth weights (p = 0.002) for those using insulin plus dietary management versus those treated with diet alone.
- We graded the overall evidence regarding comparisons of diet plus insulin to diet alone as very low, given that only one small RCT met our inclusion criteria.
- We found no evidence to indicate whether the relative effect of different treatment approaches on maternal and infant outcomes varied with the level of glucose at the initiation of medical therapy.
- We expect that the ongoing Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study, an observational study of 23,325 pregnant women, should provide data on maternal and neonatal outcomes at various maternal glucose levels and potentially indicate thresholds at which medical therapy should be initiated.
- We found no RCTs or observational studies comparing metformin to insulin in gestational diabetics that met our criteria for review. The Metformin in Gestational Diabetes (MiG) Trial is an ongoing randomized trial of over 500 women that should provide future insight into the benefits and risks of metformin use throughout pregnancy.
- There were insufficient data regarding the teratogenic effects of intrauterine exposure to metformin or its potential effect on infant growth and motor development.

Key Question 2

What is the evidence that elective cesarean delivery or the choice of timing of induction in women with gestational diabetes results in beneficial or harmful maternal and neonatal outcomes?

- One RCT and seven observational studies evaluated two of our five maternal outcomes of interest and 11 of the 12 neonatal outcomes of interest.
- One RCT of 200 women reported that elective induction at 38 weeks of gestation, as compared to expectant management (induction at 42 weeks' gestation or if the EFW was 4,200 gm or greater), reduced infant birth weight and the rate of macrosomia but did not alter other maternal or neonatal outcomes, including the rate of cesarean delivery.
- Two observational studies of low quality also reported a reduction in infant birth weight or rates of macrosomia in women induced at 38 weeks of gestation, as compared to historical controls.

- Five additional observational studies examined the effects of various delivery management protocols, but each had serious limitations, including reliance on historical controls, no adjustment for potential confounders, or no adjustment or stratified analysis based on severity of gestational diabetes (class A1 [diet-controlled] versus class A2 [insulin-controlled]). In addition, the studies covered a wide time period (4-19 years), with no adjustment for changes in clinical practice.
- We were unable to draw firm conclusions from the limited data available.
- We graded the overall strength of the evidence as very low, given the limited number of RCTs and the serious design limitations in the conduct of the observational studies.

Key Question 3

What risk factors, including but not limited to family history, physical activity, pre-pregnancy weight, and gestational weight gain, are associated with short-term and long-term development of type 2 diabetes following a pregnancy with gestational diabetes?

- We developed an *a priori* list of risk factors for type 2 diabetes, based on guidance from the AHRQ, the ACOG, and members of our technical panel, and then grouped these risk factors into nine categories:
  1. Family history of type 2 diabetes
  2. Sociodemographics
  3. Lifestyle factors
  4. Parity
  5. Pregnancy-related factors
  6. Postpartum factors
  7. Measures of anthropometry
  8. Oral contraceptives
  9. Physiological measures
- Sixteen studies evaluated at least one risk factor and reported adjusted measures of association.
- We identified 11 cohort studies that evaluated the relationship between 11 different anthropometric measures and the development of type 2 diabetes; 8 studies reported adjusted measures of association from multivariate models.
- Seven of the eight studies that evaluated anthropometric measures (pre-pregnancy body mass index [BMI], pregnancy BMI, weight, waist-to-hip ratio) using multivariate analysis reported that these measures were positively associated with the risk of developing type 2 diabetes.
- We graded the evidence on anthropometric measures and the risk of developing type 2 diabetes as moderate because of the inconsistency in the anthropometric measures used across the studies.
- We identified five studies that included family history of type 2 diabetes in the multivariate analysis, but only one study reported the actual magnitude of the association of family history with the risk of type 2 diabetes, and this association was not statistically significant (relative risk [RR] = 1.7; 95 percent CI: 0.6 to 4.6).

- We graded the evidence on family history as very low because only one study reported the actual measure of association.
- Five studies assessed age as a risk factor for developing type 2 diabetes among gestational diabetics, but only one study reported the actual measure of association; women who were 30 years of age and older at diagnosis of gestational diabetes had a higher likelihood of developing type 2 diabetes, but the relative risk was not statistically significant.
- We did not identify any studies of lifestyle behaviors that met our criteria for inclusion in this review.
- Gestational age at diagnosis of gestational diabetes was inversely associated with a higher likelihood of the development of type 2 diabetes, but the modeling of gestational age varied across studies and therefore limited our ability to synthesize the data.
- Two studies evaluated the association between the use of progesterone-only contraception or combination oral contraception (estrogen and progesterone) and the risk of developing type 2 diabetes in women with gestational diabetes. One study reported a two-fold increase in the risk of developing diabetes with the use of progestin-only oral contraceptives as compared to combination oral contraception; one study reported no increased risk in women using depo-medroxyprogesterone acetate as compared to combined oral contraceptives.
- FBG, 2-hour glucose value, and the area under the curve from the diagnostic antepartum oral glucose tolerance test (OGTT) were associated with a significantly higher risk of developing type 2 diabetes in women with gestational diabetes.

Key Question 4

What are the performance characteristics (sensitivity, specificity, and reproducibility) of tests for diagnosing type 2 diabetes after pregnancy in patients with a history of gestational diabetes? Are there differences in the performance characteristics of the test results based on subgroup analysis?

- We identified eight studies that reported 10 evaluations of the performance of a reference test versus a comparison (screening) test for the diagnosis of type 2 diabetes in the postpartum period.
- Our review yielded three general comparisons: (1) two different diagnostic threshold values applied to the 75-gm OGTT (the World Health Organization [WHO] 1985 criterion compared with the WHO 1999 criterion), (2) FBG level greater than 7.0 mmol/L (126 mg/dL) (the American Diabetes Association [ADA] 1997) compared to the 75-gm OGTT (WHO 1999), and (3) FBG greater than 7.0 mmol/L (126 mg/dL) (ADA 1997) compared to the 75-gm OGTT (WHO 1985).
- The sensitivity for the FBG greater than 7.0 mmol/L (126 mg/dL) alone as compared with a complete OGTT using the same FBG threshold (FBG greater than 7.0 mmol/L (126 mg/dL) or a 2-hr plasma glucose level after 75-g OGTT greater than 11.1 mmol/L (200 mg/dL) varied across the three studies, ranging from 46 to 89 percent.
- With a threshold greater than 7.0 mmol/L, the FBG had high specificity when compared to the 75-gm OGTT but had highly variable sensitivity.

- No studies included in this review reported measures of reproducibility.
- We graded the strength of the evidence regarding postpartum screening for type 2 diabetes as very low because of the limited number of studies within each category of comparisons and the heterogeneity in the study populations.

Discussion

Conclusions

Although the overall quality of the evidence was very low, we were able to draw some conclusions regarding treatment options for maternal glucose control, the timing and method of delivery, the risk factors for the development of type 2 diabetes, and the performance characteristics of screening tests conducted in the postpartum period to identify those who have developed type 2 diabetes.

When patients ask about the effect of the use of insulin analogues or glyburide as compared to insulin, clinicians should be aware that little clinical difference has been demonstrated in the infant birth weights associated with the use of these three regimens. Clinicians should also be aware that while the use of an alternative to regular insulin is unlikely to result in any adverse maternal or infant outcomes, there were insufficient data to allow us to determine whether insulin analogues or glyburide are more efficacious than regular insulin in achieving maternal glucose targets. Also, there was no evidence supporting a difference in terms of the prevention of episodes of maternal or neonatal hypoglycemia. To date, only insulin has been approved by the Food and Drug Administration for use in gestational diabetes. Because of the limited data available, it was unclear what glucose thresholds should be used to initiate treatment with insulin, insulin analogues, or glyburide in patients who are being treated with diet alone. Furthermore, there were insufficient data regarding the potential benefits or risk of metformin use.

There was also insufficient evidence to permit us to develop guidelines for elective labor induction or cesarean delivery in women with gestational diabetes. Well-designed clinical trials are needed to provide a stronger base of evidence for the management of gestational diabetes.

Based on multivariate models, measures of obesity appeared to be the strongest risk factor for type 2 diabetes in women with gestational diabetes. We have concluded that there are insufficient data to justify recommending alternative tests to the 75-gm OGTT for the detection of type 2 diabetes in women with gestational diabetes. Further studies conducted in diverse populations and high-risk subgroups and incorporating measures of reproducibility will help to move this area of investigation toward the development of clinically acceptable testing guidelines.

Limitations

This review has several important limitations. First, the heterogeneous nature of the studies prevented a quantitative summary of much of the data. For Key Question 1, we were able to provide a summary measure of the weighted mean difference in infant birth weight in the three RCTs comparing insulin and glyburide. However, the pooled estimate provided data on only one of several important maternal and neonatal outcomes related to medical treatment in gestational

diabetics. We were unable to conduct additional analysis because the number of trials comparing similar treatments was very limited. Also, maternal and neonatal outcomes were not consistent across studies. Few of the same outcome measures were included in two or more studies, and the definitions of outcomes varied across studies. Our review of five observational studies comparing of glyburide and insulin did not alter our limited conclusions from the RCTs. We were further limited by a lack of data on the potential risk of glyburide use. We were unable to provide evidence on the potential risks and benefits of metformin because of a lack of published studies that met our inclusion criteria.

We were also unable to draw substantial conclusions from our review of seven observational studies and a single RCT on elective induction and cesarean delivery. The observational studies had serious limitations, with no adjustment for potential confounders, severity of gestational diabetes, or variation in the definitions of major outcomes. There was substantial heterogeneity in the study populations and the time periods of these observational studies.

The lack of multivariate analysis in some studies, as well as inconsistencies in the covariates included in the multivariate models of other studies, made it difficult to compare results across the 16 studies on risk factors for type 2 diabetes. We found limited evidence for the magnitude of association of traditional risk factors (sociodemographics, parity, family history) with the development of type 2 diabetes in women with gestational diabetes. We were also limited by the lack of availability of any studies on the possible relationship of lifestyle behaviors to the risk of type 2 diabetes.

Finally, heterogeneity in the study populations and the time intervals of postpartum testing made it difficult to draw firm conclusions regarding the effectiveness of postpartum glucose screening in women with a history of gestational diabetes.

Future Research Implications

- Researchers should focus on conducting studies that will lead to the development of evidenced-based guidelines for maternal glucose control in gestational diabetes and physician recommendations for labor induction, elective cesarean, or expectant management.
- Well-designed RCTs with *a priori* hypotheses, power analysis, appropriate effect sizes, and intention-to-treat analysis can provide better data on treatment efficacy.
- Consistency in the definition and collection of maternal and infant outcome measures is essential to our ability to draw confident conclusions about potential benefits and harms of treatment options among women with gestational diabetes.
- The best evidence for delivery management in women with gestational diabetes will be garnered from the conduct of well-designed RCTs comparing elective induction and cesarean delivery to expectant management. Alternatively, observational studies with consistency in outcomes measures and multivariate adjustment for potential confounders can provide important, relevant information.
- Those conducting longitudinal studies of women with a history of gestational diabetes should develop and follow standard protocols for retention in an effort to improve followup rates. Future studies should collect data on pertinent covariates and adjust for relevant confounders in multivariate analysis.
- Studies measuring the sensitivity, specificity, and reproducibility of screening tests for type 2 diabetes in women with a history of gestational diabetes can help physicians in the

early identification of women with type 2 diabetes and avoid potential medical complications of diabetes.

- A comparison of screening and reference tests in certain subgroups (i.e., those with a family history type 2 diabetes or prior gestational diabetes) is also warranted.
- In order to develop broadly acceptable guidelines for postpartum screening for type 2 diabetes in women with prior gestational diabetes, additional research should be conducted to assess test reproducibility as well as test performance based on varying intervals of postpartum screening.

Evidence Report

Chapter 1. Introduction

The American College of Obstetricians and Gynecologists (ACOG) has requested an evidence report from the Agency for Healthcare Research and Quality (AHRQ) through the Evidence-based Practice Center program (EPC) to systematically and critically examine the literature on specific aspects of the management of gestational diabetes mellitus (gestational diabetes). With the ongoing increase in obesity and sedentary lifestyles, the prevalence of diabetes mellitus among reproductive-aged women is rising, both globally and in the United States.[1] There are currently 1.85 million reproductive-aged women in the United States with gestational diabetes, type 1 or type 2 diabetes mellitus (type 2 diabetes), or glucose intolerance.[2] Gestational diabetes, the most common medical complication of pregnancy, is defined as carbohydrate intolerance of variable degree, with an onset or first recognition occurring during pregnancy. Population-based studies estimate that gestational diabetes affects about 200,000 (7 percent) of the over 4 million births occurring annually in the United States and is associated with both maternal and neonatal complications.[3-5] Furthermore, women with gestational diabetes are at high risk for future diabetes; 15 to 60 percent will develop type 2 diabetes mellitus within 5 to 15 years of delivery.[6] Therefore, the diagnosis and subsequent management of gestational diabetes after delivery has important implications for the prevention of type 2 diabetes. A systematic review of evidence to guide decisions about glucose management, labor management, postpartum risk assessment, and screening of women with gestational diabetes would be useful for clinicians and public health officials.

In an effort to promote maternal wellbeing and avoid adverse neonatal outcomes, such as macrosomia, birth trauma, and neonatal hypoglycemia, clinical recommendations have been developed by the ACOG[7] and the American Diabetes Association (ADA) for the obstetrical management of gestational diabetes. The guidelines emphasize the importance of glucose control to minimize the risk of macrosomia and its associated complications. When dietary management fails to achieve adequate glucose control, an anti-hyperglycemic medication should be used. Traditionally, insulin has been considered the gold standard for management because of the ability to achieve tight maternal glucose control without the risk of transfer of insulin across the placenta.[8] However, an oral diabetes medication (i.e., glyburide) is being used increasingly in women with gestational diabetes despite the lack of approval by the Food and Drug Administration for this indication.[8-10] Metformin is currently used in the non-pregnant woman with polycystic ovarian syndrome (PCOS) to treat insulin resistance and normalize ovulation.[11] Metformin use in women with gestational diabetes is still in the experimental stages. Given the increasing use of different medications for gestational diabetes, it is time for a critical appraisal of the literature regarding the potential benefits and harms associated with the medications that can be used for the treatment of gestational diabetes.

To date, the evidence has been somewhat limited regarding the comparative effectiveness and safety of oral diabetes agents and insulin preparations for women with gestational diabetes. The Cochrane Collaboration has conducted a review of randomized clinical trials comparing the effects of alternative management strategies (e.g., dietary management, insulin, or an oral diabetes agent) in women with impaired glucose tolerance or gestational diabetes.[12] The final analysis included three trials involving women with impaired glucose tolerance, but no trials involving women with gestational diabetes. No statistically significant differences were found in terms of cesarean delivery rates, neonatal intensive care unit admissions, or large-for-gestational age (LGA; weight greater than 90th percentile) infants among women with impaired glucose

tolerance undergoing intensive treatment with insulin, as compared to those receiving dietary advice alone. Further review is needed to assess the evidence now available on the value of medical therapies for glucose control in gestational diabetes. In the current report, one of our goals was to synthesize current knowledge regarding the medical treatment benefits and harms associated with the metabolic management of gestational diabetes, by comparing insulin therapy to oral diabetes medications, including the sulfonylureas and metformin. Our maternal and neonatal outcomes of interest were chosen on the basis of established measures of maternal and infant morbidity and guidance by our team of technical experts, as described in the Methods chapter.

Both the ACOG and the ADA have provided guidelines for labor management of pregnancies complicated by gestational diabetes. The ACOG states that primary cesarean delivery may be indicated in women with gestational diabetes whose estimated fetal weight (EFW) is 4,500 grams (gm) or greater.[7] The ADA recommends delivery during the 38th week, unless obstetric considerations dictate alternative management.[13] Many institutions have implemented protocols for labor management of women with gestational diabetes, based largely on anecdotal or individual institutional experience. Variations in clinical management continue because patients and health care providers have differing perceptions of the potential benefits and risks of different management strategies. Neither health care providers nor patients are armed with the knowledge necessary to adequately weigh the potential benefits and harms associated with these strategies. The lack of consensus has led to controversy regarding best practices for labor management. Evidence relating to labor management can provide valuable epidemiological evidence to clinicians in daily practice as well as to professional organizations that seek to make clinical policy recommendations about the optimal delivery of obstetrical care to women with gestational diabetes.

In this report, we have systematically reviewed and summarized the available literature on outcomes associated with a range of labor management strategies, including elective induction of labor, elective cesarean delivery, and expectant management of labor. For the purposes of this report, we refer to "elective" cesarean delivery as a procedure performed after discussion between the provider and patient with the goal of avoiding adverse neonatal outcomes that occur more often in diabetic pregnancy, such as shoulder dystocia, nerve palsy, or fracture. We have also reviewed the evidence regarding the effect of gestational age and EFW on maternal and neonatal outcomes in pregnancies complicated by gestational diabetes.

There is growing interest in the effect of childbearing on the development of chronic medical conditions, including type 2 diabetes. Many studies have examined traditional risk factors for type 2 diabetes, including age, race/ethnicity, and a family history of type 2 diabetes. However, no review to date has systematically examined risk factors for type 2 diabetes in women with a history of gestational diabetes. Such a review is needed and should cover the available data on metabolic or hormonal risk factors in this population as well as emerging data on other risk factors such as homocysteine levels[14 15] and glutamic acid decarboxylase (GAD) antibodies.[16] A review of this body of evidence could assist policymakers in the development of guidelines targeted at primary prevention of type 2 diabetes. We have therefore systematically reviewed the evidence on risk factors for type 2 diabetes in women with gestational diabetes, assessing the magnitude of individual risk factors and study quality.

Because women with gestational diabetes are at high risk for future diabetes, postpartum testing is crucial for early diagnosis of type 2 diabetes and the prevention or delay of onset of diabetic complications. The ACOG recognizes the increased risk of diabetes in women with

gestational diabetes but offers no standard recommendation for postpartum testing.[7] The ADA recommends postpartum screening at 6 weeks postpartum using either a fasting blood glucose (FBG) or an oral glucose tolerance test (OGTT).[13 17] Women with a normal result should be reassessed every 3 years. Women with impaired fasting glucose or impaired glucose tolerance should receive annual testing. The 4th International Workshop on Gestational Diabetes has recommended that postpartum glucose testing be performed at 6 to 12 weeks postpartum.[18]

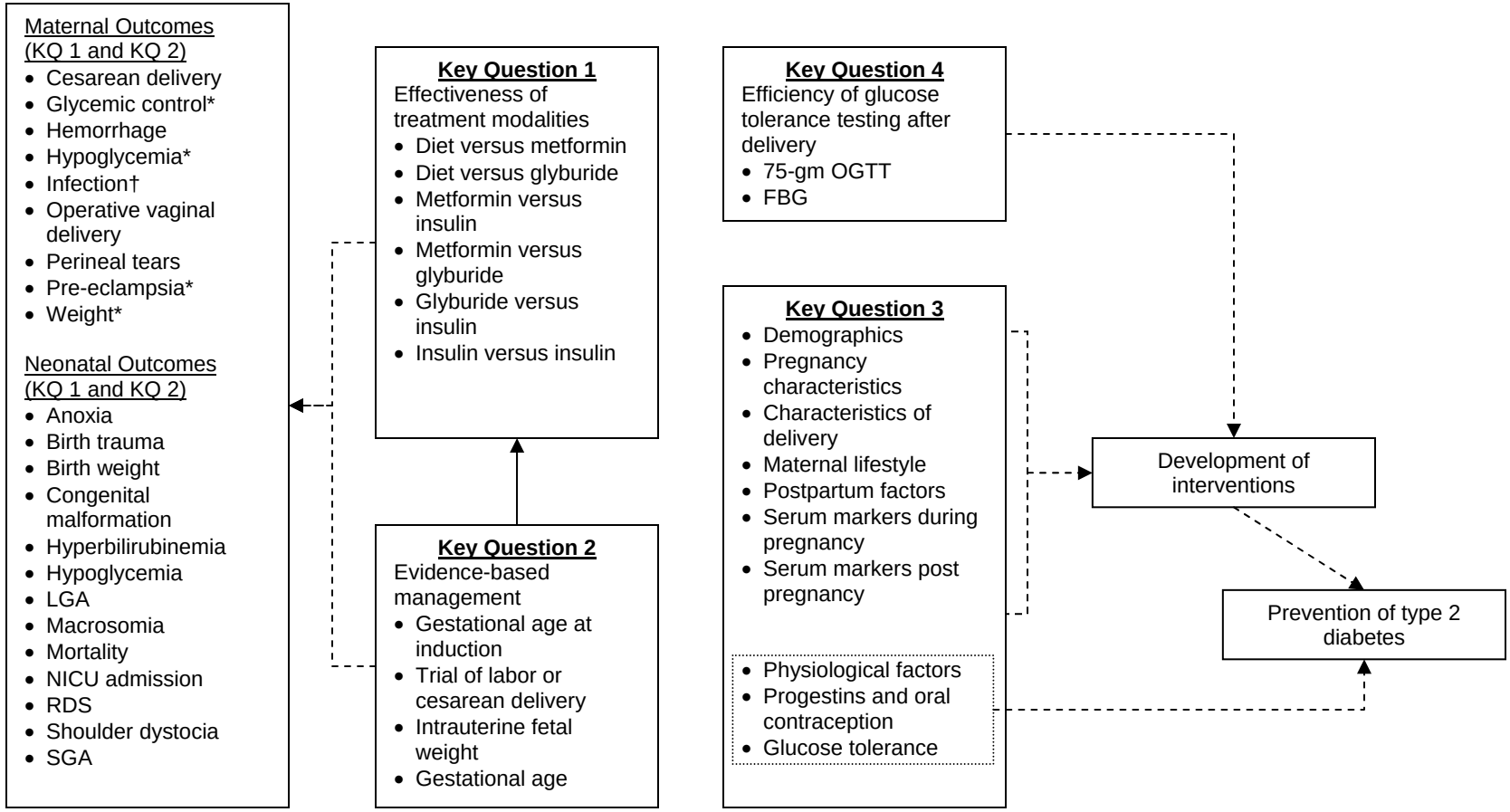
Despite the general recommendation for postpartum screening, no consensus exists regarding the overall performance characteristics of the OGTT or FBG in the postpartum period or in women with a history of gestational diabetes. Emerging data suggest that many women with gestational diabetes do not receive appropriate postpartum testing,[19 20] perhaps because of limited knowledge regarding the performance of the screening tests in postpartum women, differences in the recommendations by professional organizations, and the challenges posed by the 2- to 3-hour (hr) timeframe required for an OGTT for a busy new mother. Knowledge of the performance of the FBG in comparison to the standard OGTT could help to improve patient adherence to postpartum testing. In addition, evidence related to the sensitivity and specificity of screening tests for type 2 diabetes may inform the development of evidence-based guidelines by professional organizations, prevent provider confusion about the timing of testing, and facilitate provider adherence to recommendations for testing. We have therefore investigated the performance of currently used screening tests for type 2 diabetes of pregnancies for women with a history of gestational diabetes, assessing their sensitivity and specificity and summarizing the evidence with regard to reproducibility.

To improve the outcomes of pregnancies in women with gestational diabetes, several approaches should be considered, including: (1) novel approaches to maternal glycemic control; (2) modifications of the clinical assessment for timing and method of delivery; (3) identification of risk factors for subsequent development of type 2 diabetes; and (4) clarification of the performance characteristics of postpartum glucose screening tests. The use of oral diabetes agents and/or new insulin preparations, for example, might promote better glucose control, decrease maternal hypoglycemia, and reduce abnormal fetal growth. The adaptation of new guidelines for cesarean delivery and labor induction in women with diabetes might reduce the incidence of birth trauma or nerve damage (e.g., brachial plexus palsy). A better understanding of the efficiency of postpartum glucose screening tests and screening intervals might help to identify a greater number of reproductive-aged women who are at risk of type 2 diabetes and who could be targeted for primary prevention. For example, it is possible that screening women beyond the currently recommended time interval of 6 weeks after delivery might increase the sensitivity of diabetic screening protocols. A greater number of women could then receive counseling on lifestyle modifications (i.e., nutrition, exercise). Furthermore, among those women who screen negative for glucose intolerance after the index pregnancy, lifestyle modifications might reduce the risk of development of gestational diabetes in subsequent pregnancies.

Conceptual Framework and Key Questions

As shown in our conceptual framework (see Figure 1), we focused our evidence review on four independent, yet interrelated, areas of clinical management. The solid lines summarize the four key questions that are the focus of our review. Key Questions 1 and 2 include maternal management prior to and at the time of delivery. Also, prior clinical studies have supported a

Figure 1. Conceptual framework for labor and postpartum management of women with gestational diabetes mellitus



* Outcome was evaluated only for Key Question 1.
† Outcome was evaluated only for Key Question 2.

FBG = fasting blood glucose; gm = gram; KQ = key question; LGA = large for gestational age; NICU = neonatal intensive care unit; OGTT = oral glucose tolerance test; RDS = respiratory distress syndrome; SGA = small for gestational age; type 2 diabetes = type 2 diabetes mellitus

direct association between prenatal maternal glucose management and EFW and the timing of delivery, two areas of focus in Key Question 2. The link between Key Questions 1 and 2 is reflected in the commonality of several of the maternal and neonatal outcomes. From a biological perspective, metabolic control can directly influence the effects of intrauterine weight and gestational age on clinical decisionmaking in labor management.

Maternal outcomes of interest included maternal hypoglycemia, glycemic control, pre-eclampsia, postpartum hemorrhage, maternal weight, and cesarean delivery, representing measures of maternal morbidity and quality of care. Neonatal outcomes of interest included macrosomia, neonatal hypoglycemia, birth trauma, birth weight, and respiratory distress syndrome, representing measures of neonatal morbidity and subsequent childhood wellbeing.

In Key Question 3, we examined multiple risk factors for development of type 2 diabetes. Assessment of the literature yielded two primary categories of risk factors: traditional epidemiological factors and physiological factors. As shown in the conceptual framework, these factors may be instrumental in the development of targeted interventions for this particular population of women. In Key Question 4, we assessed the performance of screening tests in detecting type 2 diabetes in women with gestational diabetes.

Our key questions were:

1. What is the evidence for the risks and benefits of oral diabetes agents (e.g., second-generation sulfonylureas and metformin), as compared to all types of insulin, for both the mother and neonate in the treatment of women with gestational diabetes?
   a. How does maternal outcome vary based on the level of glucose at the initiation of a medication?
   b. How does neonatal outcome vary based on the level of glucose at the initiation of a medication?

   Maternal outcomes
   - cesarean delivery
   - glycemic control (FBG, 1-hr and 2-hr postprandial glucose (PPG)
   - hemorrhage
   - hypoglycemia
   - operative vaginal delivery
   - perineal tears
   - pre-eclampsia
   - weight

   Neonatal outcomes
   - anoxia
   - birth trauma
   - birth weight
   - congenital malformations
   - hyperbilirubinemia
   - hypoglycemia
   - LGA
   - macrosomia
   - mortality
   - neonatal intensive care admissions
   - respiratory distress syndrome
   - shoulder dystocia
   - small for gestational age (SGA)

2. What is the evidence that elective cesarean delivery or the choice of timing of induction in women with gestational diabetes results in beneficial or harmful maternal and neonatal outcomes?
   a. What is the evidence for elective cesarean delivery at term, as compared to an attempt at vaginal delivery (spontaneous or induced) at term, with regard to beneficial or harmful maternal and neonatal outcomes in gestational diabetes?

i. cesarean versus spontaneous labor and vaginal delivery
ii. cesarean versus induced labor and vaginal delivery
iii. cesarean versus any attempt at vaginal delivery at term

b. What is the evidence for labor induction at 40 weeks, as compared to labor induction at an earlier gestational age (less than 40 weeks) or spontaneous labor, with regard to beneficial or harmful maternal and neonatal outcomes in gestational diabetes?
   i. labor induction at less than 40 weeks versus labor induction at 40 weeks
   ii. labor induction at 40 weeks versus spontaneous labor
   iii. labor induction at less than 40 weeks versus spontaneous labor

c. How is the EFW related to outcomes of management of gestational diabetes with elective cesarean delivery or the timing (i.e., gestational age range) of labor induction?

d. How is gestational age related to outcomes of management of gestational diabetes with elective cesarean delivery or the choice of timing (i.e., gestational age range) of labor induction?

Maternal outcomes

- cesarean delivery
- hemorrhage
- infection
- operative vaginal delivery
- perineal tears

Neonatal outcomes

- anoxia
- birth trauma
- birth weight
- congenital malformations
- hyperbilirubinemia
- hypoglycemia
- LGA
- macrosomia
- mortality
- neonatal intensive care admissions
- respiratory distress syndrome
- shoulder dystocia
- SGA

3. What risk factors, including but not limited to family history, physical activity, pre-pregnancy weight, and gestational weight gain, are associated with short-term and long-term development of type 2 diabetes following a pregnancy with gestational diabetes?

4. What are the performance characteristics (sensitivity, specificity, and reproducibility) of tests for diagnosing type 2 diabetes after pregnancy in patients with a history of gestational diabetes? Are there differences in the performance characteristics of the test results based on subgroup analysis?

A systematic review of the evidence on labor and postpartum management of gestational diabetes can provide support for clinical guidelines, thereby arming clinicians with the knowledge necessary to provide evidenced-based, quality care to a growing population of women. For the current 200,000 pregnancies that are complicated by gestational diabetes annually in the United States, evidence-based clinical practice will be essential in promoting treatment effectiveness, evidenced-based labor management, effective assessment of risk factors

for later development of type 2 diabetes in women with gestational diabetes, and efficient postpartum screening for type 2 diabetes.

Chapter 2. Methods

The ACOG has requested an evidence report to review and synthesize published literature regarding the intrapartum management and postpartum followup of women with gestational diabetes. Our EPC established a team and a work plan to develop the evidence report. The project consisted of recruiting technical experts, formulating and refining the specific questions, performing a comprehensive literature search, summarizing the state of the literature, constructing evidence tables, synthesizing the evidence, grading the strength of the evidence, and submitting the report for peer review.

Topic Development

The topic for this report was nominated in a public process. At the beginning of the project, we recruited a panel of external technical experts to provide input at key steps, including the selection and refinement of the questions to be examined. The panel included external experts who have strong expertise in gestational diabetes (see Appendix A[a]).

We worked with the technical experts and representatives of the AHRQ and ACOG to develop the key questions that are presented in the Conceptual Framework and Key Questions section of Chapter 1 (Introduction). The key questions focused on: (1) the risks and benefits of using oral diabetes medications and any type of insulin to treat gestational diabetes affecting the mother and neonate, (2) the risks and benefits of medically indicated cesarean delivery and the choice of timing of induction for the mother and neonate, (3) the risk factors associated with the short-term and long-term development of type 2 diabetes following a pregnancy with gestational diabetes, and (4) the performance characteristics (i.e., sensitivity, specificity, and reproducibility) of tests for diagnosing type 2 diabetes when conducted in postpartum gestational diabetes patients.

Search Strategy

Searching the literature involved identifying reference sources, formulating a search strategy for each source, and executing and documenting each search. We also searched for medical subject heading (MeSH) terms that were relevant to gestational diabetes. We used a systematic approach for searching the literature, with specific eligibility criteria, to minimize the risk of bias in selecting articles for inclusion in the review. The systematic approach was intended to help identify gaps in the published literature.

Our comprehensive search plan included electronic and hand searching. We ran searches of four databases, MEDLINE® (1950 through January 2007), EMBASE® (1974 through January 2007), The Cochrane Central Register of Controlled Trials (CENTRAL; Issue 1, 2007), and the Cumulative Index to Nursing & Allied Health Literature (CINAHL®; 1982 through January 2007), to identify primary literature on the association of intrapartum management and postpartum followup of women with gestational diabetes with various maternal and neonatal

[a] Appendixes cited in this report are provided electronically at: http://www.ahrq.gov/clinic/tp/gdmparttp.htm

outcomes. Hand searching for possibly relevant citations took two forms. First, from our electronic search, we identified the 13 journals (see Appendix B[a]) that were most likely to publish articles on this topic (i.e., these journals had the highest number of abstracts and articles included in the review). We scanned the table of contents of each issue of these journals for relevant articles from August 2006 through January 2007. For the second form of hand searching, reviewers received eligible articles and flagged references of interest for the team to compare to the existing database.

Search strategies specific to each database were designed to enable the team to focus the available resources on articles that were the most likely to be relevant to the key questions. We initially developed a core strategy for MEDLINE®, accessed via PubMed®, based on an analysis of the MeSH terms and text words of key articles identified a priori. The PubMed® strategy formed the basis for the strategies developed for the other electronic databases (see Appendix C[a]).

The results of the searches were downloaded and imported into ProCite® version 5 (the Thompson Corporation, Stamford, CT). We used the duplication scan feature in ProCite® to delete citations already retrieved. From ProCite®, the articles were uploaded to SRS 4.0 (TrialStat! Corporation, Ottawa, Ontario, Canada), a Web-based software package developed for systematic review data management. This database was also used to store citations in portable document format (PDF) and to track the search results at the title review, abstract review, article inclusion/exclusion, and data abstraction levels. A list of excluded articles is presented in Appendix D[a].

Study Selection

The study team scanned all titles. Two independent reviewers conducted title scans in a parallel fashion. For a title to be eliminated at this level, both reviewers had to indicate that it was obviously ineligible. If the two reviewers did not agree on the eligibility of an article, it was promoted to the next level (see Appendix E[a], Title Review Form). The title review phase was designed to capture as many studies as possible that reported on the association of intrapartum management and postpartum followup of women with gestational diabetes with various maternal and neonatal outcomes. All titles that were identified as potentially addressing these issues were promoted to the abstract review phase.

Abstracts were reviewed independently by two investigators. Abstracts were excluded if both investigators agreed that the article met one or more of the following exclusion criteria: (1) not written in English; (2) did not include any human data; (3) contained no original data that was published in a peer-reviewed journal (i.e., was a meeting abstract, editorial, commentary, or letter); (4) did not evaluate women with gestational diabetes; (5) was a case report or case series; (6) did not base the diagnosis of gestational diabetes on either a 3-hr, 100-gm OGTT or a 2-hr, 75-gm OGTT; (7) did not evaluate an outcome relevant to the key questions (see Table 1); (8) did not include a medication of interest for Key Question 1; (9) did not have an appropriate comparison group for Key Questions 1 or 2; or (10) did not apply to a key question. We included publications that did not explicitly state the test used to diagnosis gestational diabetes if we were able to confirm through referenced publications or through personal communications with the author that the study used one of the accepted diagnostic tests. Differences of opinion regarding

[a] Appendixes cited in this report are provided electronically at: http://www.ahrq.gov/clinic/tp/gdmparttp.htm

abstract eligibility were resolved through consensus adjudication. At this level of review, the reviewers were also asked to identify to which key question(s) the article might apply if it was eligible for review.

Table 1. List of outcomes reviewed

KQ1	Maternal Outcomes • Cesarean delivery • Glycemic control • Hemorrhage • Hypoglycemia • Operative vaginal delivery • Perineal tears • Pre-eclampsia • Weight	Neonatal Outcomes • Anoxia • Birth trauma • Birth weight • Congenital malformation • Hyperbilirubinemia • Hypoglycemia • LGA • Macrosomia • Mortality • Neonatal intensive care unit admissions • RDS • SGA • Shoulder dystocia
KQ2	Maternal Outcomes • Cesarean delivery • Hemorrhage • Infection • Operative vaginal delivery • Perineal tears	Neonatal Outcomes • Anoxia • Birth trauma • Birth weight • Congenital malformation • Hyperbilirubinemia • Hypoglycemia • LGA • Macrosomia • Mortality • Neonatal intensive care unit admissions • RDS • SGA • Shoulder dystocia
KQ3	• Type 2 diabetes (diagnosed by FBS > 125 mg/dL, 75-gm OGTT, 2-hr glucose > 200 mg/dL, random glucose > 200 mg/dL, self-reported type 2 diabetes, or current use of an antidiabetic medication)	
KQ4	• Sensitivity • Specificity • Reproducibility	

dL = deciliter; FBS = fasting blood sugar; gm = gram; hr = hour; KQ = key question, LGA = large for gestational age; mg = milligrams; OGTT = oral glucose tolerance test; RDS = respiratory distress syndrome; SGA = small for gestational age; type 2 diabetes = type 2 diabetes mellitus

Because of the broad array of potentially eligible articles obtained at the abstract review phase, full articles initially selected for review underwent another independent parallel review by the investigators to determine whether the articles should be included in the full data abstraction. In addition to the exclusion criteria used for the abstract review, studies were excluded if less than 90 percent of the sample was diagnosed with gestational diabetes and there was no separate analysis for gestational diabetes patients. We limited the studies for Key Question 1 to all randomized controlled trials (RCTs) and observational studies that compared two types of treatment. For Key Question 1, we decided not to include observational studies that compared either an oral diabetes medication or insulin to diet, because most of these studies had a selection-by-indication bias (i.e., treatment was determined by the severity of the diabetes).

At this phase of the review, the investigators determined which of the key questions each article addressed (see Appendix E, Article Inclusion/Exclusion Form). If the articles were still

deemed to have applicable information, they were included in the full data abstraction. Differences of opinion regarding article eligibility were resolved through consensus adjudication.

Data Abstraction

We used a systematic approach for extracting data to minimize the risk of bias in this process. By creating standardized forms for data extraction, we sought to maximize consistency in identifying all pertinent data available for synthesis.

Each article underwent double review by study investigators for full data abstraction and assessment of study quality. For all data abstracted from studies, we used a sequential review process. In this process, the primary reviewer completed all data abstraction forms. The second reviewer checked the first reviewer's data abstraction forms for completeness and accuracy. Reviewer pairs were formed to include personnel with both clinical and methodological expertise. A third reviewer re-reviewed a random sample of articles by the first two reviewers to ensure consistency in the classification of the articles. Reviewers were not masked to the articles' authors, institutions, or journal.[21] In most instances, data were directly abstracted from the article. If possible, relevant data were also abstracted from figures. Differences of opinion were resolved through consensus adjudication. For assessments of study quality, each reviewer independently judged study quality and rated items on quality assessment forms (see Appendix E, Data Abstraction Review Forms).

For all included articles, reviewers abstracted information regarding the general study characteristics (e.g., exclusion criteria, study design, study period and followup, and country) and study participants (e.g., maternal age, race, weight/body mass index [BMI], parity/gravida, gestational age, method of gestational diabetes management, and the type, timing, and results of the OGTT). For articles that applied to Key Questions 1 and 2, we abstracted information on the type of intervention, the outcomes measures and the method of ascertainment, and the results of each outcome, including the measures of variability. For articles that applied to Key Question 3, we abstracted information on the diagnosis of type 2 diabetes, the length of followup, the covariates considered and included in the models, and the measure of association and variability. For articles that applied to Key Question 4, we abstracted information on the reference test, the comparison test, the length of followup, and the results of the tests.

All information from the article review process was entered into the SRS 4.0 database by the individual completing the review. Reviewers entered comments into the system whenever applicable. The SRS 4.0 database was used to maintain and clean the data, as well as to create detailed evidence tables and summary tables (see Appendix F and Summary Tables).

Study Quality Assessment

The study aspects considered in our quality assessment varied according to the question being addressed and the type of study design. As part of our dual, independent review of study quality, we judged articles on several aspects of each study type's internal validity. Quality assessment of trials for Key Questions 1 and 2 was based on the Jadad criteria[22] and included: (1) appropriateness of the randomization scheme, (2) appropriateness of the blinding, and (3) description of withdrawals and drop-outs. For each trial, we awarded a score from 5 (high quality) to 0 (low quality). Quality assessment of observational studies for Key Questions 1, 2,

and 3 involved selecting elements from the Standards for Reporting of Observational Studies (STROBE) checklist of the reporting of observational studies;[23] it included items about reporting on the hypotheses, inclusion/exclusion criteria, study population, power and sample size calculations, definition of outcomes, loss to followup, and missing data. Quality assessment of the diagnostic test studies for Key Question 4 was designed by selecting elements from the Standards for Reporting of Diagnostic Accuracy (STARD) Initiative[24] and included items about reporting of the sampling design, loss to followup, information about diagnostic accuracy, verification of positive and negative tests, independent interpretation of tests, reproducibility, and subgroup analyses.

Data Synthesis

For each key question, we created a set of detailed evidence tables containing all the information extracted from the eligible studies. The investigators reviewed the tables and eliminated items that were rarely reported.

We conducted meta-analyses when there were sufficient data (three or more studies) and the studies were homogeneous with respect to key variables (population characteristics, study duration, intervention/exposure/comparison tests, and length of followup). When the data were not sufficient to combine the studies in a meta-analysis, we prepared a qualitative summary of the results.

In the meta-analysis, we recorded the mean difference in infant birth weight between groups, along with its measure of dispersion. We calculated a pooled estimate (weighted mean difference) of infant birth weight from the eligible RCTs using a random effects model with the DerSimonian and Laird formula for calculating between-study variance.[25] The random effects model was used because unmeasured heterogeneity was likely to exist among the trials.

We assessed heterogeneity among the trials considered for meta-analysis using a standard chi-squared test and a significance level of alpha ≤ 0.10. We also examined heterogeneity among studies with an I^2 statistic, which describes the variability in effect estimates that is due to heterogeneity rather than random chance.[26] A value greater than 50 percent may be considered to have substantial variability.

All statistical analyses were conducted using STATA (Intercooled, version 8.2, StataCorp, College Station, TX).

Data Entry and Quality Control

Initial data were abstracted by the investigators and entered directly into Web-based data collection forms using SRS® 4.0 (TrialStat! Corporation, Ottawa, Ontario, Canada). After a second reviewer reviewed the data, the adjudicated data were re-entered into the Web-based data collection forms by the second reviewer. Second reviewers were generally more experienced members of the research team, and one of their main priorities was to check the quality and consistency of the first reviewers' answers. In addition to the second reviewers checking the consistency and accuracy of the first reviewers, a lead investigator examined a random sample of the reviews to identify problems with the data abstraction. If problems were recognized in a reviewer's data abstraction, the problems were discussed at a meeting with the reviewers. In

addition, research assistants used a system of random data checks to assure data abstraction accuracy.

Rating the Body of Evidence

At the completion of our review, we graded the quantity, quality, and consistency of the best available evidence addressing the key questions by adapting an evidence-grading scheme recommended by the GRADE Working Group.[27] We assessed the strength of the study designs, with RCTs considered to be best, followed by non-randomized controlled trials and observational studies. To assess the quantity of evidence, we focused on the number of studies with the strongest design. We also assessed the quality and consistency of the best available evidence, including assessment of the limitations affecting individual study quality (using the individual study quality assessments), certainty regarding the directness of the observed effects in the studies, the precision and strength of the findings, and the availability (or lack) of data to answer the key question. We classified evidence bodies pertaining to the key questions into the following categories: (1) "high" grade, indicating confidence that further research is very unlikely to change our confidence in the estimated effect in the abstracted literature; (2) "moderate" grade, indicating that further research is likely to have an important impact on our confidence in the estimates of effects and may change the estimates in the abstracted literature; (3) "low" grade, indicating the further research is very likely to have an important impact on confidence in the estimates of effects and is likely to change the estimates in the abstracted literature; (4) "very low" grade, indicating any estimate of effect is very uncertain; and (5) "insufficient" grade, indicating the lack of enough evidence to make any estimate of effect.

Peer Review

A draft of the completed report was sent to the technical experts and peer reviewers, as well as to the representatives of AHRQ. In response to the comments of the technical experts, peer reviewers, and AHRQ, revisions were made to the evidence report, and a summary of the comments and their disposition was submitted to AHRQ.

Chapter 3. Results

We present the findings of our review using a standard format for each of the four key questions. First, we present the conceptual framework for each question, incorporating relevant background information and potential implications for clinical practice. Next, we summarize the population characteristics of each study. We then summarize the findings, emphasizing those results that are most relevant to our conceptual framework. We outline the methodological issues related to the heterogeneity of study design and outcome analyses and then summarize our assessment of the quality of each study using established quality criteria published in the literature. Finally, we assign a grade to the overall body of evidence on each question or sub-question.

Search Results

A summary of the search results for the primary literature review is presented in Figure 2. From the search, we retrieved 11,400 unique citations. After a review of the titles and abstracts, 552 were deemed eligible for further review, and the full articles were retrieved. A total of 45 articles were included in this review.

Key Question 1

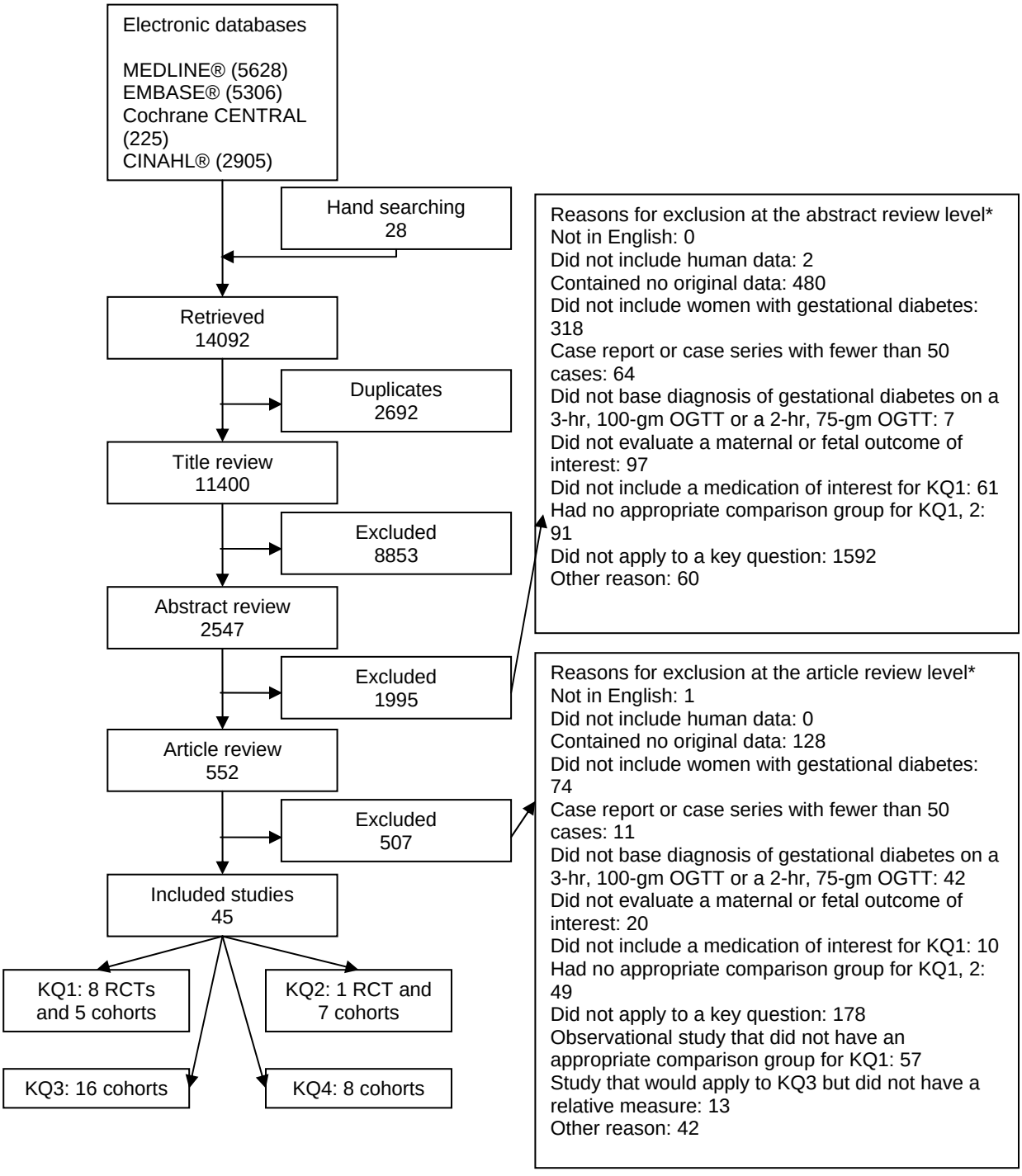
What is the evidence for the risks and benefits of oral diabetes agents (e.g., second-generation sulfonylureas and metformin), as compared to all types of insulin, for both the mother and neonate in the treatment of women with gestational diabetes?

a. How does maternal outcome vary based on the level of glucose at the initiation of a medication?
b. How does neonatal outcome vary based on the level of glucose at the initiation of a medication?

Background and Conceptual Framework

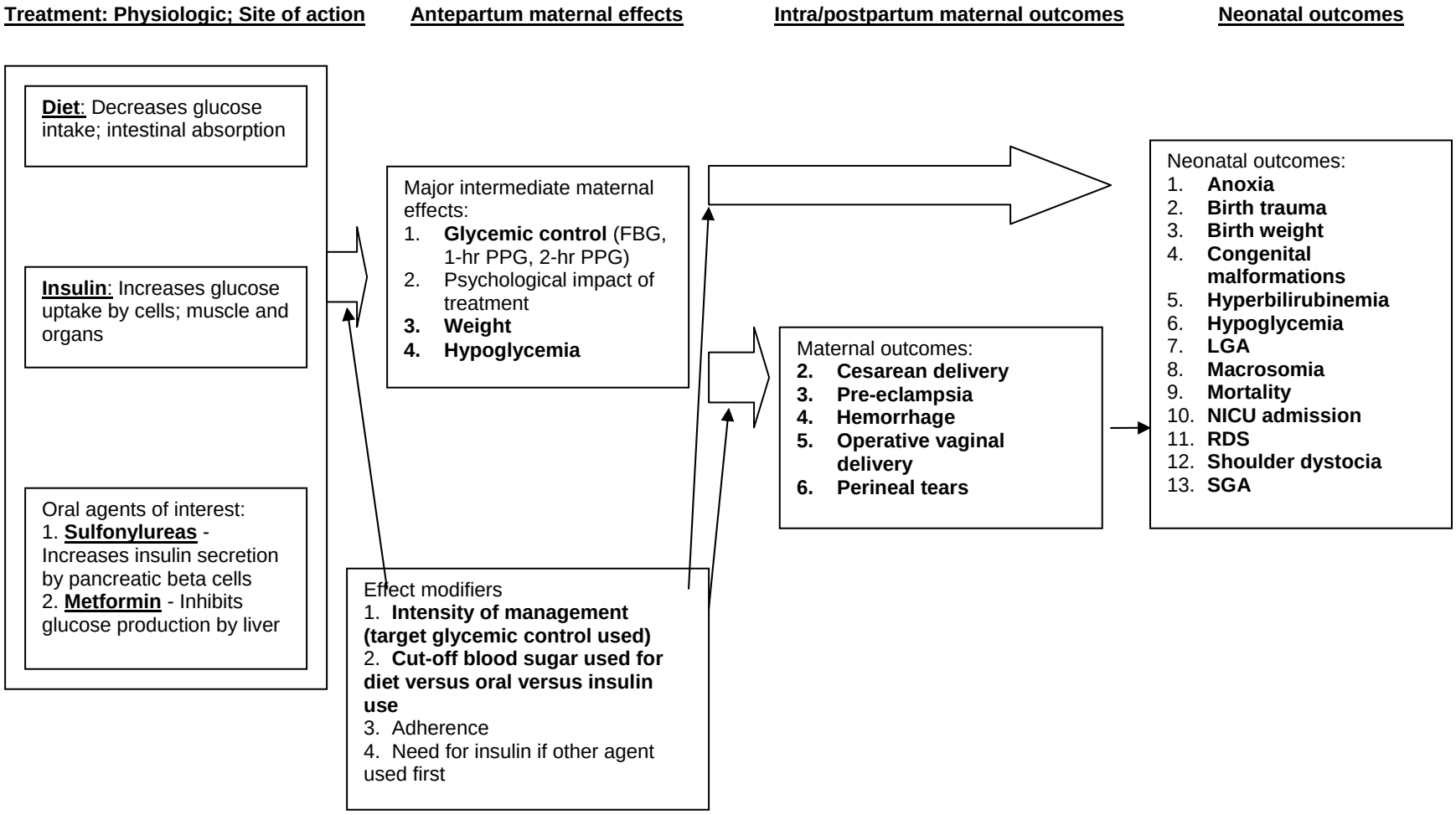
Understanding the risks and benefits of the use of insulins or oral diabetes agents during pregnancy for both maternal and neonatal outcomes is essential to the care of women with gestational diabetes and their offspring.[28 29] As shown in the conceptual framework (see Figure 3), our objective for Key Question 1 was to review RCTs and observational studies to compare the risks and benefits of medical treatment for the management of glucose levels in women with gestational diabetes. As previously highlighted, pregnancies with gestational diabetes are often characterized by many maternal and neonatal complications, including poor maternal glucose control, cesarean delivery, and neonatal hypoglycemia. Our primary goal was to summarize the maternal and neonatal outcomes across treatment modalities, to derive pooled estimates where possible, and to summarize the relevant conclusions based on the available literature.

Figure 2. Summary of the literature search and review process (number of articles)



* Total may exceed number in corresponding box, as articles could be excluded for more than one reason at this level.
CENTRAL = Central Register of Controlled Trials; CINAHL = Cumulative Index to Allied Health and Nursing Literature; gm = gram; hr = hour; KQ = key question; OGTT = oral glucose tolerance test; RCT = randomized controlled trial

Figure 3. Conceptual framework of treatment effects on maternal and neonatal outcomes



Outcomes in boldface type represent those evaluated in this systematic review.
FBG = fasting blood glucose; hr = hour; LGA = large for gestational age; NICU = neonatal intensive care unit; PPG = postprandial glucose; RDS = respiratory distress syndrome; SGA = small for gestational age

Results

Overview and population characteristics of eight RCTs comparing insulins, insulin analogues, and oral diabetes medications. We identified eight RCTs with a total of 845 participants that met our inclusion criteria for review.[30-37] Evidence Table 1 describes the primary characteristics of each of the trials. Four of the studies reported study durations of 8 months to 4 years,[30 34 35 37] while the other four studies did not report a study duration.[31-33 36] The studies were published between 1990 and 2006. For the four studies that reported the starting year of the study,[30 34 35 37] the earliest starting year was 1985. The trials were conducted in diverse countries and populations: Three trials were conducted in the United States,[30 32 36] one in Italy,[34] one in Finland,[31] one in India,[33] one in Brazil,[37] and one in Israel.[35] The trials also compared different treatment interventions: Two clinical trials[32 33] compared insulin to glyburide; one trial[37] compared insulin, glyburide, and acarbose; two studies[34 36] compared regular human insulin and insulin lispro; one study[31] compared long-acting and short-acting insulins; one study[38] compared insulin administered two-times-daily and four-times-daily; and one study[30] compared diet and insulin.

The average maternal age ranged from 25 to 34 years and did not substantially differ across groups. Only three studies reported the racial distribution of the study participants:[33 34 36] Anjalakshi et al.[33] reported that 100 percent of the study participants were Indian. Most participants (95 percent) in the study by Jovanovic et al.[36] were reported as Hispanic. All of the participants in the study by Mecacci et al.[34] were reported as Caucasian.

In the studies that reported maternal weight, the weight measures were similar between groups. Five studies[30 34-37] reported gravidity, and three studies[30 32 36] reported the parity of study participants, which ranged from nulliparity to 2.5 prior births.

Consistent with our study selection criteria, each of the eight RCTs reported the test used to diagnose gestational diabetes. Three studies[31 33 37] used the 75-gm OGTT World Health Organization (WHO) criterion. Two studies[30 35] used the National Diabetes Data Group (NDDG) criterion, and three studies[32 34 36] used the 3-hr, 100-gm OGTT with threshold values based on the Carpenter and Coustan criterion. Langer et al.[32] used the FBG threshold of 95 mg/deciliter (dL) based on the 100-gm OGTT Carpenter and Coustan criteria to determine eligibility and as the threshold value for treatment with insulin or glyburide. Bertini et al. used a FBG greater than 90 mg/dL or a 2-hr PPG greater than 100 mg/dL as threshold values for initiation of treatment with glyburide or insulin. Anjalakshi et al.[33] initiated medical therapy if the 2-hr PPG was 120 mg/dL or greater after two weeks of nutritional therapy. The average gestational age at screening and diagnosis of gestational diabetes varied across studies from 22 to 28 gestational weeks. Mecacci et al.[34] reported a median gestational age at diagnosis of 28 weeks (range: 25 to 32). Polyhonen-Alho[31] reported a gestational age range of 24 to 28 weeks.

Maternal and neonatal outcomes in eight RCTs of insulin, insulin analogues, and oral diabetes medications. Data were available for abstraction for five of the eight maternal outcomes of interest and 11 of the 13 neonatal outcomes in Key Question 1. As shown in Table 2, data were abstracted on several maternal outcomes, including: (1) average glycemic control (mg/dL), (2) episodes of maternal hypoglycemia, (3) mean difference in maternal weight; (4) cesarean delivery, and (5) episodes of pre-eclampsia. Neonatal outcomes included: 1) infant birth weight, (2) macrosomia, (3) LGA, (4) SGA, (5) hypoglycemia, (6) hyperbilirubinemia, (7) perinatal mortality, (8) respiratory distress syndrome, (9) congenital malformations, (10) birth trauma, and (11) neonatal intensive care admissions.

Table 2. List of maternal and neonatal outcomes for which data were abstracted from RCTs of medications for gestational diabetes

	Insulin versus glyburide			Insulin versus insulin lispro		Insulin versus insulin		Diet versus insulin
Maternal outcomes	**Anjalak-shi, 2006[33]**	**Bertini, 2005[37]**	**Langer, 2000[32]**	**Jovan-ovic, 1999[36]**	**Mecacci, 2003[34]**	**Nachum, 1999[35]**	**Poyhon en-Alho, 2002[31]**	**Thomp-son, 1990[30]**
Cesarean delivery for CPD					•			
Cesarean delivery, total		•	•	•	•	•		•
Glycemic control*	•		•	•	•	•		•
Hemorrhage								
Hypoglycemia		•	•	•		•		
Operative vaginal delivery								
Perineal tears								
Pre-eclampsia			•					
Weight		•	•			•		
Neonatal outcomes								
Anoxia								
Birth trauma						•	•	
Birth weight	•	•	•	•	•			•
Congenital malformations			•			•		
Hyperbilirubinemia			•			•	•	•
LGA		•	•		•	•		
Macrosomia		•	•			•	•	•
Mortality		•	•			•		
Hypoglycemia		•	•			•	•	•
NICU admission			•					
RDS						•		
SGA		•			•	•		
Shoulder dystocia								

A dot (•)indicates that the outcome was evaluated in that study.
* Includes FBG, 1-hr PPG, 2-hr PPG, HbA1c, combined glucose, preprandial glucose
2-hr PPG = 2 hour postprandial glucose; CPD = cephalopelvic disproportion; FBG = fasting blood glucose; HbA1c = hemoglobin A1c; LGA = large for gestational age; NICU = neonatal intensive care unit; RCTs = randomized controlled trials; RDS = respiratory distress syndrome; SGA = small for gestational age

Insulin versus glyburide.

Maternal outcomes. Three RCTs[32 33 37] compared the effects of insulin and glyburide on five different maternal outcomes (see Appendix F, Evidence Table 2). Because of the sparseness of the data and diversity of outcomes, we were unable to combine any of the studies in meta-analyses; therefore, we have described the results qualitatively here.

Two RCTs[32 33] evaluated maternal glycemic control. Langer et al.[32] randomized 404 women to receive insulin (n=203) or glyburide (n=201). The insulin regimen was based on maternal weight, with two-thirds of the units administered as neutral protamine Hagedorn (NPH) and one-third of the units as regular insulin. In the study by Langer, glyburide was initiated at a dose of 5.0 milligrams (mg) or 2.5 mg and increased to a maximum dose of 20 mg/day. In the study by Anjalakshi,[33] glyburide was initiated at a dose of 0.625 mg. No maximum or average dose was reported. Langer et al.[32] reported no statistically significant differences in average final FBG or 2-hr PPG levels between those receiving insulin and those on glyburide. The average (mean ± standard deviation [SD]) FBG levels were 96 ± 16 for insulin and 98 ± 13 for glyburide (p =

0.17). The average 2-hr PPG levels were 112 ± 15 for insulin and 113 ± 22 for glyburide (p = 0.6).

A smaller randomized trial[33] of 26 participants comparing glyburide to insulin also reported no statistically significant differences in mean 2-hr PPG levels during pregnancy in the insulin versus the glyburide group.

The two larger RCTs[32 37] compared the percentage of women undergoing cesarean delivery in each group. Langer[32] reported that 49 (24 percent) of the women on insulin underwent cesarean delivery, as compared to 46 (23 percent) of the women on glyburide (p > 0.05). Bertini et al.[37] reported no significant differences in the rate of cesarean delivery among three groups of women receiving insulin (44 percent), glyburide (50 percent), or acarbose (52 percent).

Bertini[37] and Langer[32] both reported on maternal hypoglycemia. Bertini defined maternal hypoglycemia based on the need for hospitalization and reported no episodes of hospitalization in any of the three treatment groups. Langer did not define maternal hypoglycemia but reported a significantly higher percentage of women with a blood glucose level under 40 mg/dL in the insulin group than in the glyburide group (20 percent versus 4 percent; p = 0.03).

Bertini[37] also compared the mean difference in maternal weight at delivery to the baseline value in each treatment group and found no significant differences.

We have concluded that maternal outcomes did not differ significantly between insulin and glyburide. However, two[33 37] of the three studies presented were limited by their small sample size and limited power to detect significant differences in some outcomes. Furthermore, we were unable to fully assess other relevant outcomes, such as maternal hypoglycemia, because of inconsistencies in the definition of outcomes. Taking into consideration the quantity, quality, and consistency of the studies comparing the effects of glyburide versus insulin on maternal outcomes, we graded the strength of evidence as very low (see Appendix F, Evidence Table 3).

Neonatal outcomes. Three RCTs reported on nine different neonatal outcomes (see Appendix F, Evidence Table 4). We have described most of the results qualitatively because of the sparseness of the data and the diversity of the outcomes (see Table 2). Three studies with relatively similar populations and interventions reported data on the mean differences in infant birth weight between the insulin and glyburide groups. As shown in Table 3, all three RCTs[32 33 37] reported lower mean birth weights for the infants in the insulin group than for the infants in the glyburide group. In the three RCTs, infants in the insulin group were reported as being 120 gm, 244 gm, and 62 gm smaller, respectively, than the infants in the glyburide group. We performed a meta-analysis using a random effects model, combining data from the Anjalakshi 2006 RCT[33] with data from the Bertini 2005[37] and Langer 2000[32] RCTs. We report the results as the weighted mean difference in infant birth weight in the insulin group as compared to the glyburide group. These three RCTs, with a total of 478 infants, provided a weighted mean infant birth weight difference of 93 gm (95 percent confidence interval (CI): -191 to 5 gm). Infants in the insulin group were on average 93 gm smaller than infants in the glyburide group (see Table 3 and Figure 4). This finding is not statistically significant, and the clinical relevance of such a small difference is unclear. While exclusion of any one study's results would not have markedly altered our results, the largest study by Langer et al. contributed the most to the overall mean difference in birth weight.

Langer et al. reported no significant differences between treatment groups in the percentage of infants with hypoglycemia. Among the 201 women on glyburide, 9 percent of the infants experienced hypoglycemia, as compared to 6 percent of those with mothers on insulin (p = 0.25). Bertini et al. reported a higher percentage of infants with macrosomia (birth weight greater than

Table 3. Meta-analysis of three RCTs on the effect of insulin and glyburide on infant birth weight: random effects model

Author, year	N for analysis	Mean difference in birth weight,† grams (standard error)	Regression coefficient	95% CI
Anjalakshi, 2006[33]	23	-120 (161)	-90	-193, 12
Bertini, 2005[37]	51	-244 (133)	-68	-174, 37
Langer, 2000[32]	404	-62 (57)	-194	-395, 7.3
Pooled estimates	Total participants = 478	-93		-191, 5

95% CI = 95 percent confidence interval

†Mean difference = the average difference in birth weight between infants in the insulin group and infants in the glyburide group.

Figure 4. Meta-analysis of three RCTs on the effect of insulin and glyburide on mean difference in infant birth weight

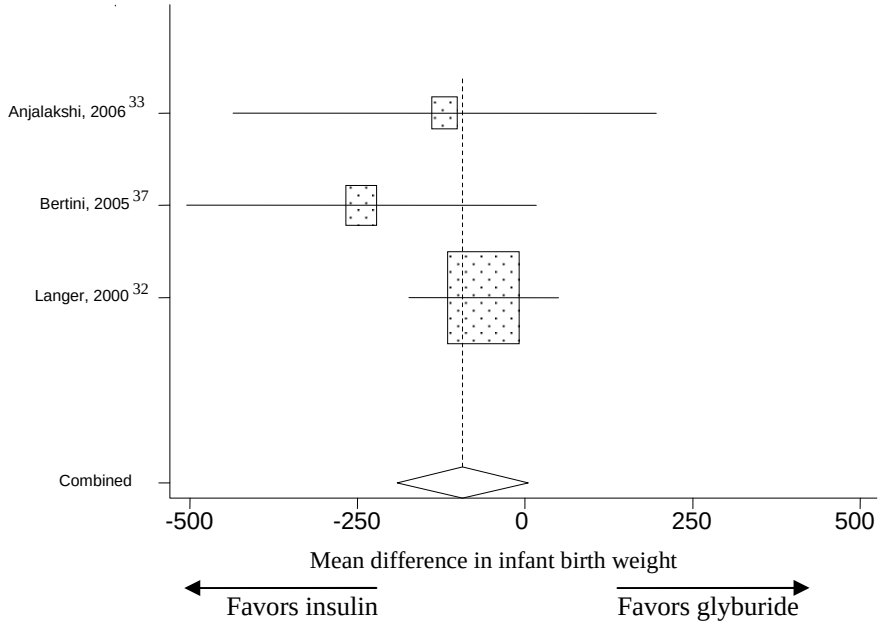


Figure legend. The shaded boxes represent the mean difference in infant birth weight between the treatment groups in each study. The diamond represents the pooled mean difference in birth weight between infants born to mothers treated with insulin and infants born to mothers treated with glyburide.

4,000 gm) and LGA among the women on glyburide than among those on insulin or acarbose. A significantly higher percentage of infants had hypoglycemia in the glyburide group than in the insulin or acarbose groups (33 percent compared to 4 percent and 5 percent, respectively; p = 0.006). However, Bertini reported no difference in SGA infants or in perinatal mortality between the group on insulin and the group on glyburide.

We concluded that the use of insulin may be associated with an average 93-gm lower infant birth weight when compared to glyburide. However, this difference was not statistically significant. It is unlikely that this finding has substantial clinical relevance, given the small difference in infant size. We graded the strength of the evidence as very low (see Appendix F, Evidence Table 3) for studies comparing the effects of glyburide and insulin on neonatal outcomes. While there was consistent evidence on infant birth weight from the three RCTs, the lack of consistency in the reporting of other relevant neonatal outcomes across the three studies made it difficult to draw firm conclusions. The large trial by Langer and colleagues[32] certainly

provided credible estimates for several neonatal comparisons, but the findings were limited to one sample of women and had limited generalizability.

Regular insulin versus insulin lispro.

Maternal outcomes. Two RCTs[34 36] compared the effects of regular insulin and insulin lispro on at least one of three maternal outcomes: cesarean delivery, average blood glucose level, and maternal hypoglycemia (see Appendix F, Evidence Table 2). Jovanovic[36] and Mecacci[34] recruited 42 and 49 participants, respectively, in two trials comparing regular insulin to insulin lispro. In the trial by Jovanovic, the initial dose of both regular insulin and insulin lispro was 0.7 units/kilogram (kg) combined with NPH two times per day and adjusted weekly. In the trial by Mecacci and colleagues, regular insulin and insulin lispro were started at a dosage of 1 unit/10 gm of carbohydrates in meals three times per day. The mean dosage was 34.3 units/day in the regular insulin group and 35.1 units/day in the lispro group.

The mean decrease in glycosylated hemoglobin from the time of entry into the study until delivery was greater in the women on lispro (mean difference from baseline -0.35 percent) than in those on regular insulin (mean difference from baseline -0.07 percent; $p = 0.002$).[36] Maternal hypoglycemia, reported as the mean (standard error [SE]) percentage of all blood determinations in the hypoglycemic range, was not significantly different in the insulin lispro group and the group receiving regular insulin (0.88 percent ± 0.25 percent versus 2.2 percent ± 0.86 percent; $p > 0.05$).[36] Mecacci reported significantly higher maternal 1-hr PPG levels in the insulin lispro group than in the regular insulin group (108 mg/dL ± 11 versus 88 mg/dL ± 11, respectively; $p < 0.001$).[34] However, both pre-prandial and 2-hr PPG levels were similar in the two groups ($p > 0.05$ for pre-prandial and 2-hr PPG). Both Jovanovic and Mecacci reported no significant differences in the proportion of women undergoing cesarean delivery; Jovanovic reported no differences across all cesarean deliveries,[36] and Mecacci reported no differences between groups for cesarean delivery specifically for cephalopelvic disproportion.[34]

We concluded that maternal glucose control, as measured by glycosylated hemoglobin or 1-hr glucose levels, did not differ between women treated with insulin lispro and those receiving regular insulin. The rate of cesarean delivery in the two groups was also similar. However, taking into consideration the quantity, quality, and consistency of the studies comparing the effects of regular insulin and insulin lispro on maternal outcomes, we graded the overall body of evidence as very low (see Appendix F, Evidence Table 3). There were only a limited number of maternal outcome measures reported in either RCT: Only cesarean delivery and maternal glucose control were reported by both studies. While there was consistency in the findings reported across both studies, the available data were limited to two RCTs with small sample sizes (total N = 92). Also, there was only a limited ability to detect differences in outcomes. The absence of a difference in the rate of cesarean delivery, for example, was likely a reflection of the small number of participants in each RCT and the limited power to detect clinically or statistically significant differences.

Neonatal outcomes. While Jovanovic and colleagues did not provide actual data, they reported no difference in the proportion of infants with macrosomia or neonatal hypoglycemia who were born to women receiving regular insulin, as compared to women receiving insulin lispro (see Appendix F, Evidence Table 4).[36] Mecacci et al. reported no difference in mean infant birth weight or the number of LGA or SGA infants born to women receiving regular insulin and those receiving insulin lispro.[34]

Based on limited evidence from these two studies, we concluded that neonatal outcomes do not differ substantially between regular insulin and insulin lispro. Taking into consideration the

quantity, quality, and consistency of the studies comparing the effects of regular insulin versus insulin lispro on neonatal outcomes, we graded the strength of the evidence as very low (see Appendix F, Evidence Table 3).

Long-acting insulin versus short-acting insulin.

Maternal outcomes. Polyhonen-Alho et al. randomized 23 participants to short-acting or long-acting insulin (see Appendix F, Evidence Table 2).[31] Three doses of short-acting insulinwere given before breakfast (4 international units [IU]), lunch (6 IU), and dinner (4 IU). Long-acting insulin was administered at 14 IU each morning. There were no reported maternal outcomes in the study by Poyhonen-Alho et al.Therefore, for this comparison, we graded the strength of the evidence regarding maternal outcomes as insufficient (see Appendix F, Evidence Table 3).

Neonatal outcomes. In their comparison of long-acting to short-acting insulin, Poyhonen-Alho et al.[31] reported a higher percentage of infants with macrosomia in the group receiving long-acting insulin than in the group receiving short-acting insulin (see Appendix F, Evidence Table 4). They reported no statistically significant differences in the occurrence of nerve palsy or infant metabolic abnormalities between the two groups. We concluded that long-acting insulin may be associated with a greater risk of macrosomia than is short-acting insulin. We graded the strength of evidence on neonatal outcomes for this comparison as very low (see Appendix F, Evidence Table 3) because of the sparseness of the data, the limited sample size, and the fact that the available data came from only one study.

Twice-daily versus four-times-daily insulin.

Maternal outcomes. Nachum et al. compared outcomes in 136 women randomized to receive regular insulin twice-daily with those in 138 women randomized to receive regular insulin four-times-daily.[35] The exact units of insulin were not reported. There was no risk difference in cesarean delivery between the two groups (see Appendix F, Evidence Table 2). Maternal weight gain during pregnancy was also similar between the two groups, and the average maternal glucose levels were similar. Both groups reported one participant with hypoglycemia. We concluded that no evidence exists to suggest a difference in maternal outcomes between twice-daily and four-times-daily use of insulin. For this comparison, we graded the strength of the evidence on maternal outcomes as very low (see Appendix F, Evidence Table 3).

Neonatal outcomes. In contrast to their findings for maternal hypoglycemia, Nachum et al. reported a higher proportion of neonatal hypoglycemia in infants born to women on twice-daily insulin, as compared to four-times-daily insulin (6 percent versus 1 percent; $p = 0.02$) (see Appendix F, Evidence Table 4).[35] The proportion of infants with hyperbilirubinemia was also higher in the group treated with twice-daily dosing, as compared to four-times-daily dosing (21 percent versus 11 percent; $p = 0.02$). The proportion of infants with macrosomia (birth weight > 4,000 gm) was similar in the twice-daily and four-times-daily insulin groups (19 percent versus 16 percent, respectively). The proportion of LGA infants (30 percent versus 26 percent) was also similar in the two groups. There was no difference in the proportion of infants with congenital abnormalities, birth trauma, or respiratory distress syndrome. Average infant birth weight was not reported. Based on this single study, we concluded that twice-daily use of insulin may be associated with worse neonatal outcomes than four-times-daily use, but we graded the strength of the evidence on neonatal outcomes as very low (see Appendix F, Evidence Table 3).

Diet versus insulin.

Maternal outcomes. Thompson[30] randomized 95 women to dietary management or insulin plus dietary management. The diet regimen was 35 kilocalories per kg of ideal body weight. A

fixed dose of 20 units NPH and 10 units regular insulin was administered daily. There was no reported difference in the proportion of women undergoing cesarean delivery (see Appendix F, Evidence Table 2). Baseline and FBG levels during the study were also similar between the two treatment groups.

Taking into consideration the quantity, quality, and consistency of the evidence comparing the effects of diet versus insulin on maternal outcomes, we graded the strength of the evidence as very low (see Appendix F, Evidence Table 3). Thus, the strength of evidence was too low to allow us to draw a meaningful conclusion about whether maternal outcomes differ for the two treatments.

Neonatal outcomes. In that same study, there were significant differences in the proportion of infants with macrosomia (> 4,000 gm) and in mean birth weight (see Appendix F, Evidence Table 4).[30] For example, only 5.9 percent of the infants in the diet and insulin group met the criteria for macrosomia (≥ 4,000 gm), as compared to 26.5 percent of infants in the group treated with diet alone. Similarly, infant birth weight was higher in the diet-alone group than in the diet and insulin group ($p = 0.002$). There was no difference in neonatal hypoglycemia or hyperbilirubinemia. Although this one study suggested that neonatal outcomes might be better with the use of insulin plus dietary management as compared to diet alone, we graded the strength of the evidence as very low (see Appendix F, Evidence Table 3). Additional studies in diverse samples of gestational diabetics with well-defined measures of neonatal outcomes are needed to make it possible to draw meaningful conclusions regarding these outcomes.

Metformin versus insulin. There is no currently published evidence on maternal and neonatal outcomes in women with gestational diabetes who have been treated with metformin versus insulin.[39] Recently published data on metformin treatment in pregnancy are primarily based on small cohort studies in women with PCOS, in whom it has been used to treat infertility.[40-43] Women with PCOS and women with type 2 diabetes who continue to receive metformin through the first trimester of pregnancy have demonstrated few adverse pregnancy events. An ongoing prospective RCT (the Metformin in Gestational Diabetes [MiG] trial) comparing metformin with insulin in women with gestational diabetes is currently underway in New Zealand and Australia.[44] The goal of the trial is to recruit 750 women over a 2-year period, collecting data on multiple maternal and neonatal outcomes. The primary outcome is a composite of neonatal morbidity, including hypoglycemia, respiratory distress, phototherapy, birth trauma, low 5-minute Apgar score, and prematurity. The secondary outcomes include maternal glycemic control, neonatal body composition, and markers of neonatal insulin sensitivity. An interim report of 453 participants showed no adverse events.[44] We anticipate that the results of this trial will provide meaningful insight into the potential risks and benefits of metformin therapy. The results of the MiG trial are likely to provide further evidence on the short-term (e.g., congenital anomalies) and as yet potentially unrecognized long-term effects of placental transfer and *in utero* fetal exposure to metformin.

Adverse drug events. We found little data concerning the potential risks of oral diabetic agents, insulin analogues, or insulin. Table 4 summarizes the potential adverse drug events for the newborn, which include: (1) congenital anomalies, (2) hyperbilirubinemia, (3) perinatal mortality, (4) birth trauma, (5) respiratory distress syndrome, and (6) neonatal hypoglycemia. As shown in Table 4, Langer[32] reported no difference in the number of infants with hyperbilirubinemia in the glyburide group compared to the insulin group (4 percent versus 6 percent, respectively; $p = 0.36$). Langer[32] also reported essentially no difference in the number of infants with a congenital anomaly between pregnant women treated with glyburide and those

treated with insulin. There were five infants with a congenital anomaly in the glyburide group and four infants in the insulin group (p = 0.74). Nachum,[35] in a comparison of twice-daily insulin versus four-times-daily insulin, found no difference in the number of infants with a congenital anomaly (2 percent versus 1 percent, respectively) or birth trauma (2 percent versus 1 percent, respectively) in either group (see Table 4). Although the data were limited, there was no evidence of differences in neonatal intensive care admission with twice-daily or four-times-daily insulin (p = 0.68). Further investigations with sufficient power to detect meaningful differences will provide much needed evidence regarding potentially adverse neonatal and early childhood effects of medical treatments. While there is currently little evidence on metformin, long-term followup of infants will provide evidence on the downstream consequences of placental transport and intrauterine exposure to metformin.

There were few reports of maternal hypoglycemia. Bertini[37]reported none; Langer[32] reported a higher number of women with FBG less than 40 mg/dL in the glyburide than in the insulin group. Maternal hypoglycemia was not significantly different in the insulin lispro group and the group receiving regular insulin (0.88 percent ± 0.25 percent versus 2.2 percent ± 0.86 percent; p > 0.05).[36] The twice-daily insulin and four-times-daily insulin groups each had one case of maternal hypoglycemia.[35]

Quality assessment of the RCTs. We assessed five parameters of quality for each of the RCTs. Participants were randomized in each of the eight RCTs, with five of the studies[30 32 35-37] describing the randomization scheme (see Appendix F, Evidence Table 5). None of the trials were blinded. Only half of the trials[30 34 36 37] reported and described participant withdrawals and the reasons for losses to followup.

Limitations. There are specific limitations of the RCTs that deserve further comment. First, as outlined in Table 2, maternal and neonatal outcomes were not consistent across studies. Few of the same outcome measures were included in two or more studies. Furthermore, the definitions of outcomes varied across studies. For example, among the three trials of the effects of insulin and glyburide, the diagnosis of maternal hypoglycemia was based on three different measures (< 40 mg/dL; < 40 mg/dL on two or more occasions; hypoglycemia requiring hospitalization). The small number of the trials comparing medical treatments also limited our ability to draw substantial conclusions. None of the trials included a power analysis or effect size estimation for various outcome measures. None of the trials included an intention-to-treat analysis (see Appendix F, Evidence Table 2).

Observational studies of the effect of insulin and oral diabetes medications on maternal and neonatal outcomes.

Overview and population characteristics of five observational studies. We identified five observational studies that examined a total of 911 patients with gestational diabetes and met our inclusion criteria for review.[45-49] Evidence Table 6 (see Appendix F) describes the characteristics of each study. Each of the five studies was conducted in the United States between 1999 and 2005. The study duration ranged from 2 to 3 years across the five studies. Two studies[46 48] compared maternal and neonatal outcomes in women treated with insulin and women treated with glyburide. Two studies[45 47] examined factors related to glyburide success or glyburide failure. Glyburide "successes" were women with gestational diabetes who maintained target glucose levels on glyburide alone. Glyburide "failures" were those who were switched to insulin or for whom insulin was added to the glyburide therapy. One study[49] compared maternal and neonatal outcomes in women treated with insulin and women treated with glyburide and also reported on factors related to glyburide failure.

Table 4. Adverse events reported in RCTs of medications for gestational diabetes. Numbers are n (%)

Author, year	Treatment, N	Hyperbili-rubinemia	Congenital malformation	Perinatal mortality	Birth trauma	Other neonatal outcome	Maternal hypoglycemia
Insulin versus glyburide							
Anjalakshi, 2006[33]	G1: Insulin, 13						
	G2: Glibenclamide, 10						
Bertini, 2005[37]	G1: Insulin, 27			0 (0)			0 (0)
	G2: Glyburide, 24			0 (0)			0 (0)
	G3: Acarbose, 19			0 (0)			0 (0)
Langer, 2000[32]	G1: Insulin, 203	8 (4)‖	4 (2)	2 (1)		NICU admission: 14 (7)	
	G2: Glyburide, 201	12 (6)‖ p = 0.36†	5 (2) p = 0.74†	2 (1) p = 0.99†		NICU admission: 12 (6) p = 0.68†	
Insulin versus insulin lispro							
Jovanovic, 1999 [36]	G1: Regular human insulin, 23						
	G2: Insulin lispro, 19						
Mecacci, 2003 [34]	G1: Regular human insulin, 24						(2.2)
	G2: Insulin lispro, 25						(0.88) p > 0.05†
Insulin versus insulin							
Nachum, 1999 [35]	G1: Insulin twice daily, 136	29 (21)^	2 (2)	1 (1)	3 (2)	RDS: 0 (0.00)	1 (0.72)
	G2: Insulin four times daily, 138	15 (11)^	1 (1)	0 (0.00)	2 (1)	RDS: 1 (1)	1 (0.72)
Poyhonen-Alho, 2002 [31]	G1: Short-acting insulin, 11	3 (27.27)			0 (0.00)		
	G2: Long-acting insulin, 12	3 (25.00)			1 (8.33)		
Diet versus insulin							
Thompson, 1990 [30]	G1: Diet, 50	0 (0.00)Ω					
	G2: Diet and insulin, 45	0 (0.00)Ω					

† Comparing G1 to G2.

‖ Serum bilirubin > 12 mg/dL.

^ Serum bilirubin > 205mmol/L at >= 34 weeks of gestation or > 137 mmol/L at < 34 weeks.

Ω Serum bilirubin > 10 mg/dL.

RCT = randomized controlled trial; dL = deciliter; G = group; L = liter; mg = milligram; mmol = millimole; NICU = neonatal intensive care unit; RDS = respiratory distress syndrome

Four studies[45-47 49] used the 100-gm Carpenter and Coustan criterion (2003 ADA criterion), and one study[48] used the NDDG criterion to diagnose gestational diabetes. Four studies[45 47-49] reported the percentage of participants with prior gestational diabetes. All five studies reported the gestational age of pregnancies at the time of diagnosis of gestational diabetes; these ages ranged from 18 to 33 weeks of gestation.

All five studies reported the average maternal age at gestational diabetes diagnosis, which ranged from 26.4 to 32.8 years. Three studies reported the racial distribution of the participants.[46 48 49] The majority of the participants (87 percent) in the study by Chmait et al.[45] were of Hispanic origin. Jacobson and Rochon reported a racially diverse cohort of African-American, Caucasian, Asian, and Hispanic women (see Appendix F, Evidence Table 6). Three studies[47-49] reported baseline measures of body weight in terms of the mean pre-pregnancy BMI (ranging from 26 to 33.9 kg/m^2). One study[47] did not report the actual BMI but also reported no significant differences in BMI between study groups. The proportion of nulliparous women ranged from 7.7 percent to 33 percent across the five studies.

The initial glyburide dose was 2.5 mg daily in three of the four studies. Two studies reported an initial dose between 2.5 mg and 5 mg per day. Dosages were escalated on the basis of glucose control to a maximum of 20 mg/day in each study.[45-49] The initial insulin dose in three[45-47] of the four studies was 0.7 units/kg. One study[49] reported a standard regimen consisting of a combination of NPH and regular insulin injected subcutaneously three times daily. One study[48] did not report the initial insulin dose. Insulin levels were adjusted, with four studies reporting no maximum dose. Jacobson[48] reported a mean dose of 34.4 units per day in 249 of the 268 women treated with insulin.

Observational studies. Because of the differences in study design, the use of non-comparable groups, and the differences in outcome measures, we chose not to conduct a meta-analysis of the five observational studies included in our review. We offer a summary of the relevant findings and study conclusions and discuss their potential relevance for future research. We include the data on 5 maternal and 11 neonatal outcomes from the observational studies. The maternal outcomes were: (1) operative vaginal delivery, (2) pre-eclampsia, (3) cesarean delivery, (4) glucose control, and (5) maternal hypoglycemia. The neonatal outcomes were: (1) hypoglycemia, (2) hyperbilirubinemia, (3) macrosomia, (4) LGA, (5) SGA, (6) perinatal mortality, (7) infant birth weight, (8) neonatal intensive care admissions, (9) birth trauma, (10) congenital malformations, and (11) shoulder dystocia.

Summary of the observational studies of maternal and neonatal outcomes. Jacobson et al.[48] retrospectively compared 268 women treated with insulin between 1999 and 2000 to 236 women treated with glyburide between 2001 and 2002. Their study also included 80 women treated with insulin from 2001 to 2002. Sociodemographic data were collected from clinical databases and a retrospective chart review. Jacobson reported a higher final average FBG (97.7 mg/dL ± 12.2 [standard deviation (SD)] versus 90.2 ± 12.7; $p < 0.001$), 1-hr PPG (137.8 mg/dL ± 23.6 [SD] vs 131.4 ± 23.3; $p < 0.001$) and 2-hr PPG (118.8 mg/dL ± 19.6 versus 117.6 ± 23.2; $p < 0.05$) in the insulin group than in the glyburide group (see Appendix F, Evidence Table 7). Conversely, the average number of FBG levels that met the criterion for maternal hypoglycemia was significantly higher in the glyburide group than in the insulin group ($p < 0.001$). Also, in multivariate analysis, women treated with glyburide had a higher likelihood of developing pre-eclampsia (odds ratio [OR] = 2.32; 95 percent CI: 1.17 to 4.63) than did women on insulin therapy. There were no differences in cesarean delivery ($p = 0.7$) or operative vaginal delivery ($p = 0.8$) rates between the two groups.

In multivariate analysis, after adjustment for race/ethnicity, FBG on OGTT, BMI, and gestational age at diagnosis of gestational diabetes, the use of glyburide therapy was not statistically associated with neonatal hypoglycemia, hyperbilirubinemia, macrosomia, or delivery of LGA or SGA infants when compared to insulin therapy (see Appendix F, Evidence Table 8).[48] As shown in Evidence Table 8, the 95 percent CI for each outcome included 1. However, glyburide therapy was significantly associated with a lower likelihood of neonatal intensive care admission (OR = 0.5; 95 percent CI: 0.34 to 0.93). While Jacobson concluded that glyburide was as effective as insulin in the management of gestational diabetes, baseline differences between the two treatment groups suggested that the women on glyburide may have been healthier or had less underlying insulin resistance than those in the insulin group. Women in the original insulin group (1999 - 2000), for example, had a higher average BMI (31.9 kg/m^2 ± 6.8 versus 30.6 ± 7.0; p = 0.04) and higher FBG on the baseline OGTT (105.4 mg/dL ± 12.9 versus 102.4 ± 14.2; p = 0.005) than did women in the glyburide group. While Jacobson et al. adjusted for several important covariates, they did not adjust for prior gestational diabetes status, which might also indicate underlying insulin resistance.

Conway et al.[47] followed 75 women who elected to be treated with glyburide after failing to achieve adequate glucose control with diet alone.[47] The study compared pregnancy outcomes in 12 women with glyburide failure who were converted to insulin therapy to the outcomes in 63 women who were successfully treated with glyburide until delivery. The initial glyburide dose was 2.5 mg/day and was escalated on the basis of glucose control to a maximum of 20 mg/day. There was no difference in the proportion of macrosomic infants in the glyburide failure group and the glyburide success group (8 percent versus 11 percent; p = 1.0) (see Appendix F, Evidence Table 8). Also, there was no difference in average infant birth weight (3267 gm ± 815 in the failure group versus 3327 gm ± 634 in the success group; p = 0.78). The absence of significant differences may be due in part to the limited power of the study to detect a small difference between groups.

Chmait[45] conducted a prospective, cohort study of 69 women with gestational diabetes who failed diet alone and elected to proceed with glyburide therapy. Of the 69 participants, 13 participants were started on glyburide therapy but later required the addition of insulin or were transitioned from glyburide to insulin therapy because of inadequate glucose control. Fifty-six (81 percent) of the participants achieved adequate glucose control on glyburide.

While the mean FBG and 1-hr PPG levels on the diagnostic OGTT were similar for the glyburide failure group (105 mg/dL and 206 mg/dL, respectively) and the glyburide success group (94 mg/dL and 199 mg/dL respectively; p > 0.1 for both measures), there were significant differences in glucose values during treatment (see Appendix F, Evidence Table 7).[45] The mean FBG levels during treatment with glyburide (114 mg/dL) and the mean 1-hr PPG levels (145 mg/dL) were both significantly greater for the glyburide failure group than for the glyburide success group (FBG 88 mg/dL; 1-hr PPG 124 mg/dL; p < 0.001 for both measures). There was no difference in the proportion of cesarean deliveries between the two groups (38 percent in failure group versus 34 percent in success group; p > 0.05). Also, there were no differences in the proportion of macrosomic infants (10 percent in the failure group versus 18 percent in the success group; p = 1.0) or average infant birth weight (3608 gm ± 398 in the failure group versus 3430 gm ± 714 in the success group; p = 0.78) (see Appendix F, Evidence Table 8). There were no differences in hyperbilirubinemia or neonatal intensive care admissions.

Chmait concluded that women with gestational diabetes with FBG levels under 110 mg/dL and 1-hr PPG levels under 140 mg/dL were more likely to successfully continue glyburide

therapy throughout pregnancy. However, these findings were based on a small sample size without any reported adjustment for confounders. Also, because the majority of participants were Hispanic, the findings may not apply to other populations.

Yogev et al.[46] conducted a prospective study of 82 participants recruited from a diabetes clinic in which they sought to determine the rate of asymptomatic maternal hypoglycemia in women treated with diet, insulin, or glyburide. Of these 82 participants, 27 were treated with diet alone, 25 with glyburide, and 30 with insulin. As compared to the women on glyburide, the women on insulin had a 4.4-fold higher likelihood of having an episode of asymptomatic hypoglycemia (OR = 4.4; 95 percent CI: 1.4 to 13.9) (see Appendix F, Evidence Table 7). There were no episodes of hypoglycemia among the participants treated with diet alone.

Finally, Rochon et al. conducted a retrospective study of 101 participants recruited from a prenatal diabetes clinic in order to identify characteristics that might predict failure of glyburide therapy and to evaluate whether those women who had failed glyburide were more likely to undergo adverse pregnancy outcomes.[49] These gestational diabetics, who had undergone a 1-week trial of diet but were not meeting glycemic goals (FBG between 60 and 90 mg/dL and 2-hr PPG of 120 mg/dL or less), were then started on glyburide. Those who were consistently 15 percent to 25 percent above the FBS or 2-hr PPG target values were switched to insulin therapy. Eighty (79 percent) of the 101 participants were identified as glyburide "successes" compared to 21 (21 percent) who were categorized as glyburide "failures." Rochon and colleagues reported few statically significant differences in the maternal or neonatal outcomes for the success and failure groups. The rate of neonatal intensive care admissions was higher in the glyburide success group than in the glyburide failure group (33 percent versus 10 percent; $p = 0.04$). Infant birth weight was similar between the success and failure groups (3,415 gm ± 620 compared to 3,319 ± 559; $p = 0.5$). The absence of significant differences in birth weight may reflect, at least in part, the limited power of the study to detect a small difference between groups.

There was no difference in the percentage of cesarean deliveries (38 percent versus 43 percent) between the success and failure groups. The rate of shoulder dystocia (10 percent versus 11 percent) was also similar in both groups. Although congenital anomalies were not included as one of the outcomes, Rochon and colleagues reported two neonatal intensive care admissions in the glyburide success group that were due to a congenital anomaly. Also, most admissions to the neonatal intensive care unit were related to neonatal hypoglycemia (10 infants in the success group and 2 in the failure group). The authors concluded that there are few adverse maternal or neonatal outcomes in pregnancies in which glyburide therapy has failed and insulin is required. They also concluded that the rate of neonatal intensive care admissions was higher in the glyburide success group than in the glyburide failure group, primarily because of neonatal hypoglycemia.

Quality assessment of cohort studies. The quality of each of the five cohort studies was assessed using a modified version of the STROBE criteria.[23] Each study reported reproducible inclusion and exclusion criteria and recruited participants using a consecutive sample of participants (see Appendix F, Evidence Table 9). Only two of the five studies had a prespecified, clearly presented hypothesis.[46 48] None reported power analyses to estimate effect size. As previously stated, insufficient power may have accounted for the absence of detectable differences in infant birth weight in the studies by Conway[47] and Rochon.[49] While the loss-to-followup rate was reported in four[45-47 49] of the five studies, only one study[45] described the characteristics of those lost to followup. Two studies reported the actual percentage of missing

data,[45 46] but only one of these two studies[45] described how the missing data were handled in the analysis.

Limitations. In addition to the quality assessment outlined above, two additional limitations deserve further comment: First, only one study[48] adjusted for potential confounders. Jacobson adjusted for several relevant covariates, including race/ethnicity, FBG, BMI, and gestational age at diagnosis of gestational diabetes. Additional adjustment for relevant labor complications, such as maternal hypertension or intrapartum infection, might help to elucidate the association of insulin therapy with maternal and neonatal outcomes. Second, there was no discussion of potential selection bias in the conduct of the observational study or the potential influence of this bias on the associations reported. Because of the observational design and lack of adjustment for confounders, it is difficult to draw conclusions with confidence.

Given the limitations of the observational studies, we based our conclusions on the available RCTs. None of the observational studies was strong enough to justify a modification of the conclusions drawn from the RCTs.

Key Question 1a. How does maternal outcome vary based on the level of glucose at the initiation of a medication?

Key Question 1b. How does neonatal outcome vary based on the level of glucose at the initiation of a medication?

Maternal glycemia and maternal and neonatal outcomes. We found no evidence for variation in maternal or neonatal outcomes on the basis of the glucose level at the initiation of treatment with an oral agent or insulin. One ongoing study may provide evidence to address this important clinical question. We look forward to the publication of the findings from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study.[50] The HAPO Study is a 5-year, prospective, observational study designed to examine the association of various levels of maternal glycemia in the third trimester with adverse pregnancy outcomes in a multi-national, multicultural, ethnically diverse cohort of women. This investigator-initiated observational study has recruited 23,325 pregnant women from nine countries. All participants undergo glucose tolerance testing. Those participants with levels below the pre-defined threshold are provided with standard obstetrical care, and their providers are blinded to their glucose levels. Maternal blood is obtained for measurement of serum C-peptide and hemoglobin A1c (HbA1c) and cord blood for serum C-peptide and plasma glucose; a capillary specimen is obtained between 1 and 2 hr after delivery for measurement of neonatal plasma glucose. Neonatal anthropometrics are obtained, and followup data are collected at 4-6 weeks post-delivery. The primary outcomes are cesarean delivery, increased fetal size (macrosomia/LGA/obesity), neonatal morbidity (hypoglycemia), and fetal hyperinsulinemia. Preliminary findings, presented at the 67th Annual Scientific Session of the ADA,[51] suggest a linear association between rising maternal glucose levels in the third trimester and the likelihood of cesarean delivery. Large babies (defined as being in the largest 10 percent of the newborn population) were born to only 5 percent of women with the lowest fasting plasma glucose levels (less than 75 mg/dL) but to 27 percent of those with the highest levels (greater than 100 mg/dL). Women with the highest glucose levels had a 6.6 times greater risk of delivering an infant with macrosomia than did women with the lowest glucose levels (OR = 6.6; 95 percent CI: 4.6 to 9.6). Rising glucose levels were also associated with a linearly higher likelihood that the newborn would be above the 90th percentile for total

skinfold thickness (5.4 percent at the lowest glucose levels versus 28 percent at the highest, OR = 1.52, 95 percent CI: 1.40 to 1.59). These findings suggest that the likelihood of adverse outcomes increases linearly with rising maternal glucose levels even when the range of maternal glucose levels is considered normal. These findings should provide further information on the level of glycemia at which adverse events may occur, although the glucose levels may be below the threshold values for gestational diabetes. Also, these findings may provide insight into the level of glucose at which therapy with an oral agent or insulin should be added to diet therapy.

Conclusions

We found limited evidence on the risks and benefits of oral diabetes agents, insulin analogues, and insulin. The available evidence, to date, suggested little difference in maternal or neonatal outcomes for treatment with oral agents versus any type of insulin, but inconsistencies in clinical outcomes measures across studies and lack of data make it difficult to draw firm conclusions. No studies compared metformin to insulin or other oral agents. Our meta-analysis showed a small, non-significant lower infant birth weight in pregnant women treated with insulin as compared with those treated with glyburide. This small difference of 93 gm is unlikely to have significant clinical relevance. Further studies are needed to determine whether there is a consistent and clinically definable difference in infant birth weight. There appeared to be little difference in various reported measures of maternal glucose control in women treated with glyburide versus insulin (FBG and 2-hr PPG) or in women treated with insulin lispro versus regular insulin (glycosylated hemoglobin and 1-hr PPG). It is unclear whether differences in maternal hypoglycemia are associated with different treatment regimens: Only one study of glyburide and insulin[37] defined threshold values for maternal hypoglycemia as part of the study protocol. In one study comparing insulin lispro to regular insulin, maternal hypoglycemia was based on the need for hospitalization rather than threshold glucose values. No available evidence met our inclusion criteria for variations in maternal or neonatal outcomes being based on glucose levels at the initiation of oral agents or insulin. However, as we have indicated above, ongoing investigations, such as the HAPO Study, may provide evidence to suggest threshold values at which clinicians should add oral diabetic agents, insulin analogues, or insulin to diet therapy. The results of the MiG trial should provide evidence regarding the relative benefits and harms of treatment with metformin versus insulin. Finally, additional data regarding congenital anomalies, the long-term consequences of glyburide use, and the effects of metformin transport across the placenta should inform clinical practice and clinical guidelines for the use of oral diabetic agents in pregnancy.

Key Question 2

What is the evidence that elective cesarean delivery or the choice of timing of induction in women with gestational diabetes results in beneficial or harmful maternal and neonatal outcomes?

a. What is the evidence for elective cesarean delivery at term, as compared to an attempt at vaginal delivery (spontaneous or induced) at term, with regard to beneficial or harmful maternal and neonatal outcomes in gestational diabetes?
    i. cesarean versus spontaneous labor and vaginal delivery

ii. cesarean versus induced labor and vaginal delivery
iii. cesarean versus any attempt at vaginal delivery at term

b. What is the evidence for labor induction at 40 weeks, as compared to labor induction at an earlier gestational age (less than 40 weeks) or spontaneous labor, with regard to beneficial or harmful maternal and neonatal outcomes in gestational diabetes?
   i. labor induction at less than 40 weeks versus labor induction at 40 weeks
   ii. labor induction at 40 weeks versus spontaneous labor
   iii. labor induction at less than 40 weeks versus spontaneous labor
c. How is the EFW related to outcomes of management of gestational diabetes with elective cesarean delivery or the timing (i.e., gestational age range) of labor induction?
d. How is gestational age related to outcomes of management of gestational diabetes with elective cesarean delivery or the choice of timing (i.e., gestational age range) of labor induction?

Maternal outcomes
- cesarean delivery
- hemorrhage
- infection
- operative vaginal delivery
- perineal tears

Neonatal outcomes
- anoxia
- birth trauma
- birth weight
- congenital malformations
- hyperbilirubinemia
- hypoglycemia
- LGA
- macrosomia
- mortality
- neonatal intensive care admissions
- respiratory distress syndrome
- shoulder dystocia
- SGA

Background and Conceptual Framework

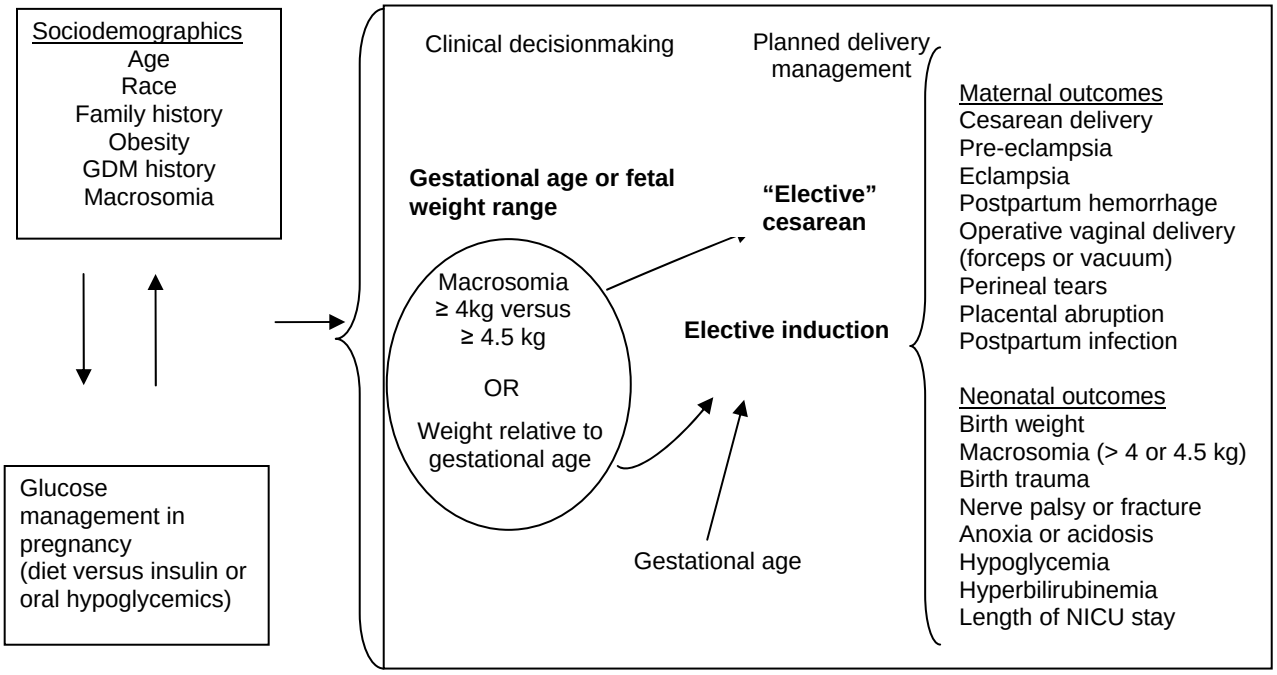
Clinicians use a variety of clinical parameters in their clinical decisionmaking for intrapartum management. Estimates of fetal weight, gestational age, and maternal glucose control are measures of particular importance in pregnancies complicated by gestational diabetes. Clinical management can also be influenced by patient preference and provider perception. Management options include expectant management, labor induction, or "elective" cesarean delivery. In the context of diabetic pregnancies, we refer to "elective" cesarean delivery as a procedure performed following discussion between the patient and clinician, with the goal of avoiding adverse neonatal outcomes such as shoulder dystocia, nerve palsy, or fracture.

Medical institutions have traditionally developed protocols for labor management of women with gestational diabetes, incorporating a combination of anecdotal experience, published literature, and recommendations by national clinical organizations. Both the ACOG and the ADA[7 13] have provided guidance with regard to labor management of pregnancies complicated by gestational diabetes. The current guidelines, however, are based primarily on retrospective studies that summarize individual hospitals' experiences with maternal and neonatal outcomes. Limitations in the available literature on the management of women with gestational diabetes

may have contributed to delays in the development of broadly accepted guidelines for clinical management and to the current variation in practice patterns and clinical outcomes.

Our objective was to conduct a systematic review of the available literature on the effect of EFW and gestational age on maternal and neonatal outcomes in pregnancies involving gestational diabetes. We also focused on the effect of delivery options (i.e., expectant management, induction, and elective cesarean delivery). We developed a conceptual framework to guide the review of Key Question 2, incorporating the key steps in clinical decisionmaking for labor management (see Figure 5). We focused on gestational age and EFW and the potential influence of these measures on options for delivery. Although they are outside the scope of this review, we include contributing maternal and metabolic factors in the conceptual framework, since these are key elements in the broader context of labor management of women with gestational diabetes.

Figure 5. Conceptual framework of the effects of gestational age, fetal weight, and labor management on maternal and neonatal outcomes



GDM = gestational diabetes mellitus; kg =kilogram; NICU = neonatal intensive care unit

Results

Overview and population characteristics of studies of the effect of labor management on outcomes. Evidence Table 10 describes the characteristics of each of the eight studies that met our criteria for review (see Appendix F). Five studies were conducted in the United States[52-56] and three in Israel.[57-59] The studies were conducted between 1983 and 2004, and the study periods ranged from 4 to 19 years. We identified one RCT that compared the effect of two labor induction protocols on maternal and perinatal outcomes.[55] We also identified four observational studies that examined the effect of EFW and/or gestational age on delivery management and outcomes.[53 57-59] One observational study[56] compared the effect of labor induction in a class A2 gestational diabetes sample at 38 weeks of gestation to expectant management of a class A1

sample. Gestational diabetes class A1 is managed with diet alone, while gestational diabetes class A2 requires insulin or glyburide in addition to diet to manage glucose levels. One retrospective cohort study compared a trial of labor to repeat cesarean delivery in a sample of women with gestational diabetes and a prior cesarean delivery.[52] Another study[54] examined the risk of shoulder dystocia in gestational diabetes patients undergoing a trial of labor.

Outcomes from eight studies. The eight studies identified for this review were heterogeneous with regard to methodology, comparison groups, the time period in which the study was conducted, the length of the study period, the populations included, and the outcome measures of maternal and infant well-being (see Table 5 and Appendix F, Evidence Table 10). Because of the extent of this heterogeneity, we were unable to provide any quantitative synthesis of the literature. We have summarized each study individually, incorporating a summary of the objectives, study design, results, and conclusions presented by the authors. Also, we identify methodological issues that might influence these conclusions. We have categorized our summary of the studies first in terms of study design (RCTs followed by observational studies) and then in terms of the primary exposure (i.e., fetal weight, gestational age, delivery method) under study. The categories we considered were: (1) gestational age and timing of induction, (2) EFW and elective cesarean or timing of labor induction, (3) gestational age or EFW and timing of labor induction, (4) gestational age at delivery, and (5) gestational age and/or EFW and timing of labor induction and/or elective cesarean delivery.

Impact of gestational age on the timing of labor induction. We identified one RCT that addressed the impact of labor induction at term, as compared to expectant management, on maternal and neonatal outcomes in gestational diabetes.[55] Kjos 1993 recruited 200 women from one tertiary care center. The study sample included 187 women with class A2 gestational diabetes and 13 women with pre-existing (class B non-insulin-requiring) diabetes. Inclusion criteria were clearly stated: good glucose control in at least 90 percent of measured levels, 38 completed weeks of gestation, good compliance with clinic appointments and home glucose monitoring, no antepartum testing abnormalities, singleton gestation with cephalic presentation, EFW less than 3800 gm at 38 weeks with no evidence of fetal growth restriction, no other medical or obstetrical complications, and no more than two previous cesarean deliveries. Women who met the inclusion criteria, agreed to randomization, and had an established diagnosis of diabetes were eligible to participate in the study. Women were randomized to either expectant management or induction of labor at 38 weeks. Of those with pre-existing diabetes, nine were in the active induction group and four were in the expectant management group. The two treatment groups did not differ significantly in terms of maternal age, gravidity, parity, maternal weight, or gestational age at entry into the study. The racial distribution of the study participants was not reported. Gestational age was calculated from the first day of the last menstrual period and adjusted if ultrasound estimation (before 22 weeks) differed from the menstrual age by 10 days or more. Amniocentesis and measurement of the lecithin-to-sphingomyelin (L/S ratio) was used if gestational age could not be accurately determined. Labor was induced with intravenous oxytocin at 38 weeks or in the presence of fetal lung maturity. Vaginal prostaglandin was used for cervical ripening if indicated (Bishop's score less than four) and if the patient had no contraindications to therapy.

Maternal outcomes. Thirty of 100 women in the active induction group had spontaneous labor or cesarean delivery prior to scheduled induction, and 56 of 100 women in the expectant management group required induction or cesarean delivery prior to the onset of labor for medical indications (see Appendix F, Evidence Table 11).[55]

Table 5. Summary table of eight studies examining the effect of delivery management on maternal and neonatal outcomes

Author, year	Type of study	Control group intervention/ protocol	Study group intervention/ protocol	Population	Key limitations of study	Key conclusions
Kjos, 1993[55]	Randomized controlled trial	Expectant management	Induced at 38 weeks	GDMA2 Pre-gestational diabetics (6.5%)	Randomization process not described High rate of induction in control group	↓ macrosomia, ↓ birth weight in study group
Conway, 1998[53]	Prospective cohort study with HC; protocol-based	Expectant management	US at 37-38 weeks CD if EFW>4,250gm Induced if LGA and EFW<4,250gm	GDMA1 GDMA2 Pre-gestational diabetics (8.6%)	No adjustment for confounders No stratified analysis for GDM class No power calculation	↑ CD, ↓ macrosomia, ↓ shoulder dystocia in study group
Lurie, 1996[58]	Prospective cohort study with HC; protocol-based	Induced if EFW>4000gm CD if EFW>4,500gm (sub-group analysis: delivered > 40 weeks)	Induced at 38 weeks, CD if EFW>4,500gm	GDMA1 GDMA2	No adjustment for confounders No stratified analysis for GDM class Small number of subjects	↓ macrosomia, ↓ shoulder dystocia (only if compared to controls delivered after 40 weeks)
Lurie, 1992[57]	Retrospective cohort study; groups based on gestational age at delivery	Induced if EFW>4000gm CD if EFW>4,500gm, delivery > 40 weeks	Induced if EFW>4,000g CD if EFW>4,500gm, delivery < 40 weeks	GDMA1 GDMA2 Stratified analysis	No adjustment for confounders Outcomes not clearly defined	↓birth weight in GDMA2 patients delivering before 40 weeks
Peled, 2004[59]	Retrospective cohort study comparing four protocol periods	HC A: Induced at 42 wks CD if EFW>4,500gm HC B: Induced at 40 weeks if LGA CD if EFW>4,000gm HC C: Induced at 40 weeks if LGA CD if EFW>4,000gm	Period D: Induced at 38 weeks if LGA CD if EFW>4,000gm	GDMA1 GDMA2	No adjustment for confounders Limited information on baseline characteristics Exclusion criteria not reported No stratified analysis for GDM class Long study period (19 years)	Decreasing rates of macrosomia and shoulder dystocia with level of intervention
Rayburn, 2005[56]	Retrospective cohort study; protocol-based	Expectant management of GDMA1	Induction of GDMA2 at 38 weeks	GDMA2 versus GDMA1	Significant differences in baseline characteristics between groups Outcomes not clearly defined	No differences in maternal or neonatal outcomes
Marchiano, 2004[52]	Retrospective cohort study	Trial of labor	Elective repeat CD	GDMA1 with previous CD	Results only generalizable to patients with previous CD	↑ macrosomia in elective CD group
Keller, 1991[54]	Retrospective cohort study	Trial of labor		GDMA1 GDMA2	No adjustment for confounders Lack of appropriate comparison group Limited information on baseline characteristics	↑ shoulder dystocia with ↑ birth weight

CC = concurrent control group; CD = cesarean delivery; EFW = estimated fetal weight; GDM = gestational diabetes mellitus; GDMA1 = diet-controlled gestational diabetes; GDMA2 = gestational diabetes requiring medical therapy; gm = gram; HC = historical control group; LGA=large for gestational age; US=ultrasound

In the final intention-to-treat analysis, there was no difference in cesarean delivery rates between the two groups (25 percent in the active induction group versus 31 percent in the expectant management group; $p = 0.43$). The average gestational age at delivery in the induction group was 1 week less than the gestational age in the expectant management group (39 weeks versus 40 weeks; $p < 0.05$).

Neonatal outcomes. Even after adjustment for gestational age at delivery, maternal weight, and maternal age, the average infant birth weight in the expectant management group (3,672 gm; 95 percent CI: 3,595 to 3,749 gm) was significantly greater than that in the active induction group (3,446 gm; 95 percent CI: 3,368 to 3,522 gm; $p < 0.01$) (see Appendix F, Evidence Table 12).[55] The proportion of infants with macrosomia, defined as a birth weight of 4,000 gm or more, was higher in the expectant management than in the active induction group (27 percent versus 15 percent; $p = 0.05$). When defined as a birth weight greater than the 90th percentile, the proportion of infants with macrosomia was also higher in the expectant management than in the induction group (23 percent versus 10 percent; $p = 0.02$). There was no significant difference in the number of cases of shoulder dystocia or in the average 5-minute Apgar score between the two groups. Also, there were no episodes of neonatal hypoglycemia requiring treatment and no perinatal deaths in either treatment group.

The findings of this RCT suggested that infants born to women undergoing induction at 38 weeks have significantly lower average birth weights and perhaps a lower risk of macrosomia than do those born to women treated with expectant management. The absence of any difference in cesarean delivery rates suggested that maternal morbidity among women undergoing 38-week induction is similar to that of women undergoing expectant management. The similarity in demographics of the two groups suggested appropriate randomization. Adjustment for key covariates, including gestational at delivery, maternal weight, and age strengthened our confidence in the observed associations.

Impact of EFW on elective cesarean delivery and timing of labor induction. We identified one observational study on the effect of EFW on maternal and neonatal outcomes related to elective cesarean delivery and the timing of induction of labor.[53] Conway et al. prospectively followed diabetic women (91.4 percent with gestational diabetes) who were delivered at a tertiary care institution between 1993 and 1995 according to an institutional protocol. Based on this protocol, women with diabetes underwent ultrasonographic estimates of fetal weight between 37 and 38 weeks of gestation. Women whose EFW was greater than or equal to 4,250 gm underwent cesarean delivery; those in whom the EFW was estimated at less than 4,250 gm but considered LGA (defined as 90th percentile or greater for the gestational age in their population) underwent labor induction. We will refer to this group who delivered between 1993 and 1995 as the study group. Outcomes for this study group were compared to those of a historical control group of diabetic women who delivered between 1990 and 1992, prior to the implementation of the new protocol. The study and control groups did not differ significantly in terms of their mean maternal age, racial composition, gestational age at delivery, or proportion of women with gestational diabetes or pre-gestational diabetes. Twenty-seven percent of the patients in the study group did not undergo ultrasound evaluation.

Maternal outcomes. As shown in Evidence Table 10 (see Appendix F), the authors reported that the average gestational age at delivery was similar for the study group and the historical control group (39.2 weeks versus 39.3 weeks; $p > 0.05$).[53] The cesarean delivery rate, however, was significantly higher in the study group (25.1 percent versus 21.7 percent; $p < 0.04$) (see Appendix F, Evidence Table 11). The authors suggested that the higher proportion of cesarean

deliveries in the study group could be attributed to the implementation of the new protocol. When the elective cesarean deliveries for EFW of 4,250 gm or more (53/343) and cesarean deliveries for failed induction for LGA (7/343) were excluded from the study group, there was no difference in cesarean delivery rate between groups.

Neonatal outcomes. There were significantly fewer macrosomic infants (defined as weighing 4,000 gm or more) in the study group than in the control group (8.9 percent versus 11.6 percent; $p = 0.04$) (see Appendix F, Evidence Table 12). There was a greater likelihood of shoulder dystocia in the control group (OR = 1.9, 95 percent CI: 1.0 to 3.5) than in the study group. In a subgroup analysis of the macrosomic infants delivered vaginally, there was also a statistically significant greater likelihood (OR = 2.9, 95 percent CI: 1.0 to 8.4) of shoulder dystocia in the control than in the study group.

Based on this prospective, observational study, it appears that in women with gestational diabetes, a protocol involving elective cesarean delivery for macrosomia and induction at 38 weeks for LGA may reduce the number of macrosomic infants and the risk of shoulder dystocia, but it may also be associated with an increase in the number of cesarean deliveries. However, the lack of adjustment for the severity of the diabetes or other potentially confounding variables in this study may have resulted in an overestimate of the effect of the protocol on outcomes. Furthermore, temporal changes in the management of women with gestational diabetes may have also influenced the outcomes reported.

Relationship of gestational age and fetal weight to the timing of labor induction. We identified one cohort study[58] that examined the relationship of gestational age and EFW to the timing of induction. Lurie et al[58] prospectively followed a sample of women and compared outcomes with a historical control group in order to determine whether labor induction at 38 to 39 weeks of gestation might reduce the incidence of shoulder dystocia in women with gestational diabetes class A2. The study group (n = 96) was induced at 38 weeks or, if the EFW was greater than 4,500 gm, underwent elective cesarean delivery. The study group was compared to a historical cohort of women (n = 164) who delivered between 1983 and 1989 and in whom labor was induced only if the EFW was greater than 4,000 gm or, if the EFW was greater than 4,500 gm, underwent elective cesarean delivery. This historical cohort was the same study population described by Lurie et al. in an earlier paper,[57] which will be discussed subsequently. Gestational age was based on the first day of the last menstrual period and serial crown rump measurements in the first trimester. Amniocentesis was performed to assess fetal lung maturity, using the L/S ratio prior to induction. Baseline participant characteristics, including maternal age and parity, were similar between the two groups. There were no reported data on maternal race, weight, or glucose control.

Maternal outcomes. Women in the study group delivered significantly earlier than did women in the control group (38.4 weeks versus 39.2 weeks; $p < 0.001$) (see Appendix F; Evidence Table 11). A slightly higher proportion of women in the study group than in the control group underwent cesarean delivery, but the difference was not statistically significant (23 percent versus 19 percent; $p > 0.05$). The rates of vacuum-assisted delivery were similar for the two groups (5.2 percent versus 5.5 percent; $p > 0.05$).[58]

Neonatal outcomes. Neither infant birth weight nor the proportion of macrosomic infants was significantly different between the two groups (see Appendix F, Evidence Table 12). The proportion of infants with shoulder dystocia was lower in the elective induction group than in the historic control group, but the difference did not reach statistical significance (1.4 percent versus

5.3 percent; $p > 0.05$). Clavicular fractures, nerve palsies, mortality, and respiratory distress were rare events overall, and their incidence was not significantly different between groups.

Additional analysis. The authors conducted a second analysis in which the outcomes in the study group were compared to those in a subset of the historical cohort of women who delivered after 40 weeks of gestation ($n = 62$). The proportion of deliveries complicated by shoulder dystocia was significantly reduced (from 10.2 percent to 1.4 percent; $p < 0.05$) in the study group when compared to this subset of the historical control group. Also, only nine percent of the infants in the study group had a weight greater than 4,000 gm, as compared to 24 percent in the historical control group ($p < 0.05$).

In summary, the authors of this paper found that the decrease in shoulder dystocia in the study group was only statistically significant if the study group was compared to the subgroup of control patients that delivered after 40 weeks. In addition to a lack of adjustment for severity of diabetes and a consideration of the temporal changes that had occurred in the management of patients with gestational diabetes, this study was further limited by its small population size.

Impact of gestational age at delivery. In their 1992 paper, Lurie et al[57] conducted a retrospective chart review of all gestational diabetic women who delivered over a 5-year period, examining maternal and neonatal outcomes for women with gestational diabetes class A1 and A2 who delivered after 40 weeks of gestation or prior to 40 weeks. The groups were matched with regard to age, parity, and fetal presentation**.** Gestational age was based on the date of the last menstrual period and ultrasound measurements of crown rump lengths in the first trimester. Outcomes were reported separately for gestational diabetes classes A1 and A2.

Maternal outcomes. Among women with gestational diabetes class A1 (diet-controlled gestational diabetes), the mean gestational age at delivery was 40.9 weeks for those who delivered after 40 weeks and 38.2 weeks for those who delivered before 40 weeks (p not reported). There were no differences in the numbers of vacuum-assisted vaginal deliveries (0/65 versus 4/65) or cesarean deliveries (7/65 versus 9/65; $p = 0.0997$) between women delivering after 40 weeks of gestation and those delivering prior to 40 weeks of gestation (see Appendix F, Evidence Table 11).

Similar findings were obtained for the women with gestational diabetes class A2 (insulin-requiring gestational diabetes). The mean gestational age at delivery was 40.5 weeks in the group delivering after 40 weeks and 37.5 weeks in the group delivering before 40 weeks (p not reported). There were no differences in the number of vacuum-assisted deliveries (1/59 versus 4/59) or cesarean deliveries (15/59 versus 13/59; $p = 0.6216$).

Neonatal outcomes. For women with either class A1 or A2 gestational diabetes, the rate of macrosomia (defined as birth weight greater than 4,000 gm) was higher in the group of women delivering after 40 weeks than in those delivering prior to 40 weeks, but the difference was not statistically significant: for gestational diabetes A1, 24.6 percent in the group delivering after 40 weeks versus 15.4 percent for those delivering before 40 weeks ($p = 0.1853$); for gestational diabetes A2, 20.3 percent in the group delivering after 40 weeks versus 6.8 percent for those delivering before 40 weeks ($p = 0.057$) (see Appendix F, Evidence Table 12). The mean birth weights in the two groups were not significantly different in the case of gestational diabetes A1 patients (3,439.00 gm versus 3,617.85 gm; $p = 0.0619$). However, infants of gestational diabetes A2 patients who delivered after 40 weeks had a significantly higher mean birth weight (3,639 gm) than did infants born to those who delivered before 40 weeks (3,275 gm) ($p = 0.0003$). There was no significant difference in the rate of shoulder dystocia, birth trauma, neonatal

metabolic complications, respiratory distress syndrome, or mortality between the two groups in either population.

In this retrospective cohort study, the only significant difference between patients delivering after 40 weeks and those delivering before 40 weeks was a higher mean birth weight in the subset of class A2 gestational diabetes patients, which was to be expected, given that gestational age is a strong predictor of birth weight. The authors concluded that the timing of delivery does not have a significant impact on clinically important maternal or neonatal outcomes. However, although the authors did perform a stratified analysis for class of gestational diabetes, the study did not adjust for other potential confounders or for delivery management in the groups.

Impact of gestational age and/or EFW on the timing of labor induction and/or elective cesarean delivery. Peled[59] conducted a protocol-based chart review to evaluate the effect of gestational age and EFW on labor management. In this study, the charts of 2,060 patients with gestational diabetes treated over a 19-year period were abstracted for maternal and neonatal outcomes. The investigators compared four time periods, each with a distinct management protocol for the timing of labor induction or elective cesarean delivery, based on EFW and gestational age and target thresholds for maternal glycemia (Period A: 1980-1989; Period B: 1990-1992; Period C: 1993-1995; Period D: 1996-1999). Gestational age was calculated from the first day of the last menstrual period and confirmed by first trimester ultrasound when possible. EFW was estimated either clinically or by ultrasound. Outcomes among women in Period D (the study group) were compared with outcomes among women in the three prior periods (historical control groups). Women in the study group were induced at 38 weeks of gestation if the EFW was consistent with LGA (defined as greater than 90th percentile) or underwent elective cesarean if the EFW was greater than 4,000 gm. In Period A, patients underwent elective cesarean if the EFW was greater than 4,500 gm; otherwise, they were induced at 42 weeks. In both Periods B and C, patients underwent elective cesarean delivery if the EFW was greater than 4,000 gm, and they were induced at 40 weeks if LGA was diagnosed. It is noteworthy that the groups differed in terms of the level of glycemic control in the institution's protocol. For patients in Periods C and D, insulin was started at lower fasting glucose levels (> 5.3 mmol/L) and 2-hr postprandial levels (> 6.6 mmol/L) than in Periods A and B (> 5.8 mmol/L and > 7.8 mmol/L, respectively). Furthermore, patients had lower glycemic goals in Periods C and D (< 5.3 mmol/L) than in Period B (< 5.8 mmol/L) or Period A (no goal set). Thus, although glycemic control did not alter decisions regarding delivery, it is important to keep in mind that patients in the four periods differed in terms of their level of glucose control. Prostaglandin E2 gel or tablets was used for labor inductions over the 19-year period of the study. The authors also included both class A1 and A2 gestational diabetes patients but did not report outcomes separately for the two groups. The proportions of women treated with insulin during the four study periods were variable: 13 percent in Period A, 16.4 percent in Period B, 28 percent in Period C, and 32 percent in Period D. There was no other comparison of baseline characteristics (e.g., age, race, parity) in the four groups.

Maternal outcomes. The mean gestational age at delivery was similar for all four groups (between 38 and 39 weeks). The cesarean delivery rate decreased over time, from 21 percent in Period A to 18 percent in Period B and 16 percent in Period C, but it increased to 34 percent in Period D (see Appendix F, Evidence Table 11). A similar increase in the cesarean delivery rate was noted by the author in a concurrent non-gestational diabetes population included in the same study.[59]

Neonatal outcomes. There was a reduction in the proportion of infants with birth weights greater than 4,000 gm (3.86 percent in the study group versus 20.6 percent in Period A, 16.3 percent in Period B, and 11.7 percent in Period C). The proportion of deliveries complicated by shoulder dystocia (none in Period D, versus 1.5 percent in Period A, 1.2 percent in Period B, and 0.6 percent in Period C) also decreased over the study period. Perinatal mortality rates also decreased from 8 percent in Period A to 3 percent in Period B, to 0 percent in Period C, and 0.77 percent in Period D. While p values were reported for comparisons between the gestational diabetes population and the non-gestational diabetes population, they were not reported for comparisons between time periods (the relevant comparison groups for this analysis).

Although this study provides data on a large population of patients with gestational diabetes, the lack of information on baseline characteristics (e.g., age, race, parity, severity of disease) in the four groups and the lack of adjustment for any differences between groups severely limited our ability to draw any substantial conclusions from this study. Also, the authors did not adjust for or discuss the influence of other potential obstetrical management patterns over the 19-year period. Clinical management of diabetic patients had changed substantially over the 19-year period of the study. Modifications in practice patterns have likely influenced the outcomes reported in these investigations. While examining trends in outcomes is useful, it is not possible to fully adjust for changes in practice patterns, leading to some level of bias in the reported associations.

Additional studies. We identified three additional studies that met our initial inclusion criteria but which focused on aspects of labor management that are outside our primary area of evidence review for Key Question 2. Nevertheless, given the paucity of data addressing labor management among women with gestational diabetes, we believe the findings of these studies and their relevance to delivery management deserve limited discussion.

Impact of gestational age on the timing of induction of labor in patients with different levels of disease severity. In a retrospective cohort study, Rayburn examined maternal and neonatal outcomes under an institutional protocol in which class A2 gestational diabetes patients were routinely induced at 38 weeks and class A1 gestational diabetes patients were managed expectantly.[56] It is important to note that the control group, the gestational diabetes A1 patients who were managed expectantly (n = 137), underwent induction if there were any obstetrical indications for delivery, including pre-eclampsia, gestational hypertension, or poor glucose control; if the cervix was "favorable" at 40 weeks; or if the patient reached 42 weeks of gestation. The authors reported that only 53 percent of patients in the control group required induction, a rate that was significantly different from that in the study group (90 percent, $p < 0.001$). The gestational age at delivery was significantly different between groups (38.1 weeks in the study group as compared to 39 weeks in the control group, $p < 0.001$). The study found no differences in the rates of cesarean delivery or shoulder dystocia, macrosomia, respiratory difficulties in the neonate, or neonatal intensive care admissions.

The significant limitation of this investigation is that the study and control groups by definition had different severity levels of disease (class A1 versus class A2). There were also significant differences in the racial composition (the study group was 70 percent Hispanic, versus 60 percent in the control group; $p < 0.01$) and parity in each group (18 percent were nulliparous in the study group, versus 31 percent in the control group, $p = 0.01$).[56]

Impact of elective cesarean delivery versus a trial of labor in patients with previous cesarean delivery. Marchiano conducted a retrospective cohort study to examine outcomes related to elective repeat cesarean delivery versus a trial of labor in a population of women with

gestational diabetes;[52] 423 women with class A1 gestational diabetes and singleton pregnancy who had undergone one previous cesarean delivery were included in the study.

The repeat cesarean delivery rate was 30 percent for those who attempted a trial of labor. The rate of macrosomia (defined as infant birth weight > 4,000 gm) for those who attempted a trial of labor was 18 percent, as compared to 33 percent for those who underwent elective cesarean ($p < 0.0001$) delivery. A sub-group analysis of women who attempted a trial of labor indicated a cesarean delivery rate of 43 percent for those whose infants weighed 4,000 gm or more, as compared to 28 percent for those with infants weighing less than 4,000 gm.

Although these results are relevant to the management of women with gestational diabetes, the results are only generalizable to those with prior cesarean delivery. Furthermore, the authors used actual infant birth weight rather than EFW in the analysis. Because EFW can vary from actual weight at delivery, it is difficult to draw useful conclusions from these results in terms of clinical decisionmaking for elective cesarean delivery versus an attempt at vaginal delivery.

Shoulder dystocia in patients with gestational diabetes. Keller 1991[54] performed a retrospective chart review of 210 patients with gestational diabetes from a tertiary care center in Chicago. Of the 210 patients, 173 underwent a trial of labor, 34 had elective repeat cesarean delivery, and 3 had an elective cesarean delivery for EFW greater than 4,000 gm (individual patient/provider decision). In those who underwent a trial of labor, the rate of cesarean delivery was 30.6 percent and the rate of forceps use was 4.6 percent. When birth weight categories were examined, the cesarean delivery rate was 33 percent in the greater than 4,500 gm group, 34 percent in the 4,000 to 4,499 gm group, and 29 percent in the 3,500 to 3,999 gm group.

The risk of shoulder dystocia in those patients who delivered vaginally was 12.5 percent overall and ranged from 9 percent in the lowest birth weight group to 14 percent in those weighing 4,000 to 4,499 gm and 38 percent in those infants weighing over 4,500 gm. Fractures and nerve injuries were rare (seven total) and were not related to birth weight category. The study also reported that the risk of shoulder dystocia in patients with class A1 gestational diabetes was not significantly different (OR = 0.78, 95 percent CI: 0.25 to 2.27) from that in patients with class A2 gestational diabetes.[54]

These findings by Keller offer a descriptive analysis of labor outcomes in women with gestational diabetes. Given the lack of a comparison group and any adjustment for confounders, as well as the limited sociodemographic and clinical information on the study sample, it is difficult to draw any reasonable conclusions from this study regarding labor management in women with gestational diabetes.

Quality assessment. We assessed the quality of the single RCT[55] identified for this review using the Jadad criteria.[22] The study reported pre-specified hypotheses, the inclusion criteria were clearly stated, power calculations were presented with effect sizes, the outcomes were clearly described, and adjustment was performed for several potential confounders. However, the methods for randomization, including sequence generation and assurance of allocation concealment, were not clearly described (see Appendix F, Evidence Table 13).

No observational studies met all of our quality criteria (see Appendix F, Evidence Table 13). Of the seven observational studies, only two had pre-specified hypotheses.[53 58] Of the eight studies, all but one[59] reported inclusion and/or exclusion criteria, and sampling was consecutive in all eight studies. Outcomes were not clearly defined in two of the studies.[56 57] Power calculations were only performed in two studies.[56 58] The analysis was adjusted for potential confounders in two studies.[52 56]

Limitations. Several limitations to these studies deserve further comment. First, there was heterogeneity in the severity of the gestational diabetes reported in the one RCT and four primary observational studies, making it difficult to assess the magnitude and direction of any association of the effect of gestational age or EFW with labor management. All four of the primary observational studies included women with gestational diabetes A1 and gestational diabetes A2, but only one reported outcomes stratified by insulin requirement.[57] Furthermore, the RCT[55] and one of the observational studies[53] included pre-gestational diabetics, even though this condition represented only a small proportion of the sample (less than 10 percent). The results of these studies might have varied substantially if the study population had been limited to women with gestational diabetes class A1 or A2 or if the outcomes were stratified by severity.

Second, the four primary observational studies were conducted over a wide timeframe. It is difficult to account for the rise in the prevalence of gestational diabetes during this timeframe or the modifications in physician practice patterns and obstetrical technology that have certainly influenced maternal and neonatal outcomes. For example, while the intention of the study by Peled[59] was to assess the impact of different management approaches over the 19-year period, it was impossible to discern the potential contribution of changes in glycemic target levels to delivery management over the four time periods.

Third, none of the four primary observational studies adjusted for potential confounders. Therefore, the magnitude of the associations between gestational age or EFW and outcomes may have been overestimated.

Fourth, the high rates of induction of labor in the expectant management group (49 percent) and of cesarean delivery in both groups in the RCT by Kjos et al[55] illustrate the low threshold for intervention in current practice for patients with diabetes. They also highlight the potential role of medical liability in the design of studies of labor management. Physicians' concerns regarding medical liability, provider perception of risk, and maternal demand for cesarean delivery may limit the ability to conduct well-designed clinical trials of labor management.

Conclusions

One experimental study in this field suggested that active induction of labor at 38 weeks of gestation reduces birth weight, macrosomia, and LGA without increasing the rate of cesarean section. It was difficult to fully assess these outcomes, however, on the basis of a single clinical trial of only 200 patients. The current body of observational studies also suggested a potential reduction in macrosomia and shoulder dystocia with elective labor induction and elective cesarean delivery for macrosomia or LGA infants. We systematically searched the literature for evidence that the choice of timing of induction or elective cesarean delivery resulted in beneficial or harmful maternal or neonatal outcomes, as described in detail in the Key Question. Given the substantial heterogeneity in the studies reviewed and the serious limitations in study design and analysis of the existing literature, we were unable to draw any firm conclusions about the role of elective induction or cesarean delivery in the management of gestational diabetes.

Taking into consideration the quantity, quality, and consistency of the studies comparing the effects of labor management on maternal and neonatal outcomes, we graded the strength of evidence as very low (see Appendix F, Evidence Table 14).

Key Question 3

What risk factors, including but not limited to family history, physical activity, pre-pregnancy weight, and gestational weight gain, are associated with short-term and long-term development of type 2 diabetes following a pregnancy with gestational diabetes?

Background and Conceptual Framework

We conducted our systematic review of this question according to the framework outlined in Figure 6. Our objective was to include a range of risk factors that incorporated sociodemographics and pre-pregnancy measures as well as antenatal and delivery factors in both the immediate and long-term postpartum periods. The risk factors included were based on (1) traditional, established epidemiologic and physiologic risk factors for type 2 diabetes and (2) risk factors identified in the literature during our initial review of titles and abstracts.

We identified a number of studies that examined the risk factors for type 2 diabetes among women with previous gestational diabetes. These studies varied widely in terms of their design, population, measurement of risk factors, and method of analysis. No single study included all the risk factors we enumerated. Although longitudinal studies and well-done case-control studies that use multiple regression methods provide the best evidence about the independent contribution of risk factors, we also included studies that used univariate analytic methods if they reported a relative measure of association.

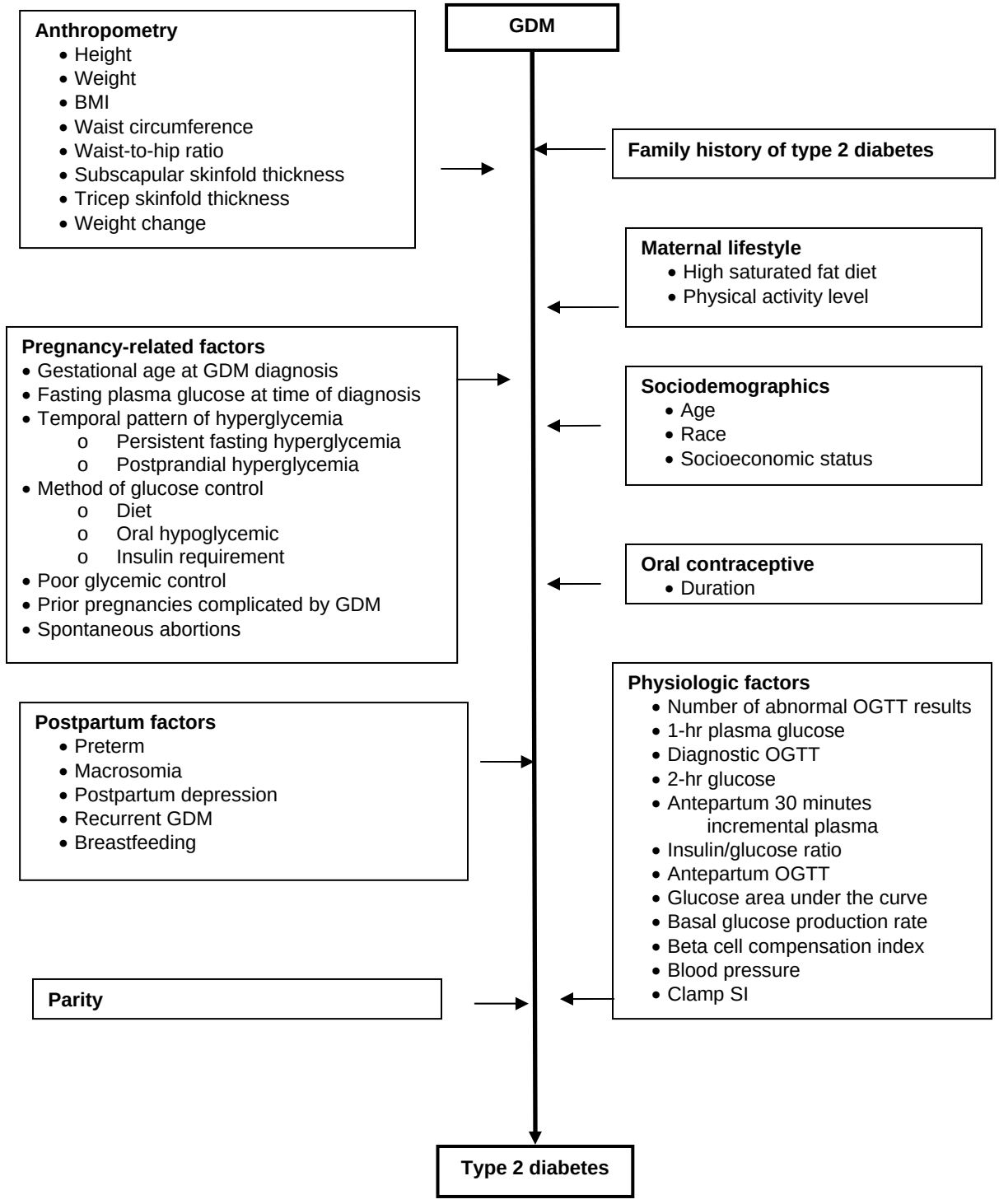
Based on our conceptual model in Figure 6, we grouped the risk factors into the following nine categories:

1. Anthropometry
2. Pregnancy-related factors
3. Postpartum factors
4. Parity
5. Family history of type 2 diabetes
6. Maternal lifestyle factors
7. Sociodemographics
8. Oral contraceptive use
9. Physiologic factors

Results

Overview and population characteristics of 16 observational studies of risk factors for the development of type 2 diabetes. We identified 16 prospective or retrospective/non-concurrent cohort studies that evaluated at least one risk factor in our categories (see Appendix F, Evidence Table 15). However, none of the studies addressed the lifestyle factors depicted in our conceptual model. The studies were conducted in diverse populations and included 10 studies in North America; three studies were conducted in Asia, two in Europe, and one in Australia. Patients were recruited from a hospital or hospital-based clinic in all cases. The followup time for the studies ranged from 6 weeks to 12 years (see Appendix F, Evidence Table 16).

Figure 6. Conceptual framework for Key Question 3 on risk factors for developing type 2 diabetes following a pregnancy with gestational diabetes mellitus



BMI = body mass index; GDM = gestational diabetes mellitus; hr = hour; OGTT = oral glucose tolerance test; SI = sensitivity index; type 2 diabetes = type 2 diabetes mellitus

The studies varied with respect to quality (see Appendix F, Evidence Table 17). All of the studies reported inclusion and exclusion criteria, and most stated how the outcome of type 2 diabetes was defined (93.3 percent). Most reported loss to followup (75 percent), with 75 percent of these having a loss to followup of greater than 20 percent. Comparisons between those participants who were successfully followed up and those who were lost to followup were reported in 33 percent of the studies. Only 50 percent of the studies stated pre-specified hypotheses. None of the studies reported power or sample size calculations or the strategy used to handle missing data.

Studies varied in terms of their reporting of the baseline characteristics of the participants. Fifty-six percent of the studies reported the racial makeup of the population, 75 percent reported parity status, and all of them reported the ages of the participants (see Appendix F, Evidence Table 16).

Family history of type 2 diabetes. We identified five studies that evaluated family history of type 2 diabetes as a risk factor for the development of type 2 diabetes in women with previous gestational diabetes (see Appendix F, Evidence Table 18).[60-64] The duration of followup for 102 to 909 participants ranged from 6 weeks to 8 years. All five studies conducted multivariate analyses, but only one study reported a relative measure of association.[61] Cho et al. reported that after adjusting for age, gestational age at diagnosis, pre-pregnancy BMI, FBG at diagnosis, and homocysteine level, women with a family history of type 2 diabetes were more likely to develop type 2 diabetes than were women without such a history (RR = 1.7; 95 percent CI: 0.6 to 4.6), but the relative risk was not statistically significant. Because of the limited data, we were unable to draw firm conclusions regarding the magnitude of the association between a family history of diabetes and the risk of type 2 diabetes in women with gestational diabetes.

Sociodemographics. We identified six studies that evaluated a total of four sociodemographic factors as risk factors for the development of type 2 diabetes in women with previous gestational diabetes (see Appendix F, Evidence Table 19).[60-63 65 66] The four sociodemographic factors examined were age, race, working status, and hospital. The duration of followup for the six samples of 100 to 909 participants ranged from 6 weeks to 11 years.

Age. Six studies[60-63 65 66] assessed age as a risk factor; five of the six studies used multivariate analysis.[60-63 66] Only one study reported the relative measure of association resulting from the multivariate analysis: Cho et al. reported that after adjustment for gestational age at the time of diagnosis, pre-pregnancy BMI, family history of type 2 diabetes, FBG at diagnosis, and homocysteine level, women greater than 30 years of age had a two-fold increased likelihood of developing type 2 diabetes (RR = 2.0; 95 percent CI: 0.68 to 6.0), but this association was not statistically significant, as evidenced by the 95 percent CI that included one.[61] In one univariate analysis, Dacus et al. observed that older age did not appear to be associated with the risk of type 2 diabetes (RR = 0.68; 95 percent CI: 0.24 to 1.9).[65]

Hospital location. Cheung et al. were able to evaluate the hospital attended for antenatal clinic visits as a risk factor for the development of type 2 diabetes in women with previous gestational diabetes, since they had recruited women from two hospitals.[60] Although they included age, parity, FBG at gestational diabetes diagnosis, BMI during pregnancy, 2-hr OGTT, number of prior gestational diabetes pregnancies, method of glucose control, and family history of type 2 diabetes, these investigators did not report a relative measure of association for the hospital attended and type of diabetes.

Work status. Cho et al. evaluated working status as a risk factor for the development of type 2 diabetes in eight multivariate models, including age, parity, family history of type 2 diabetes,

working status, blood pressure, lipid profile, and one of eight measures of adiposity (postpartum BMI, waist circumference, weight, subscapular skin fold thickness, suprailiac skin fold thickness, tricep skin fold thickness, body fat weight, or waist-to-hip ratio).[62] However, the relative measure of association was not reported for the association between working status and development of type 2 diabetes for any of the eight models.

Race. In a univariate analysis, Dacus et al. evaluated race as a risk factor for the development of type 2 diabetes in women with previous gestational diabetes. They reported that as compared to other race groups, blacks had a 50 percent increased risk of developing type 2 diabetes, but this association was not statistically significant (RR = 1.5; 95 percent CI: 0.45 to 5.0).[65]

We concluded that there are only limited data on which to base any meaningful conclusions regarding sociodemographic factors and the short- or long-term risk of type 2 diabetes among women with gestational diabetes.

Maternal lifestyle factors. We did not identify any studies that examined the relationship between lifestyle factors, such as physical activity and diet, and the development of type 2 diabetes in women with prior gestational diabetes. We therefore concluded that no evidence exists to determine whether maternal lifestyle affects the risk of developing type 2 diabetes after having gestational diabetes.

Parity. We identified four studies that evaluated parity as a risk factor for the development of type 2 diabetes in women with previous gestational diabetes (see Appendix F, Evidence Table 20).[60 62 66 67] The duration of followup for the samples of 102 to 909 participants ranged from 6 weeks to 11 years. All four studies conducted multivariate analyses, but only two studies reported a relative measure of association for parity with type 2 diabetes.[66 67] After adjustment for GAD and insulinoma antigen-2 (IA-2) antibody status, method of glucose control, BMI, age, and serum C-reactive protein (CRP) at 9 months, Lobner et al. found that compared to gestational diabetics who were nulliparous, gestational diabetics with more than two previous births had an almost three-fold increased risk of developing type 2 diabetes (relative hazard [RH] = 2.5; 95 percent CI: 1.1 to 5.3).[66] There was a 20 percent increased risk of developing type 2 diabetes associated with having had one to two previous births, as compared to nulliparity, but this association was not statistically significant (RH = 1.2; 95 percent CI: 0.8 to 1.7).[66] Metzger et al. evaluated parity as a continuous variable and reported that for each unit increase in parity, there was no statistically significant change in the log odds of developing type 2 diabetes (β = 0.19; p = 0.09).[67] We concluded that higher parity may be associated with an increased risk for type 2 diabetes among women with gestational diabetes, but further evidence is needed to draw firm conclusions regarding this potential association.

Pregnancy-related factors. We identified nine studies that evaluated seven pregnancy-related factors as risk factors for the development of type 2 diabetes in women with previous gestational diabetes (see Appendix F, Evidence Table 21).[60 61 63 65 66 68-71] These factors were: gestational age at diagnosis, method of glucose control, dosage of bedtime intermediate-acting insulin required, class A2 gestational diabetes (defined as any FBG $\geq$ 105 mg/dL), previous gestational diabetes, number of prior gestational diabetes pregnancies, 50-gm glucose challenge test (GCT), and spontaneous abortions. The duration of followup for the 88 to 1,636 participants ranged from 6 weeks to 12 years.

Gestational age at diagnosis of gestational diabetes. Five studies[61 63 65 68 70] assessed gestational age at diagnosis of gestational diabetes as a risk factor, and four of the five studies used multivariate analysis.[61 63 68 70] The studies varied in terms of their categorization of gestational age at gestational diabetes diagnosis: Two studies divided gestational age at

gestational diabetes diagnosis into quartiles and used the first quartile as the reference:[68 70] Both Kjos et al.[68] and Schaefer-Graf et al.[70] reported a protective effect of gestational age at gestational diabetes diagnosis in the fourth quartile as compared to gestational age at gestational diabetes diagnosis in the first quartile, with the effect ranging from a 52 percent to a 65 percent reduction in the likelihood of developing type 2 diabetes (RH = 0.48; 95 percent CI: 0.29 to 0.82; and OR = 0.35; 95 percent CI: 0.23 to 0.54) respectively. Both studies varied with respect to the covariates included in the multivariate model, and they did not share any common covariates. Schaefer-Graf et al.[70] included FBG at gestational diabetes diagnosis, class A2 gestational diabetes, area under the glucose curve of pregnancy OGTT, previous gestational diabetes and 50-gm GCT, while Kjos et al.[68] included postpartum OGTT glucose area under the curve, antepartum OGTT glucose area under the curve, and highest antepartum FBG. When third-quartile gestational age at gestational diabetes diagnosis was compared to the first quartile, a smaller protective effect was observed in both studies. Schaefer-Graf et al. reported a 55 percent reduction in the likelihood of developing type 2 diabetes (OR = 0.45; 95 percent CI: 0.27 to 0.76).[70] Kjos et al. reported a 27 percent reduction in the likelihood of developing diabetes, but this association was not statistically significant (RH = 0.73; 95 percent CI: 0.45 to 1.2).[68] For both studies, when second-quartile gestational age at gestational diabetes diagnosis was compared to the first quartile, no significant difference in the development of type 2 diabetes was found (Schaefer-Graf et al., OR = 1.1; 95 percent CI: 0.72 to 1.7; and Kjos et al., RH = 0.66; 95 percent CI: 0.39 – 1.1).

Cho et al. categorized gestational age at gestational diabetes diagnosis into two groups, women who were diagnosed with gestational diabetes at greater than or equal to 26 weeks and women who were diagnosed at less than 26 weeks. There was no significant difference in the development of type 2 diabetes between the two groups after adjusting for age, pre-pregnancy BMI, family history of type 2 diabetes, FBG at diagnosis, and homocysteine level (RR = 2.4; 95 percent CI: 0.88 to 6.6).[61]

Jang et al. assessed gestational age at gestational diabetes diagnosis as a continuous variable and found that for each week of increase in gestational age at gestational diabetes diagnosis, there was a 0.01 decrease in the log odds of developing type 2 diabetes (β = -0.01; SE = 0.05; p = 0.008).[63]

In a univariate analysis, Dacus et al. categorized gestational age at gestational diabetes diagnosis into two groups, comparing women who were diagnosed with gestational diabetes at less than 24 weeks and those diagnosed with gestational diabetes greater than or equal to 24 weeks. No significant difference was observed between the two groups in terms of the development of type 2 diabetes (RR = 2.5; 95 percent CI: 0.9 to 6.9).[65]

Method of glucose control. Five studies evaluated the method of glucose control during pregnancy as a risk factor for the development of type 2 diabetes.[60 65 66 69 71] Three of these studies[60 66 69] included a multivariate analysis, but only two of them[60 66] reported a relative measure of association for this risk factor. These two studies varied considerably. Cheung et al. found that as compared to women who did not use insulin, those that did use insulin during pregnancy had a three-fold higher risk of developing type 2 diabetes after adjusting for age, parity, FBG at diagnosis, BMI at index pregnancy, 2-hr OGTT, number of prior pregnancies complicated by gestational diabetes, family history of type 2 diabetes, and hospital location (RR = 3.2; 95 percent CI: 1.6 to 7.0).[60] Lobner et al. reported that as compared to women who were diet-controlled, women who received insulin during pregnancy had an almost five-fold increased risk of developing type 2 diabetes after adjustment for age, parity, GAD and IA-2 antibody

status, BMI during pregnancy, and serum CRP (RH = 4.7; 95 percent CI: 3.2 to 7.1; p < 0.0001).[66]

Two studies included a univariate analysis, but only Steinhart et al. reported a relative measure of association for the method of glucose control. This study reported an almost three-fold increased likelihood of developing type 2 diabetes in women requiring insulin as compared to those not on insulin, but this association was not statistically significant (OR = 2.8; 95 percent CI: 0.8 to 11.2).[71]

One study by Cheung et al. examined the required dosage of bedtime intermediate-acting insulin as a risk factor. For each unit (unspecified) increase in dosage, there was a 9 percent increased likelihood of developing type 2 diabetes after adjustment for FBG (RR = 1.1; 95 percent CI: 1.0 to 1.2).[60] The clinical relevance of this finding, however, is unclear, given that it is based on data from one study and is of borderline statistical significance.

50-gm GCT. The 50-gm GCT is routinely performed during pregnancy as the baseline screening test for gestational diabetes. Only one study evaluated the results of the 50-gm GCT performed during pregnancy as a risk factor for the development of type 2 diabetes.[70] Schaefer-Graf et al. categorized the GCT results into quartiles, using the first quartile as the reference. They reported that as compared to women with 50-gm GCT results in the first quartile, women with results in the second, third, and fourth quartiles had an increasingly higher risk of developing type 2 diabetes (OR = 2.9; 95 percent CI: 1.2 to 6.6; OR = 3.8; 95 percent CI: 1.7 to 8.5; and OR = 3.5; 95 percent CI: 1.6 to 7.6 for the second, third, and fourth quartiles, respectively), after adjusting for FBG at diagnosis, class A2 gestational diabetes, area under the glucose challenge curve of pregnancy OGTT, gestational age at diagnosis of gestational diabetes, and previous pregnancy complicated by gestational diabetes.

Class A-2 (insulin-requiring gestational diabetes). One study evaluated class A2 gestational diabetes, defined as requiring insulin therapy because of FBG levels greater than or equal to 105 mg/dL, as a risk factor for the development of type 2 diabetes.[70] Schaefer-Graf et al. reported that as compared to women with gestational diabetes class A1, women with gestational diabetes class A2 were 2.4 times more likely to develop type 2 diabetes, after adjusting for FBG at diagnosis, 50-gm GCT, area under the curve for a pregnancy OGTT, gestational age at diagnosis of gestational diabetes, and previous pregnancy complicated by gestational diabetes (OR = 2.4; 95 percent CI: 1.2 to 4.7).

Previous pregnancies complicated by gestational diabetes. Two studies evaluated previous pregnancies complicated by gestational diabetes as a risk factor for the development of type 2 diabetes.[60 70] These studies included multivariate analysis, but only one study reported a relative measure of association for this risk factor.[70] Schaefer-Graf et al. reported that as compared to women without a previous pregnancy complicated by gestational diabetes, those with a such a pregnancy were 60 percent more likely to develop type 2 diabetes, after adjusting for FBG at diagnosis, 50-gm GCT, area under the glucose challenge curve of pregnancy OGTT, gestational age at gestational diabetes diagnosis, and previous pregnancy complicated by gestational diabetes (OR = 1.6; 95 percent CI: 1.1 to 2.5).

Spontaneous abortion. One study that included a univariate analysis examined spontaneous abortion as a risk factor for the development of type 2 diabetes in women with previous gestational diabetes.[71] Steinhart et al. reported that as compared to women without spontaneous abortions, those with spontaneous abortions were 36 percent more likely to develop type 2 diabetes, but this association was not statistically significant (OR = 1.4; 95 percent CI: 0.5 to 3.5).

We concluded that the overall grade of evidence for pregnancy-related factors was moderate.

Postpartum factors. We identified five studies that evaluated a total of four postpartum factors as risk factors for the development of type 2 diabetes in women with previous gestational diabetes (see Appendix F, Evidence Table 22).[62 64 69 71 72] The four postpartum factors examined were additional pregnancy, breastfeeding, duration of followup, and recurrent gestational diabetes. Duration of followup for the 88 to 909 participants ranged from 6 weeks to 12 years.

Additional pregnancy. Two studies assessed additional pregnancy as a risk factor for the development of type 2 diabetes in women with previous gestational diabetes, and both used multivariate analysis.[69 72] However, only one study reported a relative measure of association for this risk factor.[72] After adjusting for postpartum weight change (per 10 pounds), OGTT glucose area, postpartum BMI, and breastfeeding, Peters et al. found that as compared to women with no additional pregnancy, those with an additional pregnancy had a three-fold increased risk of developing type 2 diabetes (RH = 3.3; 95 percent CI: 1.8 to 6.2).[72]

Breastfeeding. Two studies assessed breastfeeding as a risk factor for the development of type 2 diabetes, and both constructed multivariate models.[64 72] However, neither of these studies reported relative measures of association for this risk factor.

Duration of followup. One study evaluated the duration of followup as a risk factor for the development of type 2 diabetes in women with previous gestational diabetes and constructed eight multivariate models, involving age, parity, family history of type 2 diabetes, working status, blood pressure, lipid profile, and one of eight measures of adiposity (postpartum BMI, waist circumference, weight, subscapular skin fold thickness, suprailiac skin fold thickness, tricep skin fold thickness, body fat weight, or waist-to-hip ratio).[62] However, the relative measure of association was not reported for the association between duration of followup and development of type 2 diabetes for any of the eight models.

Recurrent gestational diabetes. One study evaluated recurrent gestational diabetes as a risk factor for the development of type 2 diabetes in women with previous gestational diabetes and conducted a univariate analysis.[71] Steinhart et al. reported that as compared to women without recurrent gestational diabetes, those with recurrent gestational diabetes had a 24-fold increased risk of developing type 2 diabetes (OR = 24.8; 95 percent CI: 3.0 to 1132.2). The width of this confidence interval, however, suggests substantial variability in the point estimate and makes it impossible for us to draw any firm conclusions from these data.

We concluded that the overall grade of the evidence for postpartum factors was very low.

Measures of anthropometry. We identified 11 cohort studies that evaluated a total of 11 different anthropometric measures: weight, height, BMI, body fat weight, subscapular skin fold thickness, suprailiac skin fold thickness, tricep skin fold thickness, waist circumference, waist-to-hip ratio, percent ideal body weight, and weight change (see Appendix F, Evidence Table 23).[60-67 69 72 73] The number of participants ranged from 170[61] to 909.[62] Followup of participants ranged from 6 weeks to 12 years. Of the 11 studies, 9 reported a relative measure of association.[60-63 65-67 72 73] Eight studies [60-63 66 67 72 73] reported an adjusted relative measure of association. We have included these adjusted relative measures in Figure 7. One study reported an unadjusted relative measure from a univariate model.[65] The studies varied in terms of the time period in which the assessment of anthropometry was conducted.

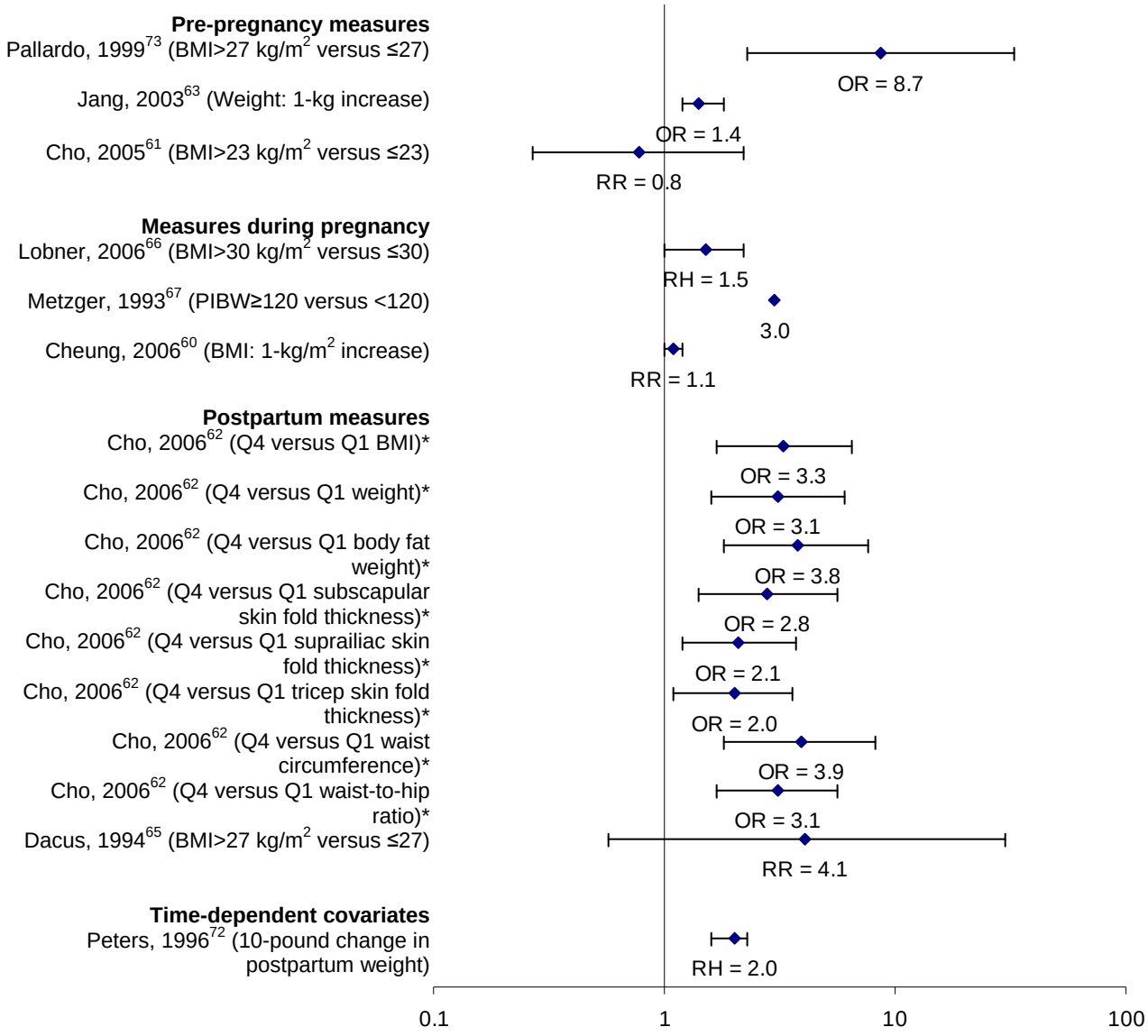
Of the 11 studies, three used pre-pregnancy measures of obesity.[61 63 73] Two of these studies reported a significant positive association between pre-pregnancy anthropometric measures and the development of type 2 diabetes.[63 73] One study reported a protective effect of a higher anthropometric measure,[61] and one study did not report the measure of association.[63] Pallardo et

al. found that as compared to women with a pre-pregnancy BMI less than or equal to 27 kg/m^2, women with a BMI greater than 27 kg/m^2 had an eight-fold increased risk of developing type 2 diabetes, after adjusting for the number of abnormal glucose results from the OGTT and C-peptide glucose score (OR = 8.7; 95 percent CI: 2.3 to 32.9).[73] Jang et al. reported that for every 1-kg increase in pre-pregnancy weight, there was a 0.36 increase in the log odds of developing type 2 diabetes, although this relationship was not statistically significant (β = 0.36, SE = 0.10).[63] One study[61] reported a reduction in the likelihood of type 2 diabetes with higher BMI: Cho et al.[61] reported that as compared to women with a pre-pregnancy BMI less than or equal to 23 kg/m^2, women with a pre-pregnancy BMI greater than 23 kg/m^2 were less likely (RR = 0.78; 95 percent CI: 0.27 to 2.2) to develop type 2 diabetes, after adjusting for age, gestational age at diagnosis of gestational diabetes, family history of type 2 diabetes, FBG at diagnosis, and homocysteine level. This reported association, however, was not statistically significant. We concluded that pre-pregnancy measures of obesity are associated with an increased likelihood of type 2 diabetes.

Three of the 11 studies used anthropometric measures during pregnancy. These studies reported a positive association between anthropometric measures and the development of type 2 diabetes.[60 66 67] For example, Lobner et al. reported that women with a BMI greater than 30 kg/m^2 were 50 percent more likely to develop type 2 diabetes than were women with a BMI less than 30 kg/m^2, after adjusting for GAD and IA-2 antibody status, method of glucose control, parity, age, and serum CRP at 9 months (RH = 1.5; 95 percent CI: 1.0 to 2.2).[66] In addition, Metzger et al. reported that as compared to women who were non-obese (<120 percent ideal body weight), women who were obese ($\geq$ 120 percent ideal body weight) had an almost three-fold increased likelihood of developing type 2 diabetes, after adjusting for 3-hr integrated insulin level and parity.[67] For each kg/m^2 increase in BMI, Cheung et al. reported a 10 percent increase in the risk of developing type 2 diabetes (relative risk [RR] = 1.1; 95 percent CI: 1.0 to 1.2), after adjusting for age, parity, FBG at diagnosis, 2-hr OGTT, the number of prior pregnancies complicated by gestational diabetes, method of glucose control, family history of type 2 diabetes, and hospital location.[60]

Five studies[62-65 72]evaluated anthropometric measures assessed during the postpartum period, but only four studies[62 64 65 72] reported a relative measure of association. As shown in Figure 7, Cho et al. assessed eight anthropometric measures, comparing women in the highest quartile to those in the lowest quartile.[62] Each of the eight measures was positively associated with the development of type 2 diabetes, after adjusting for age, duration of followup, parity, family history of type 2 diabetes, working status, blood pressure, and lipid profile, including triglycerides, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol. As compared to women in the lowest quartile of postpartum BMI and weight, women in the highest quartile had a three-fold increased likelihood (OR = 3.3; 95 percent CI: 1.7 to 6.5 and OR = 3.1; 95 percent CI: 1.6 to 6.0, respectively) of developing type 2 diabetes. In the same sample, Cho et al. reported that women in the highest quartile were 3.8 times more likely to develop type 2 diabetes (OR = 3.8; 95 percent CI: 1.8 to 7.6) than were women in the lowest quartile of body fat weight. The direction and magnitude of the association with type 2 diabetes were similar across several additional anthropometric measures. As compared to women in the lowest quartile, women in the highest quartile of (1) subscapular skin fold thickness, (2) suprailiac skin fold thickness, and (3) tricep skin fold thickness had a 2.0- to 2.8-fold higher likelihood of developing type 2 diabetes. Women in the highest quartile were over two times

Figure 7. Summary of reported measures of association between anthropometric measures and the risk of developing type 2 diabetes following a pregnancy with gestational diabetes mellitus



* Comparison is between the highest and the lowest quartile.

BMI = body mass index; kg = kilograms; m = meters; OR = odds ratio; PIBW = percent of ideal body weight; Q = quartile; RH = relative hazard; RR = relative risk

more likely to develop type 2 diabetes (OR = 2.8; 95 percent CI: 1.4 to 5.6; OR = 2.1; 95 percent CI: 1.2 to 3.7; and OR = 2.0; 95 percent CI: 1.1 to 3.6, respectively). Also, Cho et al. reported that as compared to women in the lowest quartile of waist circumference and waist-to-hip ratio, women in the highest quartile were over three times as likely to develop type 2 diabetes (OR = 3.9; 95 percent CI: 1.8 to 8.2 and OR = 3.1; 95 percent CI: 1.7 to 5.6, respectively). Two additional studies (Peters et al. and Xiang et al.) assessed postpartum BMI[64 72] and postpartum weight[64] in multivariate models but did not report the measure of association. In an unadjusted analysis, Dacus et al. reported a four-fold increased risk (RR = 4.1; 95 percent CI: 0.6 – 29.8) in

the development of type 2 diabetes in women with a BMI of 27 kg/m^2 or greater as compared to women with a BMI of less than 27 kg/m^2, but this difference was not statistically significant.[65]

Three studies evaluated anthropometric measures as time-dependent covariates, assessing the association of the change in these measures between delivery and followup with type 2 diabetes.[64 69 72] Peters et al. showed that for every 10-pound change in weight, there was a 95 percent increase in the risk of developing type 2 diabetes, after adjusting for additional pregnancy, OGTT glucose area, postpartum BMI, and breastfeeding (RH = 2.0; 95 percent CI: 1.6 to 2.3).[72] Although Kjos et al. and Xiang et al. included weight change in their multivariate analyses, the relative association of weight change with type 2 diabetes was not reported.[64 69] Height was examined in one study, but the measure of association from the multivariate model was not reported.[63] Because of multiple cohort studies and measures of association, we graded the overall evidence for anthropometric measures as moderate.

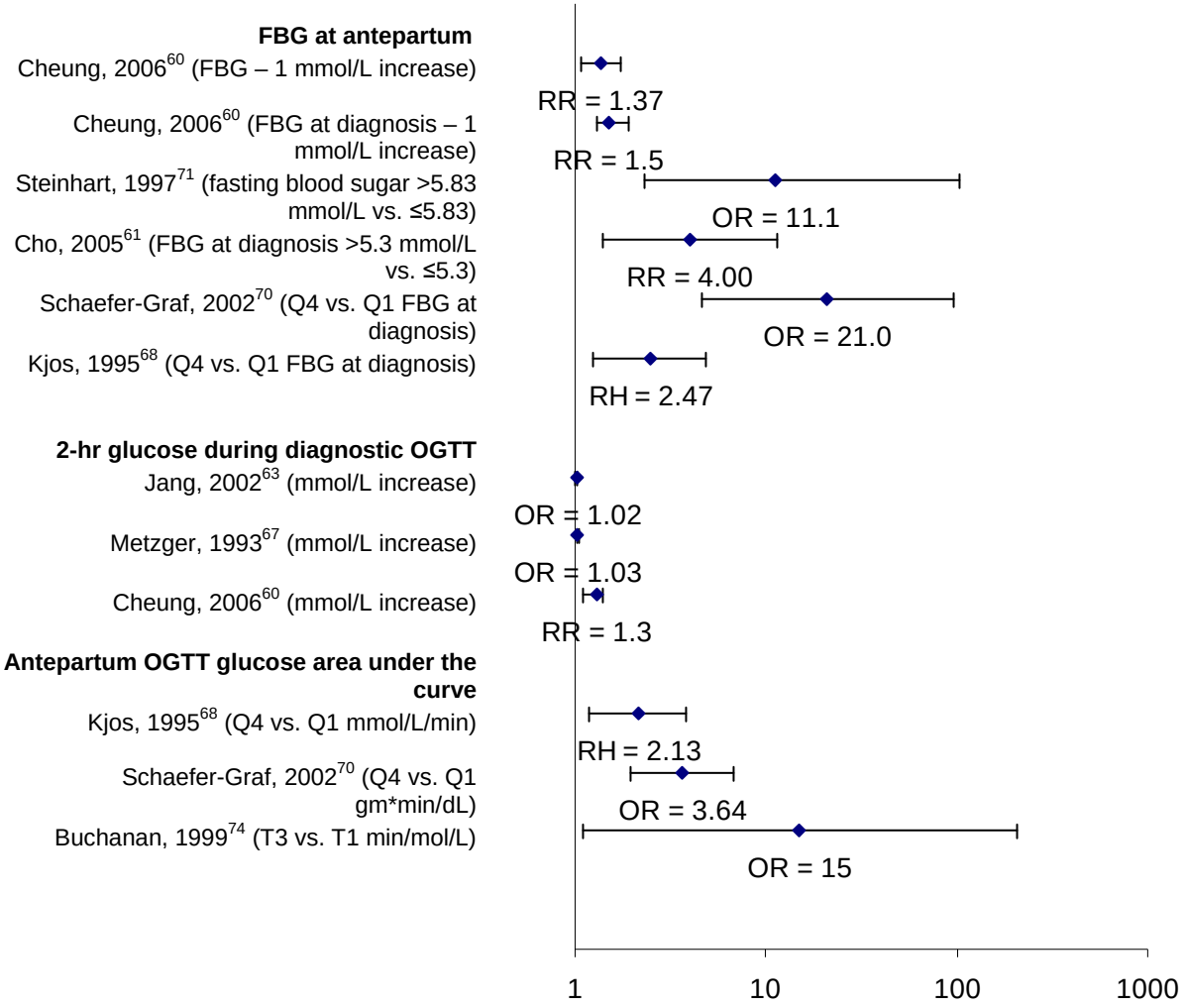
Oral contraceptive use. Two studies evaluated oral contraceptive use and the risk of type 2 diabetes in women with a prior history of gestational diabetes (see Appendix F, Evidence Table 24).[64 69] Kjos et al. found that as compared to women using a combination oral contraceptive pill, those using a progestin-only pill had a greater than two-fold increased risk of developing type 2 diabetes, following adjustment for the area under the postpartum glucose tolerance test curve, prior oral contraceptive use, method of glucose control, completion of a second pregnancy, postpartum weight loss, and duration of oral contraceptive use (RH = 2.9; 95 percent CI: 1.6 to 5.3).[69] In that same study, duration of oral contraceptive use was also a significant predictor of type 2 diabetes risk. Women using oral contraceptives for 4 to 8 months and more than 8 months had, respectively, a three-fold (RH = 3.0; 95 percent CI: 1.4 to 6.5) and nearly five-fold (RH = 4.9; 95 percent CI: 1.8 to 13.7) increased risk of developing type 2 diabetes when compared to those with lower-duration use, following multivariable adjustment for the same variables.[69]

Xiang et al. did not find that progesterone-based contraceptives were consistently associated with an increased risk of type 2 diabetes. As compared to women who used combination oral contraceptives, those using depo-medroxyprogesterone acetate did not have an increased risk of type 2 diabetes in the entire cohort, after adjusting for postpartum BMI, breastfeeding, family history of type 2 diabetes, HDL cholesterol, triglycerides, and weight gain during followup (RH = 1.1; 95 percent CI: 0.6 to 1.9).[64] This association did not differ by breastfeeding status.[64] However, after adjusting for postpartum BMI, family history of type 2 diabetes, breastfeeding, HDL cholesterol, and weight gain during followup, use of depo-medroxyprogesterone acetate in women with triglycerides above the median of the population was associated with a two-fold greater risk of developing type 2 diabetes when compared to the use of a combination oral contraceptive and triglyceride levels below the population median (RH = 2.3; 95 percent CI: 1.1 to 4.8).[64] We concluded that the limited number of studies available and the overall very low grade of evidence made it difficult to draw any firm conclusions regarding the relationship between progestin-only contraception and the development of type 2 diabetes among women with gestational diabetes.

Metabolic risk factors.

FBG: antepartum. Five studies examined antepartum FBG at gestational diabetes diagnosis as a risk factor, and in all of these studies, FBG was a significant predictor of type 2 diabetes (see Figure 8 and Appendix F, Evidence Table 25).[60 61 68 70 71] Cheung et al. found that each increasing mmol/L increment in FBG was associated with a 37 percent increase in the risk of type 2 diabetes, after adjustment for the dose of bedtime intermediate-acting insulin (RR = 1.4; 95 percent CI: 1.1 to 1.7).[60] In that same study, FBG at diagnosis was associated with a 1.5-fold

Figure 8. Summary of selected reported measures of association between measures of metabolic risk factors and the risk of developing type 2 diabetes following a pregnancy with gestational diabetes mellitus



dL = deciliter; FBG = fasting blood glucose; gm = gram; hr = hour; L = liter; min = minute; mmol = millimole; OGTT = oral glucose tolerance test; Q = quartile; T = tertile

increased risk of type 2 diabetes, after adjusting for age, parity, BMI at the index pregnancy, 2-hr OGTT result, number of prior pregnancies, method of glucose control, family history of type 2 diabetes, and hospital (RR = 1.5; 95 percent CI: 1.3 to 1.9).[60]

In unadjusted analyses, Steinhart et al. found that as compared to women with an FBG less than or equal to 5.83 mmol/L, those with an FBG greater than 5.83 mmol/L had an 11-fold increased risk of developing type 2 diabetes (OR = 11.1; 95 percent CI: 2.3 to 103.4).[71] Cho et al. found that women with an FBG greater than 5.3 mmol/L had a four-fold increased risk of developing type 2 diabetes, after adjusting for age, gestational age at gestational diabetes diagnosis, pre-pregnancy BMI, family history of type 2 diabetes, and homocysteine level (RR = 4.0; 95 percent CI: 1.4 to 11.4).[61] In another study, Schaefer-Graf et al. found an increased risk of type 2 diabetes with increasing quartiles of FBG, such that women in the highest quartile had a 21-fold increased risk of developing type 2 diabetes when compared to those in the lowest quartile (OR = 21.0; 95 percent CI: 4.6 to 96.3).[70] Finally, Kjos et al. also found an increased risk of type 2 diabetes with increasing tertiles of FBG, with women in the highest tertile having a

greater than two-fold increased risk when compared to those in the lowest tertile, after adjusting for postpartum OGTT glucose area under the curve, gestational age at gestational diabetes diagnosis, and antepartum OGTT glucose area under the curve (RH = 2.5; 95 percent CI: 1.3 to 4.9).[68]

Characteristics of the OGTT.

Antepartum OGTT results.

Number of abnormal OGTT results. One study examined the number of abnormal OGTT results as a risk factor for subsequent development of type 2 diabetes.[73] In this study, there was a three-fold increased risk of type 2 diabetes with each increase in the number of abnormal OGTT results, after adjusting for pre-pregnancy BMI and C-peptide glucose score (OR = 3.0; 95 percent CI: 1.4 to 6.4).[73]

Glucose tolerance test total. One study examined the OGTT total as a risk factor for type 2 diabetes. As compared to women with OGTT totals less than or equal to 41.63 mmol/L, those with a GTT total greater than 41.63 mmol/L had a 15-fold greater risk of developing type 2 diabetes (OR = 15.5; 95 percent CI: 2 to 678).[71]

1-hr glucose during the diagnostic OGTT. One study examined the 1-hr glucose level during the diagnostic OGTT as a risk factor for the development of type 2 diabetes.[74] Buchanan et al. found that as compared to women with the lowest tertile of 1-hr plasma glucose during the diagnostic OGTT, women in the highest tertile had a 15-fold greater risk of developing type 2 diabetes, after adjusting for beta-cell compensation index and basal production rate (OR = 15.2; 95 percent CI: 1.4 to 166.3), and a 22-fold higher risk of developing type 2 diabetes, after adjusting for the OGTT 30-min incremental insulin:glucose ratio, basal glucose production rate, and insulin sensitivity index (OR = 22; 95 percent CI: 1.5 to 328.5).[74]

2-hr glucose during the diagnostic OGTT. Three studies evaluated the 2-hr glucose level during the OGTT as a risk factor for subsequent development of type 2 diabetes and found it to be a significant predictor in multivariate analyses (see Figure 8).[60 63 67] Jang et al. found that for every 1-point increase in 2-hr glucose level, there was a 2 percent increased risk of developing type 2 diabetes (OR = 1.02; 95 percent CI: 1.00 to 1.03; p = 0.04), after adjusting for pre-pregnancy weight, gestational age at gestational diabetes diagnosis, 3-hour insulin level on the diagnostic OGTT, age, height, pre-pregnancy BMI, family history of type 2 diabetes, and postpartum weight.[63] Metzger et al. found a similar association after adjusting for 30-minute stimulated insulin secretion on the OGTT and basal insulin (OR = 1.03; 95 percent CI: 1.01 to 1.04).[67] Cheung et al. found a stronger association, in that there was a 30 percent increased risk of developing type 2 diabetes for each 1-point increase in the 2-hr glucose level during the OGTT, after adjusting for age, parity, FBG at gestational diabetes diagnosis, BMI at the index pregnancy, number of prior gestational diabetic pregnancies, method of glucose control during the index pregnancy, family history of type 2 diabetes, and hospital (RR = 1.3; 95 percent CI: 1.1 to 1.4).[60]

3-hr insulin level during the diagnostic OGTT. One study[63] examined 3-hr insulin levels and found an inverse association between the insulin level and the risk of developing type 2 diabetes, after adjusting for pre-pregnancy weight, gestational age at gestational diabetes diagnosis, 2-hr glucose level, age, height, pre-pregnancy BMI, family history of type 2 diabetes, and weight at postpartum testing. A second study measured 3-hr integrated insulin levels and found no association with the development of type 2 diabetes.

30-minute incremental insulin:glucose ratio. Two studies examined the 30-min incremental insulin:glucose ratio from the antepartum OGTT.[74 75] Both studies found it to be a predictor of

type 2 diabetes. One study showed a non-significant 90 percent lower risk of type 2 diabetes in the highest versus the lowest tertile, after adjusting for incremental glucose area, diagnostic OGTT, frequently sampled intravenous glucose tolerance acute insulin response, basal glucose production rate, and insulin sensitivity index (OR = 0.1; 95 percent CI: 0.01 to 2.2), and a 92 percent lower risk after adjusting for 1-hr plasma glucose level during the diagnostic OGTT, basal glucose production rate, and insulin sensitivity index (OR = 0.08; 95 percent CI; 0.01 to 1.1).[74]

Antepartum OGTT glucose area under the curve. Five studies examined the antepartum OGTT glucose area under the curve and the subsequent risk of type 2 diabetes (see Figure 8).[68 70 72 74 75] Kjos et al. found a graded association between the glucose area under the curve and the risk of type 2 diabetes. As compared to those in the lowest quartile, those in the highest quartile had a two-fold increased risk, after adjusting for postpartum OGTT glucose area under the curve, gestational age at gestational diabetes diagnosis, and highest antepartum fasting glucose (RH = 2.1; 95 percent CI: 1.2 to 3.9).[68] Similarly, Schaefer-Graf et al. found that women in the highest quartile of glucose area under the curve had a significantly increased risk of type 2 diabetes when compared to those in the lowest quartile, after adjusting for FBG at diagnosis, diabetes pregnancy class, gestational age at gestational diabetes diagnosis, previous gestational diabetes, and results of the 50-gm GCT (OR = 3.6; 95 percent CI: 1.9 to 6.8).[70] Buchanan et al. also found that the OGTT glucose area under the curve was a significant predictor of type 2 diabetes, after adjusting for the antepartum 30-min incremental plasma insulin:glucose ratio.[75] In another study, they also found that women in the highest tertile of incremental area under the glucose curve had a 15-fold increased risk of type 2 diabetes when compared to women in the lowest tertile, after adjusting for frequently sampled intravenous glucose tolerance acute insulin response, OGTT 30-min incremental insulin:glucose ratio, basal glucose production rate, and insulin sensitivity index (OR = 15; 95 percent CI: 1.1 to 207.9).[74]

We concluded that increasing FBS or 2-hr glucose values on the diagnostic OGTT may indicate a higher likelihood of development of type 2 diabetes in women with gestational diabetes.

Postpartum OGTT results.

Area under the curve for postpartum OGTT. Two studies by the same author examined the postpartum OGTT area under the glucose curve and the risk of developing type 2 diabetes.[68 69] In the one study in which measures of association were reported, the risk of type 2 diabetes increased with increasing quartiles of postpartum OGTT area under the glucose curve (p-value for trend < 0.0001), after adjusting for gestational age at gestational diabetes diagnosis, antepartum OGTT glucose area under the curve, and highest antepartum fasting glucose.[68] As compared to those in the lowest quartile, those in the highest quartile had an 11-fold increased risk of type 2 diabetes (RH = 11.5; 95 percent CI: 4.5 to 29.1).[68]

We graded the overall body of evidence for metabolic risk factors as moderate. There was consistency in the association of 2-hr PPG and Antepartum OGTT glucose area under the curve.

Additional measures of glucose metabolism. One study by Buchanan et al. examined several additional measures of glucose metabolism as risk factors for type 2 diabetes, including basal glucose production rate, beta-cell compensation index, clamp insulin sensitivity, and frequently sampled intravenous glucose tolerance acute insulin response.[74] A higher basal glucose production rate was associated with a non-significantly increased risk of type 2 diabetes in several multivariable models that included: (1) incremental glucose area on the diagnostic OGTT, frequently sampled intravenous glucose tolerance acute insulin response, OGTT 30-min

incremental insulin:glucose ratio, and clamp insulin sensitivity (model 1); (2) 1-hr OGTT plasma glucose and beta-cell compensation index (model 2); and (3) 1-hr OGTT plasma glucose, OGTT 30-min incremental insulin:glucose ratio, and insulin sensitivity index (model 3).[74]

Greater beta-cell compensation index was associated with a 91 percent lower risk of developing type 2 diabetes, after adjusting for OGTT 1-hr plasma glucose level and basal glucose production rate. Greater clamp insulin sensitivity was associated with a non-significantly lower risk of developing type 2 diabetes, after adjusting for OGTT 1-hr glucose level, OGTT 30-min incremental insulin:glucose ratio, and basal glucose production rate in model 1 (OR = 0.2; 95 percent CI: 0.03 to 1.2) and after adjusting for diagnostic OGTT incremental glucose area, frequently sampled intravenous glucose tolerance acute insulin response, OGTT 30-min incremental insulin:glucose ratio, and basal glucose production rate in model 2 (OR = 0.15; 95 percent CI: 0.02 to 1.2).[74] Finally, women in the highest tertile of frequently sampled intravenous glucose tolerance test acute insulin response had a 92 percent lower risk of developing type 2 diabetes than did those in the lowest tertile, after adjusting for diagnostic OGTT incremental glucose area, OGTT 30-min incremental insulin:glucose ratio, basal glucose production rate, and clamp insulin sensitivity (OR = 0.08; 95 percent CI: 0.01 to 1.0).[74]

One study examined C-peptide glucose score as a risk factor for type 2 diabetes.[73] In this study, a higher C-peptide glucose score was associated with a 54 percent lower risk of developing type 2 diabetes, after adjusting for pre-pregnancy BMI and the number of abnormal OGTT results (OR = 0.46; 95 percent CI: 0.25 to 0.85).[73] We included these additional measures of glucose metabolism in order to provide a comprehensive summary of potential risk factors for the development of type 2 diabetes. While we were unable to draw conclusions from this emerging area of investigation, this review provided insight into the physiologic pathways that are being studied to better define the risk of type 2 diabetes among women with gestational diabetes.

The grade of evidence for both anthropometric measures and metabolic risk factors was moderate (see Appendix F, Evidence Table 26). However, after considering the quantity, quality, and consistency of the reviewed literature on risk factors, we graded the overall body of evidence as very low.

Other potential risk factors for type 2 diabetes.

Blood pressure. Cho et al. found postpartum blood pressure to be a predictor of type 2 diabetes, although a relative measure for blood pressure was not reported in their multivariate models.[62]

Lipids. Two studies examined postpartum lipid parameters as predictors of type 2 diabetes,[62 64] and in both of these studies, HDL cholesterol and triglycerides were risk factors for the development of type 2 diabetes; however, a relative measure for the lipid parameters was not reported in the multivariate models.[62 64]

Homocysteine. One study assessed homocysteine levels 6 weeks postpartum and found that women with homocysteine levels greater than 6.38 mmol had a greater than three-fold increased risk of developing type 2 diabetes when compared to those with homocysteine levels below this level, after adjusting for age, gestational age at gestational diabetes diagnosis, pre-pregnancy BMI, family history of type 2 diabetes, and FBG at diagnosis (RR = 3.6; 95 percent CI: 1.1 to 11.9).[61]

Autoantibodies. One study examined GAD and IA-2 antibodies as risk factors for type 2 diabetes and found that women with positive GAD or IA-2 antibodies had a four-fold increased risk of type 2 diabetes when compared to women who were antibody negative, after adjusting for

the method of glucose control, BMI, parity, age, and serum CRP (RH = 4.1; 95 percent CI: 2.6 to 6.7).[66] We were unable to draw meaningful conclusions based on the available evidence, but we have included summaries of these traditional (i.e., lipids, blood pressure) and novel measures to provide a comprehensive review of available risk factors for the development of type 2 diabetes.

Additional studies of risk factors for type 2 diabetes. We identified 11 studies that investigated factors associated with incident type 2 diabetes following a pregnancy complicated by gestational diabetes, but these studies did not include relative measures of risk or multivariate models.[76-86] While these studies are important for qualitatively identifying risk factors, we consider them to provide the lowest level of evidence because there was no adjustment for potential confounders or relative estimates. The evidence is briefly discussed below by risk factor category.

1. Family history of type 2 diabetes: No additional studies.

2. Sociodemographics: Two studies investigated maternal age. Greenberg et al.[83] compared maternal ages according to diabetic status at followup and did not find any statistical differences, while Dalfra et al.[80] did find an association. Two studies, Kousta et al. and Ali et al.,[77 87] examined the incidence of type 2 diabetes as stratified by race. Both studies found a higher incidence among black and Asian-Indian women than in European women or women of mixed ethnicity.

3. Maternal lifestyle factors: No additional studies.

4. Parity: Only one study, Linne et al.,[79] compared parity in women with and without type 2 diabetes at followup. No association was observed.

5. Pregnancy-related factors: Younger gestational age at diagnosis was consistently associated with increased incidence of type 2 diabetes in three studies: Greenberg et al.,[83] Bartha et al.,[82] and Dalfra et al.[80] Insulin use during pregnancy was consistently associated with increased type 2 diabetes in two studies: Greenberg et al.[83] and Dalfra et al.[80] Class A2 gestational diabetes was associated with increased type 2 diabetes in one study, that of Kjos et al.[85] Greenberg et al.[83] found that cesarean delivery, shoulder dystocia, and birthweight percentile did not differ between women who did and did not develop type 2 diabetes during followup.

6. Postpartum factors: Kjos et al.[84] compared women who did and did not breastfeed following a pregnancy complicated by gestational diabetes and found that women who breastfed had a decreased incidence of type 2 diabetes.

7. Anthropometric measures: BMI was investigated in six studies: Bian et al.,[81] Greenberg et al.,[83] Pallardo et al.,[78] Dalfraet et al.,[80] Linne et al.,[79] and Bartha.[82] There was a significant relationship between higher BMI and increased type 2 diabetes in all but one study.[83] Pallardo et al.[78] found that women who had developed type 2 diabetes during followup had higher current weight but did not differ in pre-pregnancy weight, weight change, or body fat percentage from women without type 2 diabetes at followup. Waist circumference was found to be associated with type 2 diabetes by Pallardo et al.[78] but was not found to be associated by Linne et al.[79] Waist-to-hip ratio was also not associated with type 2 diabetes in the study by Linne et al.[79]

8. Oral contraceptive use: Kjos et al.[85] found no difference in the incidence of type 2 diabetes in women using non-oral contraceptives, ethinyl estradiol-norethindrone, or ethinyl estradiol-levonorgestrel.

9. Metabolic risk factors: Increased fasting glucose was consistently higher in women developing type 2 diabetes during followup in four studies: Xiang et al.,[76] Linne et al.,[79] Dalfra et al.,[80] and Greenberg et al.[83] Higher HbA1c was consistently associated with increased type 2

diabetes in two studies: Linne et al.[79] and Greenberg et al.[83] Decreased beta-cell compensation was associated with higher risk of type 2 diabetes in one study, Xiang et al.[76] Plasma glucose levels at 2- and 3-hr during the diagnostic OGTT were found to be associated with increased type 2 diabetes in one study, Dalfra et al.,[80] but not associated in another, Greenberg et al.[83] Greenberg et al.[83] did find a difference in 1-hr OGTT between women developing type 2 diabetes during followup and those who remained normoglycemic. Dalfra et al.[80] also found postprandial plasma glucose, plasma insulin at 30 min during the OGTT, and postpartum plasma glucose area under the curve to be associated with type 2 diabetes. While Linne et al.[79] found blood pressure and lipids to be similar in women with and without type 2 diabetes at followup, Pallardo et al.[78] found significant differences in triglycerides and diastolic blood pressure but not HDL cholesterol, total cholesterol, or systolic blood pressure in women with and without type 2 diabetes at followup.

Additional comments on multivariate models. While a multivariate analytic approach was used to evaluate most of the risk factors for the development of type 2 diabetes, the factors considered and adjusted for in the models differed between studies. For example, some studies focused on anthropometric measures, while others focused on physiologic measures. Still others included a broader range of key measures of interest. Studies varied with respect to the covariates included in the multivariate models (see Appendix F, Evidence Table 15). Some studies determined which variable to include in the multivariate models by identifying the most significant predictors from the univariate analysis. Other studies did not report how or why specific covariates were chosen to be included in the models. Most studies included a list of key covariates known to be associated with type 2 diabetes, including (1) age, (2) parity, (3) family history of type 2 diabetes, and (4) method of glucose control (diet versus insulin or oral medication). Age was included in all of the multivariate models. However, no one study included all of the other three key covariates. Also, no group of covariates common to all of the multivariate models was constructed for the evaluation of a given risk factor.

Two studies[60 62] with well-defined approaches to the development of the multivariate models deserve further comment. In their investigation of the relationship of eight different obesity indices with onset of type 2 diabetes, Cho et al.[62] followed 909 Korean women for a mean of 2.13 ± 1.75 years. The authors first stratified the study population into three groups (normal glucose tolerance, impaired glucose tolerance, and type 2 diabetes) and performed a univariate analysis, examining the distribution of each of the seven obesity measures and relevant sociodemographic and clinical risk factors across the three groups of participants. Data were collected on risk factors that had been defined prior to the initiation of the study. Each obesity measure was then recategorized into quartiles (75^{th} percentile compared to 25^{th} percentile), and the association of each measure with type 2 diabetes was assessed using simple logistic regression. Correlations between obesity measures and other covariates were assessed. Only those factors that were statistically significantly associated with type 2 diabetes in the univariate analysis were included as covariates with the obesity measures in the final prediction model. These factors were blood pressure, lipid profile, age, duration of followup, parity, family history of type 2 diabetes, and working status. All eight of the obesity measures were associated with type 2 diabetes. Waist circumference was the strongest predictor (OR = 5.8; 95 percent CI: 2.0 to 11.8). After adjustment for covariates, the association of waist circumference with postpartum type 2 diabetes was moderately attenuated (OR = 3.4; 95 percent CI: 1.8 to 2.2) but remained statistically significant, as did the other six obesity measures. Although there was no R^2 to assess the relative fit of the model, we conclude that the reported multivariate model was adjusted for

covariates that are relevant both clinically and statistically to obesity and type 2 diabetes and were appropriately included in the model. Cheung et al.[60] reported findings from Cox regression analyses. The authors chose to include factors that were clinically related to both type 2 diabetes and to underlying insulin resistance (as evidenced by fasting hyperglycemia in pregnancy): age, parity, BMI, number of episodes of prior gestational diabetes, family history of type 2 diabetes, and insulin use versus diet alone in pregnancy. We concluded that these authors appeared to have based the selection and adjustment of covariates on the *a priori* hypothesis of a relationship with hyperglycemia and the established association with type 2 diabetes in the development of the best predictive model. Both studies represented a systematic approach to the development of multivariate models for assessing the direction and magnitude of association of risk factors with type 2 diabetes.

Key Question 4

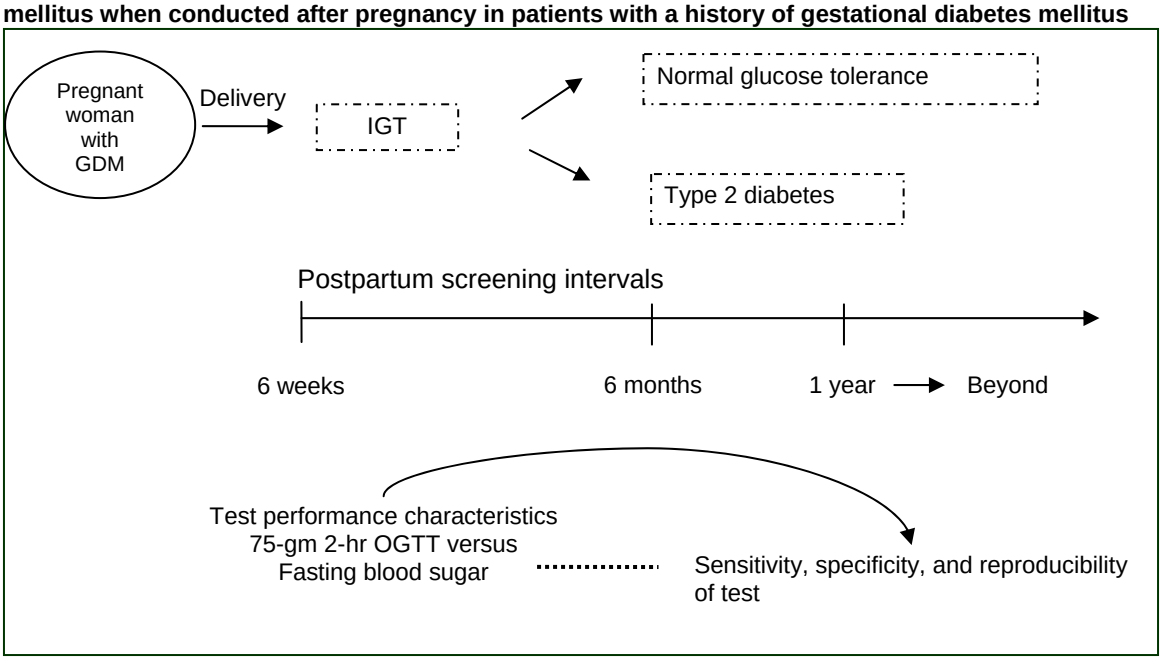
What are the performance characteristics (sensitivity, specificity, and reproducibility) of tests for diagnosing type 2 diabetes after pregnancy in patients with a history of gestational diabetes? Are there differences in the performance characteristics of the test results based on subgroup analysis?

Background and Conceptual Framework

The prevalence of type 2 diabetes is increasing in the United States and globally.[1] Early detection and treatment of diabetes has been associated with improved outcomes related to microvascular complications and may prevent macrovascular complications as well.[88] Women with gestational diabetes are at an increased risk of developing type 2 diabetes. An estimated 16 to 63 percent of women with gestational diabetes will develop type 2 diabetes in the 5 to 10 years immediately following pregnancy.[29] While postpartum screening for type 2 diabetes among women with gestational diabetes has been supported by the ADA[17] and ACOG,[7] there is debate about which screening test to use and at what interval to screen. These are important questions for both clinical providers and public health officials. The fact that only limited evidence is available with regard to screening test performance in women with a history of gestational diabetes has prolonged the debate and perhaps delayed a consensus on appropriate screening. To further define our efforts in addressing this topic, we developed a conceptual framework (see Figure 9). Our model incorporates test performance, as measured by sensitivity, specificity, and reproducibility, as well as the time interval for screening.

Despite the known risk of type 2 diabetes among women with gestational diabetes, only 75 percent of ACOG fellows reported that they routinely perform postpartum screening with the 75-gm OGTT. Followup varies widely, and many women do not receive the recommended screening for type 2 diabetes.[19 89] The barriers to use of the OGTT include the cost and inconvenience for a new mother. However, there is insufficient evidence supporting the use of an alternative screening test, such as the FBG. A recent cost-effectiveness analysis examined models for screening and found the OGTT to be cost-effective if used at 3-year intervals. Screening with the FBG was cost-effective if used at 1-year intervals.[90] More precise knowledge of the performance characteristics of these tests may help improve our estimates of the effectiveness and total costs associated with screening.

Figure 9. Conceptual framework of performance characteristics of tests for diagnosing type 2 diabetes mellitus when conducted after pregnancy in patients with a history of gestational diabetes mellitus



GDM = gestational diabetes mellitus; IGT = impaired glucose tolerance; type 2 diabetes = type 2 diabetes mellitus; gm = gram; hr = hour; OGTT = oral glucose tolerance test

In this report, we summarize and critically appraise the literature on the performance of currently available screening tests for postpartum glucose screening in order to support the development of clinical guidelines for postpartum glucose surveillance.

Table 6 summarizes the current tests available for postpartum glucose screening and their threshold values.

Table 6. Threshold values for tests to diagnose type 2 diabetes mellitus postpartum

	FBG	AND/OR	2-hr PG after 75-gm OGTT
NDDG 1979[91]	≥ 7.8 mmol/L (140 mg/dL)		≥ 11.1 mmol/L (200 mg/dL)
WHO 1985[92]	≥ 7.8 mmol/L (140 mg/dL)		≥ 11.1 mmol/L (200 mg/dL)
WHO 1999[93]	≥ 7.0 mmol/L (126 mg/dL)		≥ 11.1 mmol/L (200 mg/dL)
ADA 1997[17]	≥ 7.0 mmol/L (126 mg/dL)		NA
	≥ 7.0 mmol/L (126 mg/dL)		≥ 11.1 mmol/L (200 mg/dL)

2-hr PG = 2-hr plasma glucose; ADA = American Diabetes Association; dL = deciliter; FBG = fasting blood glucose; gm = gram; L = liter; mg = milligram; mmol = millimole; NA = not applicable; NDDG = National Diabetes Data Group; OGTT = oral glucose tolerance test; WHO = World Health Organization

Results

Overview and population characteristics for screening tests for type 2 diabetes. Our literature search identified 8 studies and 10 evaluations of a reference test and comparison test. Each of the eight studies had a cohort design. Four studies collected data retrospectively.[94-97] Each of these studies retrospectively applied the threshold glucose values of the comparison test to previously collected postpartum OGTT results. These studies used a clinic convenience

sample, including all women who returned for postpartum testing within a specified time period. Four studies collected data prospectively.[98-101] These four studies recruited patients with a history of gestational diabetes for screening for type 2 diabetes. Seven studies used the same OGTT results, but applied different diagnostic threshold criteria. One study[100] independently performed the FBG and OGTT as two separate tests for comparison (see Appendix F, Evidence Table 27).

As shown in Evidence Table 27, the population in two studies[98 100] was more than 50 percent Caucasian. One study,[95] performed in the United Arab Emigrates, had mostly Arab (80 percent) subjects. One study[101] was performed in the United Kingdom and included participants from three racial/ethnic groups: European, South Asian, and Afro-Caribbean. Three studies,[94 97 99] including the study performed in the United States,[97] did not report the racial composition of their study populations. The cohort included in the study by Reichelt et al.[99] was part of a Brazilian Cohort Study, which previously reported high representation from non-white populations.[102]

The majority of the studies screened for type 2 diabetes within 1 year of delivery.[94-97 100] Two studies[98 101] reported wide ranges of postpartum testing intervals, from 1 to 86 months and from 6 to 72 months, respectively. Only one study[99] conducted late screening of all subjects (between 4 and 8 years postpartum).

Overview of studies evaluating comparison and reference tests for type 2 diabetes. Our review yielded three general comparisons: (1) two different diagnostic threshold values applied to the 75-gm OGTT (the WHO 1985 criterion versus the WHO 1999 criterion); (2) FBG level greater than 7.0 mmol/L (126 mg/dL) (ADA 1997) and the 75-gm OGTT (WHO 1999); and (3) FBG greater than 7.0 mmol/L (126 mg/dL) (ADA 1997) and the 75-gm OGTT (WHO 1985).

For each eligible study, two of our investigators abstracted data serially to create a two-by-two table for each comparison test. The two-by-two tables contained data for the number of true positives (TP), false positives (FP), false negatives (FN), and true negatives (TN). We then calculated the sensitivity [# TP/(# TP + # FN)] and specificity [(# TN/ (# TN + # FP)] for each comparison test using the structured two-by-two tables. Since some cells included zero, standard errors and confidence intervals were calculated by means of the exact binomial formula using Stata command "cii" (Intercooled, version 8.2, StataCorp, College Station, TX).[103] An example of our calculation of the sensitivity, specificity, and standard errors is shown in Table 7, using the study by Costa et al.[100]

Table 7. Example of the calculation of sensitivity, specificity, and standard errors for tests diagnosing type 2 diabetes when conducted in postpartum gestational diabetes patients after pregnancy

		REFERENCE TEST	
		Positive by OGTT	**Negative by OGTT**
COMPARISON TEST	**Positive by FBG**	TP = 2	FP = 1
	Negative by FBG	FN = 0	TN = 117
		TP + FN = 2	FP + TN = 118

Sensitivity: # TP/(# TP + # FN)= 2/2= 100 percent, 95 percent CI: 16-100 percent
Specificity: # TN/ (# TN + # FP)=117/118=99 percent, 95 percent CI: 95-100 percent
FBG = fasting blood glucose; FN = false negatives; FP = false positives; OGTT = oral glucose tolerance test; TN = true negatives; TP = true positives

Performance characteristics.

Studies of different diagnostic threshold values applied to the 75-gm OGTT. Two studies[97 101] compared different threshold values for the OGTT. They reported the same specificity of 98 percent for the OGTT using a threshold of FBG greater than 7.0 mmol/L (126 mg/dL) (WHO

1985) and using a threshold of FBG greater than 7.8 mmol/L (140 mg/dL) (see WHO 1999) (see Figure 10 and Appendix F, Evidence Table 28). For this comparison, the sensitivity was fixed at 100 percent because the threshold values used for the comparison test would by definition always meet the criteria of the reference test.

We concluded that relatively few "false positives" resulted from lowering the FBG threshold in the 75-gm OGTT to 7.0 mmol/L. Taking into consideration the quantity, quality, and consistency of the two studies of different diagnostic threshold values applied to the 75-gm OGTT, we graded the strength of the evidence as very low (see Appendix F, Evidence Table 29).

Studies of FBG level greater than 7.0 mmol/L (126 mg/dL) (comparison test; ADA 1997) as compared to the 75-gm OGTT (reference test; WHO 1999). Three studies[94 95 99] reported data in which a single FBG greater than 7.0 mmol/L (126 mg/dL) (ADA 1997) was compared to an FBG greater than 7.0 mmol/L (126 mg/dL) or 2-hr plasma glucose after 75-gm OGTT greater than 11.1 mmol/L (200 mg/dL) (WHO 1999). The sensitivity for the FBG greater than 7.0 mmol/L (126 mg/dL) alone compared with a complete OGTT using the same FBG threshold (FBG > 7.0 mmol/L [126 mg/dL]) or 2-hr plasma glucose after 75-gm OGTT greater than 11.1 mmol/L (200 mg/dL) varied across the three studies, ranging from 46 to 89 percent (see Figure 11 and Appendix F, Evidence Table 28). For these comparisons, the specificity was fixed at 100 percent, since the threshold values for the comparison test would by definition meet the criteria for the reference test.

These three studies[94 95 99] were heterogeneous because postpartum testing occurred less than 6 months after delivery in two studies[94 95] but 4 to 8 years after delivery in the third study.[99] In addition to this longer time period after delivery, the study population in the third study[99] had a high prevalence of non-whites (previously reported by the Brazilian Gestational Diabetes Study Group)[102], which may have affected the test performance.

We concluded that use of the FBG alone with a threshold of greater than 7.0 mmol/L (126 mg/dL) had unpredictable sensitivity. Taking into consideration the quantity, quality, and consistency of the studies that compared the FBG level greater than 7.0mmol/L (126mg/dL) to the 75-gm OGTT (WHO 1999), we graded the strength of the evidence as very low (see Appendix F, Evidence Table 29).

Studies of FBG greater than 7.0 mmol/L (126 mg/dL) (comparison test; ADA 1997) as compared to the 75-gm OGTT (reference test; WHO 1985). Five studies[95 96 98 100 101] compared an FBG greater than 7.8 mmol/l (140 mg/dL) or a 2-hr plasma glucose level after 75-gm OGTT of greater than 11.1 mmol/l (200 mg/dL) (WHO 1985) as the reference test to an FBG greater than 7.0 mmol/L (126 mg/dL) (ADA 1997) as the comparison test.

These studies consistently reported high specificity (range: 94 to 99 percent). However, the sensitivities ranged from 14 to 100 percent (see Figure 12 and Appendix F, Evidence Table 28). Kousta et al.[101] reported a sensitivity of 73 percent (95 percent CI: 50 to 89 percent), Agarwal et al.[95] reported a sensitivity of 69 percent (95 percent CI: 53 to 82 percent), and Cypryk et al.[98] reported a sensitivity of 14 percent (95 percent CI: 0.04 to 58 percent). Both Holt et al.[96] and Costa et al.[100] reported sensitivities of 100 percent (with 95 percent CIs of 29 to 100 percent and 16 to 100 percent, respectively) (see Appendix F, Evidence Table 28).

One study[98] reported very low sensitivity for an FBG greater than 7.0 mmol/L (126 mg/dL) when compared to a reference OGTT with an FBG greater than 7.8 mmol/l (140 mg/dL) or 2-hr plasma glucose level after 75-gm OGTT greater than 11.1 mmol/l (200 mg/dL). This study population differed from the other studies' samples because 23 percent of the subjects were excluded from screening as a result of a new diagnosis of type 1 or 2 diabetes postpartum. Also,

the study population was entirely Polish. These two study characteristics may have reduced the spectrum of risk for type 2 diabetes in the screened population as compared to other clinical populations, thereby lowering the test's sensitivity.

We concluded that use of the FBG with a threshold greater than 7.0 mmol/L had high specificity when compared to the 75-gm OGTT but had highly variable sensitivity. Taking into consideration the quantity, quality, and consistency of the studies that compared the FBG level greater than 7.0 mmol/L (126mg/dL) to the 75-gm OGTT (WHO 1985), we graded the strength of the evidence as very low (see Evidence Table 29).

Subgroup analysis. Only one study[94] included analyses of high-risk subgroups: In this study, the FBG greater than 7.0 mmol/L (126 mg/dL) (ADA 1997) alone was compared to a complete OGTT (FBG > 7.0 mmol/L (126 mg/dL) or 2-hr plasma glucose after 75-gm OGTT greater than 11.1 mmol/L (200 mg/dL) (WHO 1999)). In 168 subjects with a family history of type 2 diabetes, the sensitivity was 47 percent (95 percent CI: 24 to 71 percent). In another 168 subjects who required insulin during pregnancy, the sensitivity was 55 percent (95 percent CI: 32 to 76 percent). We concluded that the FBG may perform better in subgroups with a family history of type 2 diabetes or that required insulin during pregnancy than in the general population, as reported in a single study.[94]

Test reproducibility. Test reproducibility affects diagnostic test accuracy. Five studies[95-97 100 101] reported the type of laboratory equipment used to test samples as an indicator of quality control. Three articles reported the kappa statistic as the measure of agreement between the results of the comparison and reference test, but not as a standard measure of single-test reproducibility.[95 98 100]

For quantitative assays such as measures of blood glucose, the STARD Initiative recommends calculating imprecision as the coefficient of variation by repeating the test over several days.[24] One study[96] reported the coefficient of variation: Holt et al. reported the coefficient of variation for plasma glucose testing using the specified laboratory equipment and assay. The coefficient of variation for this assay was 1.2 percent at 3.3 mmol/L and 1.49 percent at 16.5 mmol/L.[96]

One study did not meet our inclusion criteria because it did not report the method of diagnosing gestational diabetes, but it is notable because it focused on the question of reproducibility of the OGTT using FBG greater than 7.0 mmol/L (126 mg/dL) or 2-hr plasma glucose after 75-gm OGTT greater than 11.1 mmol/L (200 mg/dL) (WHO 1999).[104] The study population consisted of 696 Caucasian women with previous gestational diabetes at a median of 6.2 years postpartum. Women were administered an OGTT, which was repeated within 3 months when it met the criteria for diabetes. Type 2 diabetes was confirmed in only 60 percent of the women.

Quality assessment. No study fulfilled all the criteria related to methodological standards for evaluating studies of screening tests (see Appendix F, Evidence Table 30). All of the studies had notably high losses to followup (range: 20 to 82 percent). The rates were highest in those that did not recruit subjects specifically for the study but instead used a convenience sample,[94 95 97] since the clinics experienced high rates of postpartum loss to followup. Only two studies[96 97] described the subjects who were lost to followup. Two studies recruited patients specifically for their study, but did not describe the selection process or the response rates.[100 101]

Additional methodological comments. Two studies[98 101] excluded women who were diagnosed with type 1 or 2 diabetes postpartum prior to the screening test, resulting in exclusion of 14 to 23 percent of the recruited participants (see Appendix F, Evidence Table 27). Based on

our qualitative evaluation of the studies included in this review, a quantitative synthesis of the data was not feasible.

Limitations. There were several key limitations of these studies. First, six studies[95-98 100 101] used the 2-hr 75-gm OGTT with the FBG greater than 7.8 mmol/L (>140 mg/dL) (WHO 1985) threshold as a reference. This test may no longer be clinically useful, given current recommendations to use a threshold of FBG greater than 7.0 mmol/L (>126 mg/dL) as part of the OGTT (WHO 1999).

Overall, the study quality was poor. The studies were limited by their sampling methods, specifically the use of convenience samples that had high losses to followup. It is not clear whether the higher-risk patients are more or less likely to attend their postpartum followup visits to receive type 2 diabetes screening, and any such pattern may vary according to the country studied. In any case, the high loss to followup clearly limited the generalizability of the results.

Figure 10. Specificity of an FBG > 7.0 mmol/L (126 mg/dL) as compared to an FBG >7.8 mmol/L (140 mg/dL) threshold as part of the 2-hr 75-gm OGTT

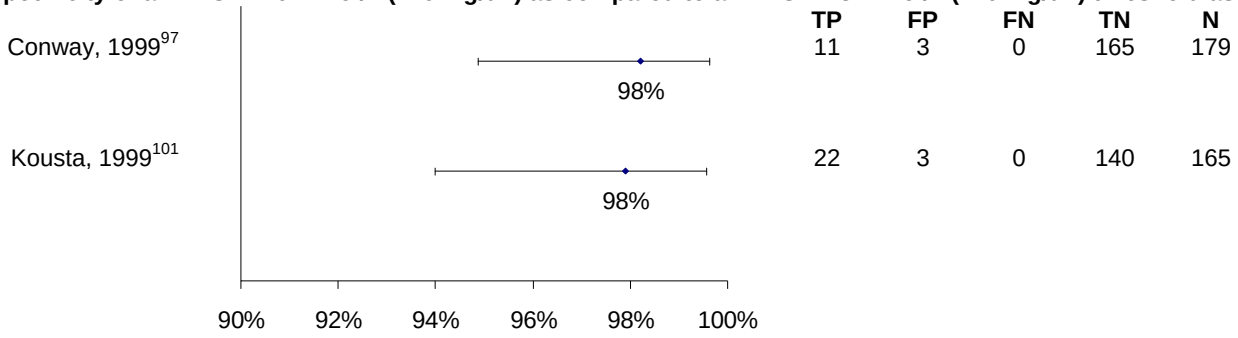


Figure 11. Sensitivity for studies of FBG level > 7.0 mmol/L (126 mg/dL) [comparison test] (ADA 1997) compared to the 75-gm OGTT [reference test] (WHO 1999)

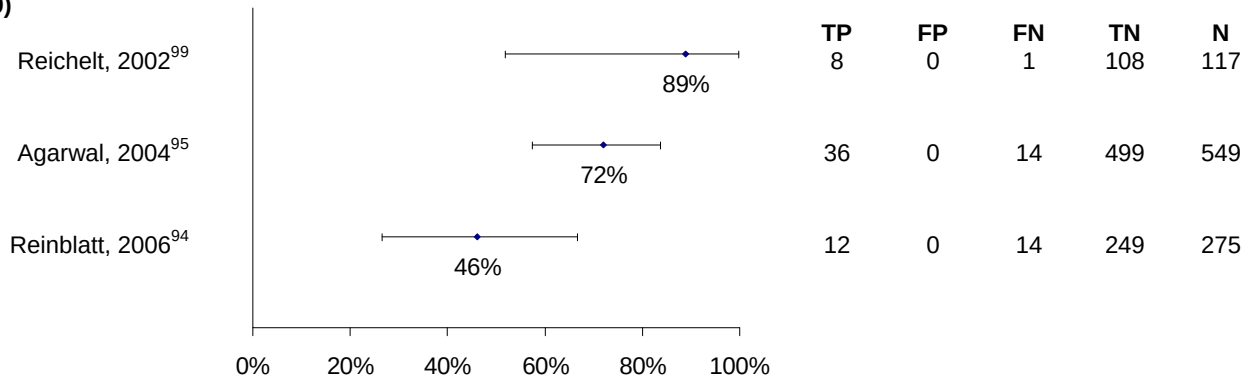
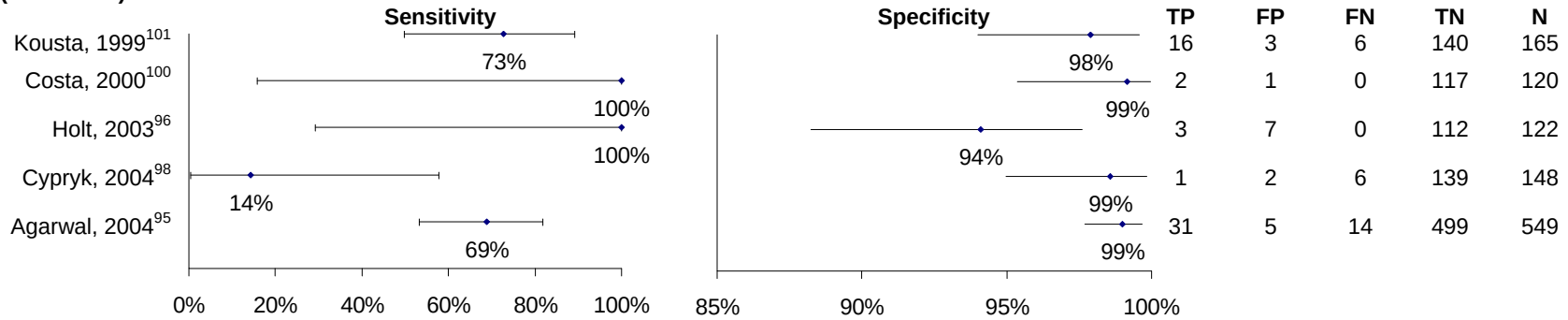


Figure 12. Sensitivity and specificity of studies of FBG > 7.0 mmol/L (126 mg/dL) [comparison test] (ADA 1997) compared to the 75-gm OGTT [reference test] (WHO 1985)



TP = true positives; FP = false positives; FN = false negatives; TN = true negatives; N = sample size; ADA = American Diabetes Association; dL = deciliter; FBG = fasting blood glucose; gm = gram; L = liter; mg = milligram; mmol = millimole; OGTT = oral glucose tolerance test; WHO = World Health Organization

Chapter 4. Discussion

Given the increase in obesity and sedentary lifestyles in the United States, the prevalence of gestational and type 2 diabetes among reproductive-aged women is expected to rise over the next decade. Both obstetrical and primary care physicians care for a growing number of women with gestational diabetes who are at increased risk of developing type 2 diabetes. For decades, obstetricians and primary care physicians have debated the optimal labor management and postpartum followup of women with gestational diabetes. Clinicians, public health advocates, and health policymakers have identified the need for evidenced-based practice guidelines for labor and postpartum management of women with gestational diabetes.

To identify the evidence on labor and postpartum management of gestational diabetes, the AHRQ, in conjunction with the ACOG, requested an evidence report on four distinct questions. We applied rigorous selection criteria and assessed the quality of each study, using a clinical and public health framework to guide our review. Our report is limited to gestational diabetes in which the diagnosis was confirmed by an OGTT, thereby ensuring that our review includes women with a definitive diagnosis of gestational diabetes. This evidence report outlines a comprehensive review of all the available research. In this final chapter, we first review the major findings pertaining to each question and the strength of the overall evidence; we then present our conclusions, make recommendations for future research, and offer clinical and public health perspectives.

Summary of the Key Findings

Key Question 1

What is the evidence for the risks and benefits of oral diabetes agents (e.g., second-generation sulfonylureas and metformin), as compared to all types of insulin, for both the mother and neonate in the treatment of women with gestational diabetes?

Relatively few studies have examined the effect of oral agents or insulin analogues, as compared to insulin, on a number of significant maternal and neonatal outcomes in women with gestational diabetes. Only three RCTs assessing the efficacy of glyburide and insulin met our inclusion criteria,[32 33 37] and only two maternal outcomes were evaluated in more than one RCT: cesarean delivery and maternal glycemic control. There was little difference in maternal outcomes between those treated with glyburide and those receiving insulin. In the largest trial (n = 404) comparing glyburide and insulin, 49 percent of the women on insulin underwent cesarean delivery, as compared to 46 percent of those on glyburide.[32] A second trial[37] reported no difference in cesarean delivery rates for 51 women on glyburide, insulin, or acarbose. Three trials found no statistically significant differences in glucose control between women treated with insulin and those receiving glyburide.[32 32 33] There was one study that considered pre-eclampsia, two studies that included maternal weight, and two studies that included information on maternal hypoglycemia. There were no available data with regard to perineal tears, operative vaginal delivery, or postpartum hemorrhage. Because of the small number of RCTs and the lack of

consistency in the maternal outcomes measured across studies, we graded the overall strength of evidence as very low.

Only four neonatal outcomes were evaluated by more than one RCT: birth weight, LGA, macrosomia, and neonatal hypoglycemia. We conducted a meta-analysis of three RCTs with a total of 478 pregnancies. There was a lower average infant birth weight in the insulin group as compared to the glyburide group (-93 gm; 95 percent CI: -119 to 5). This difference was not statistically significant and is unlikely to have substantial clinical influence. We were unable to draw any definitive conclusions regarding neonatal hypoglycemia, given the limited data available. Langer et al.[32] reported no significant difference between glyburide and insulin in the percentage of infants with hypoglycemia (9 percent versus 6 percent, $p = 0.25$), but Bertini et al.[37] reported a higher percentage of infants with hypoglycemia in the glyburide group than in the insulin or acarbose groups (33 percent compared to 4 percent and 5 percent, respectively; $p = 0.006$). Several of our neonatal outcomes of interest were not included in the RCTs reviewed. Therefore, we were unable to draw conclusions about anoxia, birth trauma, respiratory distress syndrome, or shoulder dystocia.

We extended our review of the literature on insulin and glyburide to include four observational studies.[45-48] None of the observational studies were strong enough to justify a modification of the conclusions drawn from the RCTs.

Two RCTs compared the effect of insulin lispro and regular insulin on maternal and neonatal outcomes in women with gestational diabetes.[34 36] We concluded that there was little difference in maternal glucose control (glycosylated hemoglobin or 1-hr glucose levels) between the women treated with insulin lispro and those treated with regular insulin. Neither Jovanoic[36] nor Mecacci[34] reported significant differences in mean infant birth weight between the insulin lispro and regular insulin groups. We concluded that no evidence exists to suggest that neonatal outcomes differ between those treated with regular insulin and those receiving insulin lispro. The limited number of trials, limited sample size, and paucity of information on neonatal outcomes made it difficult to draw any firm conclusions.

There was insufficient evidence to draw meaningful conclusions about the effect of long-acting versus short-acting insulin, twice-daily versus four-times-daily use of regular insulin, or diet alone versus diet plus insulin. In one study comparing long-acting to short-acting insulin, there was a higher percentage of infants with macrosomia in the long-acting insulin group than in the short-acting insulin group.[31] Limited data from one RCT[35] suggested that twice-daily insulin may be associated with worse neonatal outcomes (neonatal hypoglycemia, macrosomia, LGA, and SGA) than four-times-daily use of insulin. We found no evidence to suggest a difference in maternal outcomes between twice-daily and four-times-daily use of regular insulin. In the study by Thompson,[30] women were randomized to diet alone or diet plus a fixed insulin regimen that included 20 units of NPH insulin and 10 units of regular insulin. There was no reported difference in maternal glucose control or the proportion of women undergoing cesarean delivery in the two groups. In terms of neonatal outcomes, infant birth weight was higher in the diet-alone group than in the diet and insulin group. Similarly, there was a higher proportion of infants with macrosomia in the diet-alone group. These findings must be viewed with caution because the overall strength of the evidence for diet compared to insulin and dietary management was very low.

We did not identify any studies that compared metformin with other diabetes medications in women with gestational diabetes. Also, we found no evidence regarding maternal or neonatal outcomes as related to the level of glucose at the initiation of a medication.

Key Question 2

What is the evidence that elective cesarean delivery or the choice of timing of induction in gestational diabetes results in beneficial or harmful maternal and neonatal outcomes?

There is little evidence on the effect of gestational age or EFW on the timing of labor induction or performance of elective cesarean delivery in women with gestational diabetes. The findings from one experimental study[55] suggested that active induction of labor at 38 weeks of gestation reduced infant birth weight (3,672 gm versus 3,446 gm; $p < 0.01$) and rates of macrosomia (27 percent versus 15 percent; $p = 0.05$) when compared to expectant management, with no concomitant increase in the rate of cesarean delivery (25 percent in the active induction group versus 31 percent in the expectant management group; $p = 0.43$). While these results suggested that maternal outcomes might be better in women who undergo elective induction, we were unable to draw firm conclusions based on this one trial.

Observational studies[52-54 56-59] provided some additional evidence of a reduction in macrosomia and shoulder dystocia with elective labor induction or cesarean delivery, when compared to expectant management. For example, in the study by Conway,[53] women with diabetes underwent ultrasonographic estimates of fetal weight between 37 and 38 weeks of gestation. Women whose EFW was greater than or equal to 4,250 gm underwent cesarean delivery; those whose EFW was estimated at less than 4,250 gm but LGA (defined as $\geq 90^{th}$ percentile for the gestational age in their population) underwent labor induction. Fewer infants were macrosomic (weighing 4,000 gm or more) in the group undergoing elective cesarean or labor induction than in the expectant management group (8.9 percent versus 11.6 percent; $p = 0.04$). In addition, the incidence of shoulder dystocia was higher in the expectant management group (OR = 1.9, 95 percent CI: 1.0 to 3.5) than in the group undergoing elective cesarean or labor induction. The overall strength of evidence on this comparison was graded as very low. Only one of the observational studies adjusted for potential confounders,[56] so any measures of association may have been biased. Second, there may have been selection bias in the recruitment of women to participate in the studies. Third, there was substantial heterogeneity in terms of the comparison groups, length of followup, and outcome measures included in the analysis. Fourth, the four primary observational studies were conducted over a wide timeframe. It would be difficult to adequately adjust for changes in practice patterns and treatment modalities that occurred over the long time periods of the studies.

Key Question 3

What risk factors, including but not limited to family history, physical activity, pre-pregnancy weight, and gestational weight gain, are associated with short-term and long-term development of type 2 diabetes following a pregnancy with gestational diabetes?

Several factors were associated with the development of type 2 diabetes in women with previous gestational diabetes. Anthropometric measures before, during, and after pregnancy were found to be positively associated with the development of type 2 diabetes in 10 of 11 cohort studies. Waist circumference and BMI were the strongest anthropometric measures associated with type 2 diabetes in gestational diabetic women. Early gestational age at diagnosis of gestational diabetes (primarily less than 24 weeks) and use of insulin versus diet for glucose

control were key pregnancy-related clinical factors that were positively associated with type 2 diabetes. Physiologic measures, including FBG and 2-hr plasma glucose levels during the diagnostic OGTT, were also associated with development of type 2 diabetes. Higher blood glucose following a screening 50-gm GCT, prior gestational diabetes, and OGTT area under the curve during both the antepartum and postpartum periods were positively associated with development of type 2 diabetes, but the strength of the associations was not consistent across studies. There is conflicting data on progesterone-only contraceptive use and the risk for developing type 2 diabetes. Elevated postpartum homocysteine levels were positively associated with type 2 diabetes in one study. Surprisingly, there were no studies of lifestyle factors in women with gestational diabetes that met our review criteria.

After a review of the available evidence, we concluded that the strongest epidemiological risk factors were anthropometric measures prior to pregnancy and during both the antepartum and postpartum periods. Taking into consideration the quantity, quality, and consistency of the studies evaluating the association of risk factors for type 2 diabetes following a pregnancy with gestational diabetes, we graded the strength of the evidence as very low. While there was substantial consistency in the direction of association across studies for many of the risk factors, there was considerable variation in the covariates adjusted for in multivariate models across studies.

Key Question 4

What are the performance characteristics (sensitivity, specificity, and reproducibility) of tests for diagnosing type 2 diabetes after pregnancy in patients with a history of gestational diabetes? Are there differences in the performance characteristics of the test results based on subgroup analysis?

Several studies have pointed to poor physician compliance with postpartum glucose screening for type 2 diabetes among women with a history of gestational diabetes.[19 20] We reviewed the available studies of the diagnostic accuracy of screening for type 2 diabetes in this population. We identified 8 studies and 10 evaluations of screening tests, with three types of comparisons:

1. two different diagnostic fasting value thresholds applied to the 75-gm OGTT (the WHO 1985 criteria compared to the WHO 1999 criteria);
2. single FBG level greater than 7.0 mmol/L (126 mg/dL) (ADA 1997) compared to the 75-gm OGTT (WHO 1999); and
3. single FBG greater than 7.0 mmol/L (126 mg/dL) (ADA 1997) compared to the 75-gm OGTT (WHO 1985).

For the first comparison, we concluded that there was acceptable specificity (98 percent) for the OGTT using either a FBG value greater than 7.0 mmol/L (126 mg/dL) or greater than 7.8 mmol/L (140 mg/dL). For the second comparison, we were unable to draw meaningful conclusions. The sensitivities for a single FBG greater than 7.0 mmol/L (126 mg/dL), as compared to a complete OGTT using the same FBG threshold, ranged from 46 to 89 percent in the three studies. For the third comparison, there were five studies, which reported a high specificity of the FBG greater than 7.0 mmol/L (126 mg/dL). However, there was a wide range of sensitivity, from 14 to 100 percent.

The six studies[95-98 100 101] that used an FBG threshold greater than 7.8 mmol/L (140 mg/dL) in the reference test may be obsolete, since current guidelines recommend an FBG greater than 7.0 mmol/L (126mg/dL)[17 93 105] The wide variation in the reported sensitivities for studies that compared the OGTT as the reference test to a single FBG greater than 7.0 mmol/L (126 mg/dL) may reflect differences in the study samples' risk for type 2 diabetes, based on heterogeneity of study design and population. The overall strength of evidence was very low because of the high loss-to-followup rates (22 to 82 percent) for studies using clinic convenience samples.

Conclusions

Based on the available data outlined in Chapter 3, we have made the following conclusions:

Key Question 1: Little evidence exists to guide patients, health care providers, or policymakers in the choice of treatment for gestational diabetes. We were unable to draw firm conclusions from any of the five treatment comparisons in Key Question 1 because of the availability of only a limited number of studies within each category of comparison, a lack of consistency in the outcomes measured across studies, and heterogeneity in the definition of outcome measures. Limited evidence demonstrated no substantial clinical differences in maternal or neonatal outcomes with the use of glyburide or insulin lispro as compared to insulin in women with gestational diabetes. Our meta-analysis of three studies showed a small difference in infant birth weight. We expect little clinical relevance for the weighted mean difference of 93 gm. The results of our meta-analysis provide additional information for clinicians to incorporate into their discussions with patients about their choice of treatment but are unlikely to affect current clinical practice.

We did not identify any available evidence on variations in maternal or neonatal outcomes based on the level of glucose at the initiation of a medication. Each of the clinical trials and observational studies reviewed specified threshold glucose levels for the initiation of medical treatment as part of the study protocol. However, none of the studies compared outcomes based on glucose thresholds in their evaluation of maternal or neonatal outcomes. Findings from the HAPO study may provide further insights. Therefore, we were unable to provide evidence for this portion of Key Question 1. We were also unable to identify any published studies comparing metformin to diet, insulin, or insulin analogues in women with gestational diabetes. However, the ongoing MiG trial will likely provide evidence regarding the comparative effects of metformin and insulin on maternal and neonatal outcomes.

Key Question 2: Little evidence exists to guide health care providers in the use of EFW or gestational age in making decisions about the timing of labor induction or elective cesarean delivery. We identified only one relevant RCT. The findings from the few available observational studies were difficult to interpret because of variations in clinical practice over the time period of the studies. Furthermore, serious methodological limitations made it difficult to draw firm conclusions. While our review does provide physicians and other health care providers with a summary of the gaps in the available evidence, further study involving clinical trials or well-designed observational studies is necessary to effect modifications in clinical management and inform development of clinical pathways.

Key Question 3: There was consistent evidence that anthropometric measures (i.e., weight, BMI, and waist circumference) prior to pregnancy and during both the antepartum and

postpartum periods were positively associated with development of type 2 diabetes. These findings suggested similar risk factors for type 2 diabetes in reproductive and middle-aged women. Moreover, it appeared that weight and the distribution of weight were strong predictors of type 2 diabetes in this special population of women. Metabolic risk factors, including higher FBG at diagnosis of gestational diabetes, high glucose levels in oral glucose tolerance testing, insulin-requiring gestational diabetes, and glucose AUC for antepartum glucose tolerance testing, were consistently associated with an increased likelihood of type 2 diabetes. The relationship between progesterone-only contraception use and the risk of type 2 diabetes in women with a prior history of gestational diabetes, however, remains unclear. There was no evidence available regarding the potential effect of lifestyle factors (e.g., physical activity) on the development of type 2 diabetes in women with a prior history of gestational diabetes. Further investigation, ideally involving RCTs, would provide evidence for the primary prevention of type 2 diabetes in this high-risk group. Such evidence could then be incorporated into preconception and prenatal care education.

Key Question 4: We were unable to draw meaningful conclusions from the limited evidence available for our review. As compared to the 75-gm OGTT, the FBG had high specificity, but the sensitivity was variable across studies. As a result of heterogeneity in the study design, recruited population, and interval of followup testing, we were unable to draw firm conclusions about the performance characteristics of the FBG in women with a history of gestational diabetes. There was also insufficient evidence regarding test reproducibility. Until the appropriate intervals for followup testing are realized, further investigations would benefit from an interdisciplinary clinical approach. While obstetricians may provide immediate postpartum screening, general practitioners, internists, and other health care providers will likely provide long-term followup. With the increasing prevalence of childbearing among older women, pregnant women more commonly receive care from an obstetrician-gynecologist and either an internist or other primary care provider. Thus, an interdisciplinary dialogue among providers will be necessary to influence future care.

Future Research

While basic science research and investigations using animal models have helped us to better understand the underlying pathophysiology of gestational diabetes, there is a wide gap in our clinical knowledge with regard to how potential treatments and postpartum management can benefit both mothers and infants. Future research should be directed toward filling this gap by conducting studies that will lead to the development of evidenced-based guidelines for maternal glucose control and physician recommendations for labor induction, elective cesarean, and expectant management. In addition, future research should focus on risk factors for type 2 diabetes in this high-risk population and on developing effective screening modalities for identifying women who are at risk for developing type 2 diabetes.

Further RCTs are needed to better assess maternal and neonatal outcomes in women with gestational diabetes who are being treated with insulin, insulin analogues, metformin, or glyburide. Future trials should specify *a priori* hypotheses and conduct power analyses prior to recruitment to ensure the ability to detect small differences in maternal glucose levels that can affect fetal weight and the risk of macrosomia, as well as common outcomes such as cesarean delivery. Power analyses will aid researchers in detecting differences in less common but

critically important outcomes, such as shoulder dystocia and birth trauma. Clinical trials designed to capture these differences can offer important information and help us to draw reasonable and firm conclusions. Finally, intention-to-treat analysis will be essential to the ability to draw firm conclusions from the reported data. Consistency in the collection of outcome measures across studies is essential to our ability to draw confident conclusions. Furthermore, it would help to have more consistent definitions of clinical outcomes, including maternal and neonatal hypoglycemia, so that clinicians and investigators can better compare results across multiple studies. Observational studies in this area should be prospective, with protocols developed to minimize loss to followup. Adjustment for covariates will be of paramount importance for determining true estimates of the association of treatment choice with maternal and neonatal outcomes.

Well-designed RCTs comparing elective induction and cesarean delivery to expectant management would provide relevant, critical data to practitioners. These trials should incorporate appropriate methods of randomization and an intention-to-treat analysis, as well as power calculations with estimated effect sizes for mothers and infants. We acknowledge the potential barriers to performing clinical trials in pregnant women. Clinical trials with regard to labor management may be particularly difficult in the current obstetrical environment, which is highly litigious and influenced by patient and provider preferences for care. Well-designed observational studies are a reasonable alternative and can provide the necessary data to guide the development of clinical practice guidelines for labor management. Observational studies should primarily focus on insulin-requiring gestational diabetics (i.e., class A2), since this population is at higher risk of macrosomia or cesarean delivery. Alternatively, observational studies of diet and insulin-controlled gestational diabetics might include stratified analyses, which would provide outcome data at different levels of severity. Finally, future studies should adjust for other potential confounders, including sociodemographics and clinical factors related to intrapartum management.

Our review of 16 cohort studies identified several risk factors that are amenable to targeted interventions. One limitation of the current body of literature, however, is the inconsistency in the specific risk factors that have been assessed. Future studies should first focus on specific categories of risk factors, such as anthropometric measures (e.g., weight, BMI) or reproductive-related factors (e.g., parity). Second, future studies should collect data on pertinent covariates and adjust for relevant confounders in multivariate analysis. Third, women should be recruited for longitudinal study at the time of diagnosis of gestational diabetes. Fourth, several studies included in this review were based on convenience sampling, which may have biased the results; random or purposeful sampling of participants would yield a more representative group of participants.

Early identification of women with type 2 diabetes is paramount to achieving high quality of care and the ability to avoid diabetic complications due to delays in diagnosis. Future studies should focus on comparisons of the FBG and the standard 75-gm OGTT in postpartum women. Such comparisons would provide relevant data on the ability to screen women with a simple, time-efficient test, as compared to the burdensome OGTT. Studies should be conducted in diverse populations so that there is confidence that the findings are generalizable to other populations. The conduct of these studies in certain sub-groups (e.g., women with a family history of type 2 diabetes or prior gestational diabetes) is also warranted. Finally, studies of the reproducibility of test results will be critical to the development of broadly acceptable clinical guidelines for testing.

Implications

The results of this systematic review have important implications for clinical practice and public health policy. Clinicians and policymakers should be aware that the available data, while limited, do not suggest that there are adverse maternal or neonatal outcomes associated with the use of oral diabetic agents (i.e., glyburide), insulin lispro, or various insulin regimens. The efficacy of insulin analogs or glyburide in achieving maternal glucose targets or preventing episodes of maternal or neonatal hypoglycemia remains unclear. Several measures of maternal and neonatal morbidity, such as perineal tears, operative vaginal delivery, have not been evaluated, and several measures have only been evaluated in one or two studies. Also, it is unclear what glucose thresholds should be used to initiate insulin, insulin analogues, or glyburide in patients on diet alone.

Clinicians should also be aware that there is currently insufficient evidence to develop clear guidelines for labor induction or elective cesarean delivery in women with gestational diabetes. The conduct of well-designed clinical trials or observational studies may provide insight into evidenced-based management.

For public health policymakers, our conclusion is that measures of obesity and antepartum glucose values are the most consistent and substantiated risk factors for type 2 diabetes in women with gestational diabetes. With findings from the Diabetes Prevention Trial[106] highlighting the effect of lifestyle modifications on the primary prevention of type 2 diabetes in high-risk populations, our review suggests that the effectiveness of these interventions should be tested in women with a prior history of gestational diabetes.

Finally, we conclude that there are insufficient data to recommend alternative tests to the 75-gm OGTT for the detection of type 2 diabetes in women with gestational diabetes. Public health policymakers should work with health care researchers and national organizations (e.g., the ACOG and ADA) to further evaluate the effectiveness and timeliness of postpartum screening for type 2 diabetes in women with gestational diabetes. Further investigation can provide the data needed to develop broadly acceptable postpartum screening guidelines.

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95. Agarwal MM, Punnose J, Dhatt GS. Gestational diabetes: implications of variation in post-partum follow-up criteria. Eur J Obstet Gynecol Reprod Biol 2004; 113(2):149-53.

96. Holt RI, Goddard JR, Clarke P, Coleman MA. A postnatal fasting plasma glucose is useful in determining which women with gestational diabetes should undergo a postnatal oral glucose tolerance test. Diabet Med 2003; 20(7):594-8.

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100. Costa A, Carmona F, Martinez-Roman S, Quinto L, Levy I, Conget I. Post-partum reclassification of glucose tolerance in women previously diagnosed with gestational diabetes mellitus. Diabet Med 2000; 17(8):595-8.

101. Kousta E, Lawrence NJ, Penny A *et al*. Implications of new diagnostic criteria for abnormal glucose homeostasis in women with previous gestational diabetes. Diabetes Care 1999; 22(6):933-7.

102. Schmidt MI, Duncan BB, Reichelt AJ *et al*. Gestational diabetes mellitus diagnosed with a 2-h 75-g oral glucose tolerance test and adverse pregnancy outcomes. Diabetes Care 2001; 24(7):1151-5.

103. Brown LD, Cai TT, DasGupta A. Interval estimation for a binomial proportion. Statistical Science 2001; 16:101-33.

104. Corcoy R, Garcia-Patterson A, Albareda M, de Leiva A. Poor performance of American Diabetes Association criteria in women with gestational diabetes. Diabetes Care 2000; 23(3):430-1.

105. American Diabetes Association. Screening for Type 2 Diabetes. Diabetes Care 2003; 26 (Suppl 1):S21-S24.

106. Ramachandran A, Snehalatha C, Yamuna A, Mary S, Ping Z. Cost Effectiveness of the Interventions in the Primary Prevention of Diabetes among Asian Indians: Within trial results of the Indian Diabetes Prevention Programme (IDPP). Diabetes Care 2007.

107. Langer O, Yogev Y, Xenakis EM, Rosenn B. Insulin and glyburide therapy: dosage, severity level of gestational diabetes, and pregnancy outcome. Am J Obstet Gynecol 2005; 192(1):134-9.

List of Abbreviations

ACOG	American College of Obstetricians and Gynecologists
ADA	American Diabetes Association
AHRQ	Agency for Healthcare Research and Quality
BMI	Body mass index
CC	Concurrent control group
CD	Cesarean delivery
CENTRAL	Central Register of Controlled Trials
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CPD	Cephalopelvic disproportion
CRP	C-reactive protein
dL	Deciliter
EFW	Estimated fetal weight
EPC	Evidence-based Practice Center
FBG	Fasting blood glucose
FN	False negative
FP	False positive
gm	Grams
GAD	Glutamic acid decarboxylase
GCT	Glucose challenge test
Gestational diabetes	Gestational diabetes mellitus
HAPO	Hyperglycemia and Adverse Pregnancy Outcome
HDL	High-density lipoprotein
hr	Hour
IA-2	Insulinoma antigen-2
IGT	Impaired glucose tolerance
IU	International units
kg	Kilograms
KQ	Key Question
LDL	Low-density lipoprotein
LGA	Large for gestational age
L/S ratio	Lecithin-to-sphingomyelin
MeSH	Medical subject headings
mg	milligrams
MiG	Metformin in Gestational Diabetes
MOOSE	Meta-analysis of Observational Studies in Epidemiology
NDDG	National Diabetes Data Group
NICU	Neonatal intensive care unit admissions
NPH	Neutral Protamine Hagedom
OGTT	Oral glucose tolerance test
OR	Odds ratio

PCOS	Polycystic ovarian syndrome
PDF	Portable document format
PPG	Postprandial glucose
RCT	Randomized controlled trials
RDS	Respiratory distress syndrome
RH	Relative hazard
RR	Relative risk
SD	Standard deviation
SE	Standard error
SGA	Small for gestational age
STARD	Standards for Reporting of Diagnostic Accuracy
STROBE	Standards for Reporting of Observational Studies
TN	True negative
TP	True positive
Type 2 diabetes	Type 2 diabetes mellitus
US	Ultrasound
WHO	World Health Organization

Appendix A: Technical Experts and Peer Reviewers

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Appendix B: Hand Searched Journals

All Journals Hand Searched
August 2006 – January 2007

Acta Obstetricia et Gynecologica Scandinavica
American Journal of Obstetrics and Gynecology
American Journal of Perinatology
The Australian and New Zealand Journal of Obstetrics and Gynaecology
BJOG: An international journal of obstetrics and gynecology
Diabetic Medicine
Diabetes
Diabetes Care
Diabetes Research and Clinical Practice
European Journal of Obstetrics & Gynecology and Reproductive Biology
International Journal of Gynecology & Obstetrics
Obstetrics & Gynecology

Appendix C: Detailed Electronic Database Search Strategies

MEDLINE Strategy

Terms	Returns
(Diabetes, gestational[mh] OR gestational diabet*[tiab] OR diabetes in pregnancy[tiab] OR (diabet*[tiab] AND gestation*[tiab])) AND (((Insulin[mh] OR Insulin[tiab]) OR (sulfonylurea compounds[mh] OR hypoglycemics[tiab] OR hypoglycemic agents[tiab] OR Glyburide[tiab] OR Glipizide[tiab] OR glimepiride[tiab]) OR (Biguanides[mh] OR biguanide*[tiab] OR Metformin[tiab]) OR (Pregnancy[mh] OR Pregnan*[tiab] OR Pregnancy complications[mh] OR treatment outcome[mh] OR treatment outcome*[tiab]) OR (labor, induced[mh] OR Induced labor[tiab] OR Induction of labor[tiab] OR Obstetric Labor[mh] OR Cesarean section[mh] OR cesarean*[tiab] OR C-section[tiab] OR Abdominal deliver*[tiab]) OR (Diabetes Mellitus, Type 2[mh] OR (Diabet*[tiab] AND type 2[tiab]) OR (Diabet*[tiab] AND type II[tiab])))) AND eng[la] NOT (animals[mh]NOT humans[mh])	5628

EMBASE Strategy

(((((('pregnancy diabetes mellitus'/exp) OR ('gestational diabetes')) OR (('pregnancy'/exp) AND ('non insulin dependent diabetes mellitus'/exp))) OR (('type 2 diabetes' OR 'type ii diabetes' OR 'diabetes mellitus') AND (pregnant OR pregnancy))) AND ((((('antidiabetic agent'/exp) OR (hypoglycemic) OR ('hypoglycemic agent')) OR (insulin)) OR (('risk factor') OR ('treatment outcome'/exp) OR ('treatment outcome') OR ('pregnancy outcome'/exp) OR ('pregnancy outcome') OR (benefit) OR ('adverse event') OR (comorbidity)) OR (('labor'/exp) OR ('labor induction'/exp) OR ('induced labor') OR ('cesarean section')) OR ('reproducibility'/exp)))) AND [english]/lim AND [humans]/lim) NOT [review]/lim	5306

The Cochrane Central Register of Controlled Trials (CENTRAL)

#1	MeSH descriptor Diabetes, Gestational explode all trees	225
#2	(gestational diabetes) or (gestational diabetes):ti or (gestational diabetes):ab or (gestational diabetes):kw	
#3	(#1 OR #2)	
#4	MeSH descriptor Diabetes Mellitus, Type 2 explode all trees	
#5	(diabetes) or (diabetes):ti or (diabetes):ab or (diabetes):kw	
#6	(#4 OR #5)	
#7	MeSH descriptor Labor, Induced explode all trees	
#8	(labor) or (labor):ti or (labor):ab or (labor):kw	
#9	(Induc*) or (Induc*):ti or (Induc*):ab or (Induc*):kw	
#10	(#8 AND #9)	
#11	(#7 OR #10)	
#12	MeSH descriptor Cesarean Section explode all trees	
#13	(cesarean*) or (cesarean*):ti or (cesarean*):ab or (cesarean*):kw	
#14	(caesarean*) or (caesarean*):ti or (caesarean*):kw or (caesarean*):ab	
#15	(#14 AND NOT #13)	
#16	(#13 OR #14)	
#17	MeSH descriptor Insulin explode all trees	
#18	(insulin) or (insulin):ti or (insulin):kw or (insulin):ab	
#19	MeSH descriptor Sulfonylurea Compounds explode all trees	
#20	(glyburide) or (glyburide):ti or (glyburide):kw or (glyburide):ab	
#21	(glipizide) or (glipizide):ti or (glipizide):kw or (glipizide):ab	
#22	(glimepiride) or (glimepiride):ti or (glimepiride):kw or (glimepiride):ab	
#23	(#17 OR #18)	
#24	(#19 OR #20 OR #21 OR #22)	
#25	MeSH descriptor Metformin explode all trees	
#26	(Metformin) or (Metformin):ti or (Metformin):kw or (Metformin):ab	
#27	(#25 OR #26)	
#28	(#12 OR #16)	
#29	MeSH descriptor Pregnancy Complications explode all trees	
#30	MeSH descriptor Pregnancy explode all trees	
#31	(pregnan*) or (pregnan*):ti or (pregnan*):kw or (pregnan*):ab	
#32	MeSH descriptor Risk explode all trees	
#33	(risk*) or (risk*):ti or (risk*):kw or (risk*):ab	
#34	(#29 OR #30 OR #31)	
#35	(#32 OR #33)	
#36	(#23 OR #24 OR #27)	
#37	(#3 AND (#11 OR #28 OR #36 OR #34 OR #35))	

Cumulative Index to Nursing and Applied Health Literature (CINAHL)

((MH Diabetes Mellitus, Gestational) OR (MH Diabetes Mellitus, Non-Insulin-Dependent) OR (TX "gestational diabetes") OR ((TX "type 2 diabetes" OR TX "type II diabetes" OR (TX diabetes and TX ("type II" OR "type 2"))) AND TX Pregnancy) OR (TX Pregnancy and TX diabetes) OR (TX "diabetes in pregnancy")) AND ((MH "pregnancy outcomes" or MH "Pregnancy Complications" or MH comorbidity) OR (TX (Maternal OR neonatal OR pregnancy) and TX ("adverse event" OR benefit OR risk OR complication OR complications OR outcome OR outcomes))) OR ((MH insulin or MH hypoglycemic agents or MH sulfonylurea compounds) OR (TX (hypoglycemics OR "hypoglycemic agents" OR sulfonylurea OR metformin))) OR (TX (“diagnostic test” OR “diagnostic tests”) or MH (“sensitivity and specificity”) or MH “reproducibility of results”)) NOT (review OR "meta-analysis" OR "meta analysis" OR metaanalysis) and LA English	2907

Appendix D: List of Excluded Studies

1. National Diabetes Month. Reviewing the types of diabetes. Diabetes Self Manag 2006;23(6):38, 40-2.
   Does not include original data

2. Anonymous. Gestational diabetes mellitus. Diabetes Care 2004;27 (Suppl 1):S88-90.
   Does not include original data

3. Anonymous. Gestational diabetes mellitus. Diabetes Care 2003;26 (Suppl 1):S103-5.
   Does not include original data

4. Anonymous. Pregnancy problems echo later in life. Harv Heart Lett 2002;13(4):7.
   Does not include original data

5. Anonymous. Gestational diabetes mellitus. Diabetes Care 2000;23 (Suppl 1):S77-9.
   Does not include original data

6. Anonymous. Induction of labour at term (versus expectant management) for macrosomia results in which one of the following? Decreased birth weight. Can Fam Physician 1998;44:1610, 1619-20.
   Does not include original data

7. Anonymous. From the Centers for Disease Control and Prevention. Prenatal care, pregnancies complicated by diabetes. JAMA 1993;269(15):1932.
   Does not apply to a key question

8. Anonymous. Sulphonylureas in pregnancy. Lancet 1991;338(8776):1222.
   Does not include original data

9. Anonymous. Diabetes in pregnancy. Baillieres Clin Obstet Gynaecol 1991;5(2):257-503.
   Other

10. Anonymous. Diabetes in pregnancy. Clin Obstet Gynecol 1985;28(3):455-568.
    Does not include original data

11. Anonymous. Insulin pump shows promise for pregnant women--but problems for children. Am Pharm 1986;NS26(4):9-10.
    Does not include a medication of interest for KQ1

12. Anonymous. The lack of drug studies in pregnancy currently restricts treatment options to insulin for gestational diabetes. Drugs Ther. Perspect. 2004;20(6):17-20.
    Does not include original data

13. Anonymous. Use of glibenclamide in gestational diabetes. Pharm. J. 2000;265(7120):644.
    Does not include original data

14. Anonymous. Diabetes and congenital abnormalities. Bandolier 2006;13(3):5.
    Does not apply to a key question

15. Anonymous. Gestational diabetes mellitus. Canadian Journal of Diabetes 2003;27S99-105.
    Does not include original data

16. Anonymous. Diet, exercise delay type 2 diabetes. FDA Consumer 2001;35(5):10-11.
    Does not apply to a key question

17. Anonymous. Glyburide vs insulin for gestational diabetes. Nurses' Drug Alert 2000;24(12):91.
    Does not include original data

18. Anonymous. Insulin for gestational diabetes. Emergency Medicine 1990;22(17):45.
    Does not include original data

19. Anonymous. Reducing the risks in gestational diabetes. Emergency Medicine 1990;22(3):113.
    Does not include original data

20. Abell D A, Beischer N A, Wood C. Routine testing for gestational diabetes, pregnancy hypoglycemia and fetal growth retardation, and results of treatment. J Perinat Med 1976;4(4):197-212.
    Diagnosis of gestational diabetes not confirmed

21. Aberg A E, Jonsson E K, Eskilsson I et al. Predictive factors of developing diabetes mellitus in women with gestational diabetes. Acta Obstet Gynecol Scand 2002;81(1):11-6.
    Does not evaluate risk factors for type 2 diabetes

22. Adam P A, Schwartz R. Diagnosis and treatment: should oral hypoglycemic agents be used in pediatric and pregnant patients? Pediatrics 1968;42(5):819-823.
Does not include original data

23. Agarwal S, Gupta A N. Gestational diabetes. J Assoc Physicians India 1982;30(4):203-5.
No appropriate comparison group for KQ1

24. Agrawal R K, Lui K, Gupta J M. Neonatal hypoglycaemia in infants of diabetic mothers. J Paediatr Child Health 2000;36(4):354-6.
Does not have a comparison of interest

25. Akiel A S, Laajam M A, Moghraby S et al. Clinical experience with diabetic pregnancy in Riyadh: Analysis of 357 cases. Ann. Saudi Med. 1990;10(3):308-312.
No appropriate comparison group for KQ1

26. al-Najashi S S. Control of gestational diabetes. Int J Gynaecol Obstet 1995;49(2):131-5.
Other

27. Albareda M, Caballero A, Badell G et al. Diabetes and abnormal glucose tolerance in women with previous gestational diabetes. Diabetes Care 2003;26(4):1199-205.
Does not evaluate risk factors for type 2 diabetes

28. Albareda M, Caballero A, Badell G et al. Metabolic syndrome at follow-up in women with and without gestational diabetes mellitus in index pregnancy. Metabolism 2005;54(8):1115-21.
No relevant risk factor for KQ3

29. Albareda M, De Leiva A, Corcoy R. Reproducibility of diabetes mellitus diagnosis (WHO 1999 criteria) in women. Acta Diabetol. 2004;41(1):14-17.
Not evaluating people with gestational diabetes

30. Aldridge V, Temple R. Improving outcomes in diabetic pregnancies -- a challenge for all. Diabetes Primary Care 2000;2(2):38-41.
Other

31. Ali Z, Alexis S D. Occurrence of diabetes mellitus after gestational diabetes mellitus in Trinidad. Diabetes Care 90;13(5):527-9.
Does not evaluate risk factors for type 2 diabetes

32. Altman J-J, Brun J-M, Chanson P et al. Multicenter survey of diabetic pregnancy in France. Diabetes Care 91;14(11):994-1000.
Does not apply to a key question

33. Alur P, Kodiyanplakkal P, Del Rosario A et al. Epidemiology of infants of diabetic mothers in indigent Micronesian population-Guam experience. Pac Health Dialog 2002;9(2):219-221.
Diagnosis of gestational diabetes not confirmed

34. Arnold J M, Bromham D R, Burke B J. Induction of labour in pregnant diabetics using vaginal prostaglandin E2 pessaries. J. Obstet. Gynaecol. 1982;3(2):75-78.
Does not apply to a key question

35. Athukorala C, Crowther C A, Willson K. Women with gestational diabetes mellitus in the ACHOIS trial: Risk factors for shoulder dystocia. Aust N Z J Obstet Gynaecol 2007;47(1):37-41.
Does not apply to a key question

36. Banerjee S, Ghosh U S, Banerjee D. Effect of tight glycaemic control on fetal complications in diabetic pregnancies. J Assoc Physicians India 2004;52:109-13.
Does not apply to a key question

37. Banerjee S, Ghosh U S, Banerjee D. Foetomaternal complications in pregnancies with diabetes mellitus: association with the amount of insulin requirement, mean terminal blood glucose and HbA1C levels. J Indian Med Assoc 2003;101(12):728, 730-2, 740.
No appropriate comparison group for KQ1

38. Banerjee T. Diabetes in pregnancy. J Indian Med Assoc 76;67(11):247-50.
Does not include original data

39. Barahona M J, Sucunza N, Garcia-Patterson A et al. Period of gestational diabetes mellitus diagnosis and maternal and fetal morbidity. Acta Obstet Gynecol Scand 2005;84(7):622-7.
No appropriate comparison group for KQ1

40. Barnett R V. Diabetes in pregnancy. The obstetrician's dilemma. Ala J Med Sci 1972;9(3):282-8.
Does not include original data

41. Bartha J L, Martinez-del-Fresno P, Comino-Delgado R. Postpartum metabolism and autoantibody markers in women with gestational diabetes mellitus diagnosed in early pregnancy. Am J Obstet Gynecol 2001;184(5):965-70.
Does not report a relative measure

42. Bassaw B, Ataullah I, Roopnarinesingh S et al. Diabetes in pregnancy. Int J Gynaecol Obstet 1995;50(1):5-9.
Does not apply to a key question

43. Bastian J S. Diabetic control in pregnancy. Am J Obstet Gynecol 1988;158(3 Pt 1):677-678.
Does not include original data

44. Bates G W. Management of gestational diabetes. Postgrad Med 1974;55(6):55-8.
Does not include original data.

45. Beischer N A, Cookson T, Sheedy M et al. Norethisterone and gestational diabetes. Aust N Z J Obstet Gynaecol 1992;32(3):233-8.
Diagnosis of gestational diabetes not confirmed

46. Beischer N A, Wein P, Sheedy M T et al. Studies of postnatal diabetes mellitus in women who had gestational diabetes. Part 1. Estimation of the prevalence of unrecognized prepregnancy diabetes mellitus. Aust N Z J Obstet Gynaecol 1997;37(4):412-9.
No relevant risk factor for KQ3

47. Beischer N A, Wein P, Sheedy M T et al. Prevalence of antibodies to glutamic acid decarboxylase in women who have had gestational diabetes. Am J Obstet Gynecol 1995;173(5):1563-9.
Diagnosis of gestational diabetes not confirmed

48. Bellmann O. Therapy of gestational diabetes. Acta Endocrinol Suppl (Copenh) 1986;27750-5.
Does not have a comparison of interest

49. Ben Slama C, Nsiri B, Bouguerra R et al. Diabetic pregnancy in over 35 years old women. Ann Ist Super Sanita 1997;33(3):313-6.
Does not apply to a key question

50. Benito J A, Melchor J C, Cortazar A et al. Gestational diabetes: maternal profile and perinatal outcome according to the insulin therapy. Prog. Obstet. Ginecol. 1996;39(2):103-108.
Not written in English

51. Benjamin E, Winters D, Mayfield J et al. Diabetes in pregnancy in Zuni Indian women. Prevalence and subsequent development of clinical diabetes after gestational diabetes. Diabetes Care 1993;16(9):1231-5.
Other

52. Berkowitz G S, Roman S H, Lapinski R H et al. Maternal characteristics, neonatal outcome, and the time of diagnosis of gestational diabetes. Am J Obstet Gynecol 1992;167(4 Pt 1):976-82.
Does not apply to a key question

53. Bernstein I M, Catalano P M. Examination of factors contributing to the risk of cesarean delivery in women with gestational diabetes. Obstet Gynecol 1994;83(3):462-5.
No appropriate comparison group for KQ1

54. Bevier W C, Jovanovic-Peterson L, Burns A et al. Blood pressure predicts insulin requirement and exogenous insulin is associated with increased blood pressure in women with gestational diabetes mellitus. Am J Perinatol 1994;11(5):369-73.
Does not have a comparison of interest

55. Bhattacharyya A, Vice P A. Insulin lispro, pregnancy, and retinopathy. Diabetes Care 1999;22(12):2101-2104.
Not evaluating people with gestational diabetes

56. Bhattacharyya A, Brown S, Hughes S et al. Insulin lispro and regular insulin in pregnancy. QJM 2001;94(5):255-60.
Diagnosis of gestational diabetes not confirmed

57. Blackwell S C, Hassan S S, Wolfe H W et al. Why are cesarean delivery rates so high in diabetic pregnancies? J Perinat Med 2000;28(4):316-20.
No appropriate comparison group for KQ1

58. Bloomgarden Z T. Aspects of type 2 diabetes and related insulin-resistant states. Diabetes Care 2006;29(3):732-40.
Does not include original data

59. Bo S, Monge L, Macchetta C et al. Prior gestational hyperglycemia: a long-term predictor of the metabolic syndrome. J Endocrinol Invest 2004;27(7):629-35.
Not evaluating people with gestational diabetes

60. Bochner C J, Medearis A L, Williams J et al. Early third-trimester ultrasound screening in gestational diabetes to determine the risk of macrosomia and labor dystocia at term. Am J Obstet Gynecol 1987;157(3):703-8.
No appropriate comparison group for KQ1

61. Bonomo M, Cetin I, Pisoni M P et al. Flexible treatment of gestational diabetes modulated on ultrasound evaluation of intrauterine growth: a controlled randomized clinical trial. Diabetes Metab 2004;30(3):237-44.
Does not have a comparison of interest

62. Bonomo M, Mion E, Greco P et al. Maternal glycometabolic optimization and pregnancy outcome in gestational diabetes mellitus. Diabetes Nutr. Metab. Clin. Exp. 1998;11(1):1-7.
Other

63. Botta R M, Di Giovanni B M, Cammilleri F et al. Predictive factors for insulin treatment in women with diagnosis of gestational diabetes. Ann Ist Super Sanita 1997;33(3):403-6.
Does not have a comparison of interest

64. Bracero L A, Cassidy S, Byrne D W. Effect of gender on perinatal outcome in pregnancies complicated by diabetes. Gynecol. Obstet. Invest. 1996;41(1):10-14.
Not evaluating people with gestational diabetes

65. Brown F M, Wyckoff J, Rowan J A et al. Metformin in pregnancy: its time has not yet come. Diabetes Care 2006;29(2):485-6.
Does not include original data

66. Brown Z A, Mills J L, Metzger B E et al. Early sonographic evaluation for fetal growth delay and congenital malformations in pregnancies complicated by insulin-requiring diabetes. Diabetes Care 1992;15(5):613-619.
Does not apply to a key question

67. Brudenell J M. Delivering the baby of the diabetic mother. J R Soc Med 1978;71(3):207-211.
No appropriate comparison group for KQ1

68. Buchanan T A. Birth defects in diabetic pregnancies: where do we go from here? Eur J Endocrinol 1996;134(4):395-7.
Does not include original data

69. Buchanan T A, Kjos S L. Diabetes and pregnancy. Curr Ther Endocrinol Metab 1994;5278-83.
Does not include original data

70. Buchanan T A, Kjos S L, Montoro M N et al. Use of fetal ultrasound to select metabolic therapy for pregnancies complicated by mild gestational diabetes. Diabetes Care 1994;17(4):275-83.
Diagnosis of gestational diabetes not confirmed

71. Buchanan T A, Xiang A, Kjos S L et al. Gestational diabetes: Antepartum characteristics predict postpartum glucose intolerance and type 2 diabetes in Latino women. Diabetes 1998;47(8):1302-1310.
Other

72. Burkart W, Hanker J P, Schneider H P G. Complications and fetal outcome in diabetic pregnancy. Intensified conventional versus insulin pump therapy. Gynecol. Obstet. Invest. 1988;26(2):104-112.
Not evaluating people with gestational diabetes

73. Byrne M M, Sturis J, O'Meara N M et al. Insulin secretion in insulin-resistant women with a history of gestational diabetes. Metabolism 1995;44(8):1067-73.
Other

74. Camm J. Babies at risk from mothers' diabetes. RCM Midwives 2005;8(11):442.
Does not include original data

75. Carpenter M W, Coustan D R, Widness J A et al. Postpartum testing for antecedent gestational diabetes. Am J Obstet Gynecol 1988;159(5):1128-31.
Other

76. Carr D B, Utzschneider K M, Hull R L et al. Gestational diabetes mellitus increases the risk of cardiovascular disease in women with a family history of type 2 diabetes. Diabetes Care 2006;29(9):2078-83.
Other

77. Carrington E R. Diabetes in pregnancy. Clin Obstet Gynecol 1973;16(1):28-46.
Does not include original data

78. Caruso A, Lanzone A, Bianchi V et al. Continuous subcutaneous insulin infusion (CSII) in pregnant diabetic patients. Prenat Diagn 1987;7(1):41-50.
Other

79. Cassano F. The treatment of diabetics and prediabetics in pregnancy. Folia Endocrinol 1966;19(1):1-6.
Not evaluating people with gestational diabetes

80. Catalano P M, Bernstein I M, Wolfe R R et al. Subclinical abnormalities of glucose metabolism in subjects with previous gestational diabetes. Am J Obstet Gynecol 1986;155(6):1255-62.
Other

81. Catalano P M, Vargo K M, Bernstein I M et al. Incidence and risk factors associated with abnormal postpartum glucose tolerance in women with gestational diabetes. Am J Obstet Gynecol 1991;165(4 Pt 1):914-9.
Other.

82. Cheung N W, Oats J J, McIntyre H D. Australian carbohydrate intolerance study in pregnant women: implications for the management of gestational diabetes. Aust N Z J Obstet Gynaecol 2005;45(6):484-5.
Does not include original data

83. Chin R K. Hypertensive disorders of pregnancy and gestational diabetes mellitus in mature gravidae. Br J Clin Pract 1990;44(12):560-1.
Does not apply to a key question

84. Chollet MB, Pettitt DJ. Treatment of gestational diabetes mellitus. Clinical Diabetes 2006;24(1):35-36.
No appropriate comparison group for KQ1

85. Chung J H, Voss K J, Caughey A B et al. Role of patient education level in predicting macrosomia among women with gestational diabetes mellitus. J Perinatol 2006;26(6):328-32.
Diagnosis of gestational diabetes not confirmed

86. Cocilovo G, Tomasi F, Guerra S et al. Risk factors associated with persistence of glucose intolerance one year after gestational diabetes. Diabete Metab 1990;16(3):187-91.
Other

87. Coetzee E J, Jackson W P. Diabetes newly diagnosed during pregnancy: A 4-year study at Groote Schuur Hospital. S Afr Med J 1979;56(12):467-75.
Diagnosis of gestational diabetes not confirmed

88. Cohen A M, Schenker J G. The effect of insulin treatment on fetal mortality and congenital malformations in diabetic pregnant women. Adv Exp Med Biol 1972;27(-):377-381.
No appropriate comparison group for KQ1

89. Cole H S, Bilder J H, Camerini-Davalos R A et al. Glucose tolerance, insulin and growth hormone in infants of gestational diabetic mothers. Pediatrics 1970;45(3):394-403.
Does not apply to a key question

90. Collins V R, Dowse G K, Zimmet P Z. Evidence against association between parity and NIDDM from five population groups. Diabetes Care 1991;14(11):975-81.
Not evaluating people with gestational diabetes

91. Comtois R, Seguin M C, Aris-Jilwan N et al. Comparison of obese and non-obese patients with gestational diabetes. Int J Obes Relat Metab Disord 1993;17(10):605-8.
Does not apply to a key question

92. Corcoy R, Garcia-Patterson A, Albareda M et al. Poor performance of American Diabetes Association criteria in women with gestational diabetes. Diabetes Care 2000;23(3):430-1.
Does not include original data

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No appropriate comparison group for KQ1

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Not evaluating people with gestational diabetes

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Not evaluating people with gestational diabetes

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Not evaluating people with gestational diabetes

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Not evaluating people with gestational diabetes

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Does not evaluate a relevant maternal or neonatal outcome

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No relevant risk factor for KQ3

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No appropriate comparison group for KQ1

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Does not apply to a key question

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Diagnosis of gestational diabetes not confirmed

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Does not apply to a key question

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Not evaluating people with gestational diabetes

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Not evaluating people with gestational diabetes

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Not evaluating people with gestational diabetes

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Not evaluating people with gestational diabetes

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Does not apply to a key question

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Not evaluating people with gestational diabetes

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Does not have a comparison of interest

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Previewing at Level 34

Reviewer Comments (Add a Comment)

Refid: 1, Geremia, C. and Cianfarani, S., Insulin Sensitivity in Children Born Small for Gestational Age (SGA), *Rev Diabet Stud*, 1 (2), 2004, p.58-65
State: Excluded, Level: 2

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KQ4 Quality Form
Labor and Postpartum Management of Gestational Diabetes Mellitus

Please complete this form if study applies to KQ4

	Yes	No	
1. Was the reference test stated?	○	○	Clear
2. Did the authors report the test used to determine GDM in the study sample?	○	○	Clear

3. What was the study design?

- ☐ Retrospective (data collection planned after completion of tests)
- ☐ Prospective (data collection planned prior to testing)

4. How was the study population sampled?

- ☐ Random
- ☐ Consecutive
- ☐ Convenience
- ☐ Other type of sample
- ☐ Not stated

	Yes	No	Not reported	
5. ---SEE Q16-17 BELOW.---	○	○	○	Clear
6. Were positive and negative tests verified equally?	○	○	○	Clear
7. Were the methods for calculating or comparing measures of diagnostic accuracy reported?	○	○	○	Clear
8. Were estimates of test reproducibility done?	○	○	○	Clear

9. What types of reproducibility were assessed?

- ☐ Test-retest
- ☐ Other (specify:) _____

10. What was the lost to followup?

- ○ <10%
- ○ 10-20%
- ○ >20%
- ○ Not reported

Clear Selection

Total	130.	131.	132. N=

133. If the study reports only the sensitivity/specificity, please list it below.

%Sensitivity

%Specificity

Positive predictive value

Negative predictive value

134.

Specify Subgroup

	Reference test + (Diagnosis of test)	Reference test - (Diagnosis of test)	Total
Comparison test +	135.	136.	137.
Comparison test -	138.	139.	140.
Total	141.	142.	143. N=

144. If the study reports only the sensitivity/specificity, please list it below.

%Sensitivity

%Specificity

Positive predictive value

Negative predictive value

145. **Comments:**

Enlarge Shrink

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Total	108.	109.	110. N=

111. If the study reports only the sensitivity/specificity, please list it below.

%Sensitivity

%Specificity

Positive predictive value

Negative predictive value

112.

Specify Subgroup

	Reference test + (Diagnosis of test)	Reference test - (Diagnosis of test)	Total
Comparison test +	113.	114.	115.
Comparison test -	116.	117.	118.
Total	119.	120.	121. N=

122. If the study reports only the sensitivity/specificity, please list it below.

%Sensitivity

%Specificity

Positive predictive value

Negative predictive value

123.

Specify Subgroup

	Reference test + (Diagnosis of test)	Reference test - (Diagnosis of test)	Total
Comparison test +	124.	125.	126.
Comparison test -	127.	128.	129.

Comparison test -	83.	84.	85.
Total	86.	87.	88. N=

89. If the study reports only the sensitivity/specificity, please list it below.

%Sensitivity

%Specificity

Positive predictive value

Negative predictive value

90.

Specify Subgroup

	Reference test + (Diagnosis of test)	Reference test - (Diagnosis of test)	Total
Comparison test +	91.	92.	93.
Comparison test -	94.	95.	96.
Total	97.	98.	99. N=

100. If the study reports only the sensitivity/specificity, please list it below.

%Sensitivity

%Specificity

Positive predictive value

Negative predictive value

101.

Specify Subgroup

	Reference test + (Diagnosis of test)	Reference test - (Diagnosis of test)	Total
Comparison test +	102.	103.	104.
Comparison test -	105.	106.	107.

- [ ] Racial groups
- [ ] Age groups
- [ ] History of prior GDM
- [ ] Family history of DM
- [ ] Weight
- [ ] BMI
- [ ] Other (specify):

Please complete the tables below for calculation of sensitivity and specificity for each subgroup. **(Only fill in those cells where data has been provided in the article.)**

68.

Specify Subgroup

	Reference test + (Diagnosis of test)	Reference test - (Diagnosis of test)	Total
Comparison test +	69.	70.	71.
Comparison test -	72.	73.	74.
Total	75.	76.	77. N=

78. If the study reports only the sensitivity/specificity, please list it below.

%Sensitivity

%Specificity

Positive predictive value

Negative predictive value

79.

Specify Subgroup

	Reference test + (Diagnosis of test)	Reference test - (Diagnosis of test)	Total
Comparison test +	80.	81.	82.

Please complete the table below for calculation of sensitivity, specificity, positive predictive value and diagnostic odds ratio for subsequent testing of the comparison test.

	Reference test + (Diagnosis of test)	Reference test - (Diagnosis of test)	Total
Subsequent comparison test +	44.	45.	46.
Subsequent comparison test -	47.	48.	49.
Total	50.	51.	52. N=

If the study reports only the sensitivity/specificity, please list it below. **Report AUC and likelihood ratio only if no other data are provided.**

	%	53. Standard deviation / Standard error / 95% CI (Clear Selection)
Sensitivity	54.	55.
Specificity	56.	57.
Positive predictive value	58.	59.
Negative predictive value	60.	61.
AUC	62.	63.
Likelihood ratio	64.	65.

66. Does the study of the comparison test provide information on the test's performance in different subgroups (i.e., race/ethnicity, age groups)?

- Yes
- No (end of form - hit submit)

Clear Selection

67. If yes, check all that apply

		95% CI Clear Selection
Sensitivity	25.	26.
Specificity	27.	28.
Positive predictive value	29.	30.
Negative predictive value	31.	32.
AUC	33.	34.
Likelihood ratio	35.	36.

37. Did the comparison test occur at more than one time subsequent to initial testing?

- Yes
- No (skip to Q66)

Clear Selection

If yes, what was the time interval from delivery to subsequent testing with the comparison test?

	38. Mean Median Other (specify:) Clear Selection	39. Standard deviation Standard error Range Clear Selection
Reference test	40.	41.
Subsequent comparison test	42.	43.

Clear Selection

If yes, what was the mean (or median) time interval from delivery to each test?

	8.	9.
	○ Mean ○ Median ○ Other (specify:) _____ Clear Selection	○ Standard deviation ○ Standard error ○ Range Clear Selection
Reference test	10. _____	11. _____
Comparison test	12. _____	13. _____

14. Sample size:

Number eligible for postpartum testing	
Number in study sample	
Number lost to follow-up	
% lost to follow-up	

Please complete the table below for calculation of sensitivity, specificity, positive predictive value and diagnostic odds ratio for the comparison test. **(Only fill in those cells where data has been provided in the article.)**

	Reference test + (Diagnosis of test)	Reference test - (Diagnosis of test)	Total
Comparison test +	15.	16.	17.
Comparison test -	18.	19.	20.
Total	21.	22.	23. **N=**

If the study reports only the sensitivity/specificity, please list it below. **Report AUC and likelihood ratio only if no other data are provided.**

	%	24.
		○ Standard deviation ○ Standard error

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Previewing at Level 32

Reviewer Comments (Add a Comment)

Refid: 1, Geremia, C. and Cianfarani, S., Insulin Sensitivity in Children Born Small for Gestational Age (SGA), *Rev Diabet Stud*, 1(2), 2004, p.58-65
State: Excluded, Level: 2

Save to finish later | Submit Data

KQ4 Data Abstraction Form
Labor and Postpartum Management of Gestational Diabetes Mellitus

Please complete this form if study applies to KQ4

Please complete one form for each comparison test.

Reference test (to determine incidence of diabetes) (Please select the test used and enter the threshold values at each time point).

1. Reference test used:	2. Threshold values:	3. Units for the threshold values:
☐ 75g OGTT	Fasting	○ mg/dL
☐ 100g OGTT	1 hour	○ mmol/L
☐ Fasting plasma glucose	2 hour	Clear Selection
☐ Other test used (specify:)	3 hour	

Comparison Test, if comparison test used: (Please select the test used and enter the threshold values at each time point).

4. Comparison test used:	5. Threshold values:	6. Units for the threshold values:
☐ 75g OGTT	Fasting	○ mg/dL
☐ 100g OGTT	1 hour	○ mmol/L
☐ Fasting plasma glucose	2 hour	Clear Selection
☐ Other test used (specify:)	3 hour	

7. Does the article report the time interval(s) from delivery to testing?

○ Yes

○ No

Not reported

9. Do the authors report how missing data was handled in the analysis?

Yes

No

Clear Selection

10. Comments:

Enlarge Shrink

Save to finish later Submit Data

Form took 0.109375 seconds to render

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Previewing at Level 31

Reviewer Comments (Add a Comment)

Refid: 1, Geremia, C. and Cianfarani, S., Insulin Sensitivity in Children Born Small for Gestational Age (SGA), *Rev Diabet Stud*, 1 (2), 2004, p.58-65
State: Excluded, Level: 2

Save to finish later | Submit Data

KQ3 Quality Form

Labor and Postpartum Management of Gestational Diabetes Mellitus

Please complete this form for studies that apply to KQ3.

	Yes	No	
1. Are pre-specified hypotheses stated?	○	○	Clear
2. Are inclusion and exclusion criteria reported?	○	○	Clear

3. How was the study population sampled?

- ☐ Consecutive
- ☐ Random
- ☐ Convenience
- ☐ Other type of sample
- ☐ Not stated

	Yes	No	
4. Were power or sample size calculations used?	○	○	Clear
5. Does the article state how the outcome was defined?	○	○	Clear

6. What was the loss to follow-up?

- ☐ <10%
- ☐ 10-20%
- ☐ >20%
- ☐ Not reported

7. Did the study report comparisons of those who followed up vs. those who did not on any characteristics?

- ○ Yes
- ○ No

Clear Selection

8. What was the percent of missing data?

- ☐ <10%
- ☐ 10-20%
- ☐ >20%

57. Q6
58. Q11
59. Q16
60. Q21
61. Q26
62. Q31
63. Q36
64. Q41
65. Q46
66. Q51

Save to finish later | Submit Data

Form took 0.828125 seconds to render

	model Reported in fully adjusted model Unadjusted	Categorical (describe how this was defined, using a semicolon (;) to separate categories)	Enlarge Shrink	SE or SD 95% CI LL 95% CI UL p-value
36. Please Select	37. Included in fully adjusted model Reported in fully adjusted model Unadjusted	38. Continuous Categorical (describe how this was defined, using a semicolon (;) to separate categories)	39. Enter measure of association for each group, using a semicolon (;) to separate each group's results. Indicate reference group with "ref." Enlarge Shrink	40. Enter measure of variability for each group, using a semicolon (;) to separate each group's results. Indicate reference group with "ref." SE or SD 95% CI LL 95% CI UL p-value
41. Please Select	42. Included in fully adjusted model Reported in fully adjusted model Unadjusted	43. Continuous Categorical (describe how this was defined, using a semicolon (;) to separate categories)	44. Enter measure of association for each group, using a semicolon (;) to separate each group's results. Indicate reference group with "ref." Enlarge Shrink	45. Enter measure of variability for each group, using a semicolon (;) to separate each group's results. Indicate reference group with "ref." SE or SD 95% CI LL 95% CI UL p-value
46. Please Select	47. Included in fully adjusted model Reported in fully adjusted model Unadjusted	48. Continuous Categorical (describe how this was defined, using a semicolon (;) to separate categories)	49. Enter measure of association for each group, using a semicolon (;) to separate each group's results. Indicate reference group with "ref." Enlarge Shrink	50. Enter measure of variability for each group, using a semicolon (;) to separate each group's results. Indicate reference group with "ref." SE or SD 95% CI LL 95% CI UL p-value
51. Please Select	52. Included in fully adjusted model Reported in fully adjusted model Unadjusted	53. Continuous Categorical (describe how this was defined, using a semicolon (;) to separate categories)	54. Enter measure of association for each group, using a semicolon (;) to separate each group's results. Indicate reference group with "ref." Enlarge Shrink	55. Enter measure of variability for each group, using a semicolon (;) to separate each group's results. Indicate reference group with "ref." SE or SD 95% CI LL 95% CI UL p-value

56. Comments:

Enlarge Shrink

What is the unit for the risk factor mentioned in each question?

weeks years dollars mg/dL mmol/L kg pounds centimeters millimeters kg/m2 % Other (specify)

6. Please Select	7. Included in fully adjusted model Reported in fully adjusted model Unadjusted	8. Continuous Categorical (describe how this was defined, using a semicolon (;) to separate categories)	9. Enter measure of association for each group, using a semicolon (;) to separate each group's results. Indicate reference group with "ref." Enlarge Shrink	10. Enter measure of variability for each group, using a semicolon (;) to separate each group's results. Indicate reference group with "ref." SE or SD 95% CI LL 95% CI UL p-value
11. Please Select	12. Included in fully adjusted model Reported in fully adjusted model Unadjusted	13. Continuous Categorical (describe how this was defined, using a semicolon (;) to separate categories)	14. Enter measure of association for each group, using a semicolon (;) to separate each group's results. Indicate reference group with "ref." Enlarge Shrink	15. Enter measure of variability for each group, using a semicolon (;) to separate each group's results. Indicate reference group with "ref." SE or SD 95% CI LL 95% CI UL p-value
16. Please Select	17. Included in fully adjusted model Reported in fully adjusted model Unadjusted	18. Continuous Categorical (describe how this was defined, using a semicolon (;) to separate categories)	19. Enter measure of association for each group, using a semicolon (;) to separate each group's results. Indicate reference group with "ref." Enlarge Shrink	20. Enter measure of variability for each group, using a semicolon (;) to separate each group's results. Indicate reference group with "ref." SE or SD 95% CI LL 95% CI UL p-value
21. Please Select	22. Included in fully adjusted model Reported in fully adjusted model Unadjusted	23. Continuous Categorical (describe how this was defined, using a semicolon (;) to separate categories)	24. Enter measure of association for each group, using a semicolon (;) to separate each group's results. Indicate reference group with "ref." Enlarge Shrink	25. Enter measure of variability for each group, using a semicolon (;) to separate each group's results. Indicate reference group with "ref." SE or SD 95% CI LL 95% CI UL p-value
26. Please Select	27. Included in fully adjusted model Reported in fully adjusted model Unadjusted	28. Continuous Categorical (describe how this was defined, using a semicolon (;) to separate categories)	29. Enter measure of association for each group, using a semicolon (;) to separate each group's results. Indicate reference group with "ref." Enlarge Shrink	30. Enter measure of variability for each group, using a semicolon (;) to separate each group's results. Indicate reference group with "ref." SE or SD 95% CI LL 95% CI UL p-value
31. Please Select	32. Included in fully adjusted	33. Continuous	34. Enter measure of association for each group, using a semicolon (;) to separate each group's results. Indicate reference group with "ref."	35. Enter measure of variability for each group, using a semicolon (;) to separate each group's results. Indicate reference group with "ref."

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Previewing at Level 30

Reviewer Comments (Add a Comment)

Refid: 1, Geremia, C. and Cianfarani, S., Insulin Sensitivity in Children Born Small for Gestational Age (SGA), *Rev Diabet Stud*, 1(2), 2004, p.58-65
State: Excluded, Level: 2

Save to finish later | Submit Data

KQ3 Data Abstraction Form

Labor and Postpartum Management of Gestational Diabetes Mellitus

Please complete this form for studies that apply to KQ3.

Please complete a separate form for each outcome reported by the study.

1. List the measures that were used to define type 2 diabetes. (Check all that apply. Where applicable, enter the threshold used and specify if mg/dL or mmol/L.)

- ☐ Fasting blood sugar > _____
- ☐ Random blood sugar > _____
- ☐ Abnormal 75g OGTT
- ☐ Hemoglobin Alc > _____
- ☐ Self report
- ☐ Taking diabetes medications
- ☐ Other (specify:)

2. N of the analysis:

3. What was the time interval between delivery and time of follow-up testing?

Enlarge Shrink

Indicate variables that were included and reported in fully adjusted model or unadjusted. For each risk factor included in the **most fully adjusted model**, indicate if it was analyzed as a categorical or continuous variable (if applicable), describe how the variable was defined, and provide the measure of association and measures of variability. Note: For categorical variables, separate the different categories using a semicolon (;).

Please select risk factor.	Check all that apply for each variable.	Please briefly describe how the variable was defined.	4. Measure of Association	5. Measure of Variability
			○ RR ○ RH ○ OR ○ RD ○ Incidence ○ Other (specify:) Clear Selection	○ Standard error ○ Standard deviation Clear Selection

- [ ] Consecutive
- [ ] Random
- [ ] Convenience
- [ ] Other type of sample
- [ ] Not stated

	Yes	No	
9. Were power or sample size calculations used?	○	○	Clear
10. Does the article state how the outcome was defined?	○	○	Clear

11. What was the loss to follow-up?

- [ ] <10%
- [ ] 10-20%
- [ ] >20%
- [ ] Not reported

12. Do the authors report how loss to follow-up was handled in the analysis?

- ○ Yes
- ○ No
- ○ Not applicable (i.e., no loss to follow-up)

Clear Selection

13. What was the percent of missing data?

- [ ] <10%
- [ ] 10-20%
- [ ] >20%
- [ ] Not reported

14. Do the authors report how missing data was handled in the analysis?

- ○ Yes
- ○ No
- ○ Not applicable (i.e., no missing data)

Clear Selection

15. Comments:

Enlarge Shrink

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Previewing at Level 29

Refid: 1, Geremia, C. and Cianfarani, S., Insulin Sensitivity in Children Born Small for Gestational Age (SGA), *Rev Diabet Stud*, 1 (2), 2004, p.58-65
State: Excluded, Level: 2

Save to finish later | Submit Data

KQ2 Quality Form

Labor and Postpartum Management of Gestational Diabetes Mellitus

Please complete this form for studies that apply to KQ2.

If the study was an RCT, answer Q1-5. Otherwise, skip to Q6.

1. Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)?

- Yes (1)
- No (0)
- Not Reported/Can't Tell (0)

Clear Selection

2. If yes to q1, was the randomization scheme described AND appropriate?

- Yes: (1) appropriate randomization is if each study participant is allowed to have the same chance of receiving each intervention and the investigators could not predict which treatment was next.
- No: (-1) randomization described AND inappropriate (e.g. methods of allocation using date of birth, date of admission, hospital numbers, or alteration should not be regarded as appropriate)
- No: (0) randomization methods not described

Clear Selection

3. Was the study described as double blind?

- Yes (1)
- No (0)
- Not Reported/Can't Tell (0)

Clear Selection

4. If yes to Q3, was the method of double blinding described AND appropriate?

- Yes: (1) appropriate double blinding is if neither the person doing the assessments nor the study participant could identify the intervention being assessed OR if the use of active placebos, identical placebos or dummies is mentioned
- No: (-1) the study was described as double blind AND inappropriate (e.g. comparison of tablet vs lifestyle with no double dummy or fake tablet given to the lifestyle group)
- No: (0) no description of double blinding available and unable to tell if appropriate or not.

Clear Selection

5. Was there a description of withdrawals and drop-outs?

- Yes: (1) the number and the reasons for withdrawals in each group must be stated or state that there were no withdrawals. If subjects were not included in the analysis, they must state the number and reasons for not including them in the analysis.
- No (0)

Clear Selection

If study was an RCT, skip Q6-14. For all other study designs, answer Q6-14.

	Yes	No	
6. Are pre-specified hypotheses stated?	○	○	Clear
7. Are inclusion and exclusion criteria reported?	○	○	Clear

8. How was the study population sampled?

Enlarge Shrink

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Group 1	30.	31.	32. lower limit / upper limit	33.	34.
Group 2	35.	36.	37. lower limit / upper limit	38.	39.
Group 3	40.	41.	42. lower limit / upper limit	43.	44.
Group 4	45.	46.	47. lower limit / upper limit	48.	49.

Other statistics

	50. **Other measure** (specify:)	51. **Other measure** (specify:)	52. **Other measure** (specify:)
Group 1	53.	54.	55.
Group 2	56.	57.	58.
Group 3	59.	60.	61.
Group 4	62.	63.	64.

65. Comments:

	○ Mean ○ Median ○ Other (specify:) Clear Selection	○ Standard error ○ Standard deviation ○ Other (specify:) Clear Selection	○ 95% Confidence interval ○ Interquartile range (IQR) Clear Selection		
Group 1	7.	8.	9. lower limit upper limit	10.	11.
Group 2	12.	13.	14. lower limit upper limit	15.	16.
Group 3	17.	18.	19. lower limit upper limit	20.	21.
Group 4	22.	23.	24. lower limit upper limit	25.	26.

Mean difference from placebo/other group (For measures of variability, please record the standard error when available. If the standard error is please record either the 95% confidence interval or the standard deviation. Always record the p-value when available.)

	27. **Point estimate (select one:)**	28. **Measure of variability (select one:)**	29. **(Select one:)**	**N for the analysis**	
	○ Mean ○ Median ○ Other (specify:) Clear Selection	○ Standard error ○ Standard deviation ○ Other (specify:) Clear Selection	○ 95% Confidence interval ○ Interquartile range (IQR) Clear Selection		

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Previewing at Level 28

Refid: 1, Geremia, C. and Cianfarani, S., Insulin Sensitivity in Children Born Small for Gestational Age (SGA), *Rev Diabet Stud*, 1(2), 2004, p.58-65
State: Excluded, Level: 2

Save to finish later | Submit Data

KQ2 Outcomes Form
Labor and Postpartum Management of Gestational Diabetes Mellitus

Please complete this form if:

- **Study applies to KQ2**
- **Neonatal outcomes being reported is birth weight.**

Mark outcome of interest and how defined or what units used. **(Check only one outcome per form)**

Neonatal outcome	Definition and/or units used (check all that apply)
1. ☐ Birth weight	2. ☐ grams ☐ Other (specify:) ☐ Not reported

3. Was this an intention-to-treat analysis?

- ○ Yes
- ○ No
- ○ Not reported
- ○ Not applicable

Clear Selection

Weight outcomes should be recorded here. **(Report results for the most adjusted model.)**

Final measures (For measures of variability, please record the standard error when available. If the standard error is not available, please recor confidence interval/interquartile range or the standard deviation. Always record the p-value when available.)

	4. **Point estimate (select one:)**	5. **Measure of variability (select one:)**	6. **(Select one:)**	**N for the analysis**	

Group 2	115.	116.	117.
Group 3	118.	119.	120.
Group 4	121.	122.	123.

124. Comments:

Enlarge Shrink

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	○ Relative risk ○ Relative hazard ○ Odds ratio ○ Risk difference ○ Other (specify:) Clear Selection	**reference group**	○ Standard error ○ Standard deviation ○ Other (specify:) Clear Selection		
Group 1	89.	90. ☐	91.	92. lower limit upper limit	93.
Group 2	94.	95. ☐	96.	97. lower limit upper limit	98.
Group 3	99.	100. ☐	101.	102. lower limit upper limit	103.
Group 4	104.	105. ☐	106.	107. lower limit upper limit	108.

Other statistics

	109. **Other measure** (specify:)	110. **Other measure** (specify:)	111. **Other measure** (specify:)
Group 1	112.	113.	114.

Measure of Association (For measures of variability, please record the standard error when available. If the standard error is not available, plea record either the 95% confidence interval or the standard deviation. Always record the p-value when available.)

	65. **Point estimate (select one:)** Relative risk / Relative hazard / Odds ratio / Risk difference / Other (specify:) — Clear Selection	**Indicate reference group**	66. **Measure of variability (select one:)** Standard error / Standard deviation / Other (specify:) — Clear Selection	**95% Confidence interval**	**p-value**
Group 1	67.	68.	69.	70. lower limit / upper limit	71.
Group 2	72.	73.	74.	75. lower limit / upper limit	76.
Group 3	77.	78.	79.	80. lower limit / upper limit	81.
Group 4	82.	83.	84.	85. lower limit / upper limit	86.

Measure of Association (For measures of variability, please record the standard error when available. If the standard error is not available, plea record either the 95% confidence interval or the standard deviation. Always record the p-value when available.)

	87. **Point estimate (select one:)**	**Indicate**	88. **Measure of variability (select one:)**	**95% Confidence interval**	**p-value**

		Specifiy other numerator value:	
Group 4	45. List if different from initial N Can't tell N has not changed	46. # with 1 or more events % with 1 or more events Specify other numerator type: Specifiy other numerator value:	47.

Incidence Rate (For measures of variability, please record the standard error when available. If the standard error is not available, please recor either the 95% confidence interval or the standard deviation. Always record the p-value when available.)

	Point Estimate	48. **Measure of variability (select one:)**	95% Confidence interval	p-value
		Standard error Standard deviation Other (specify:) Clear Selection		
Group 1	49.	50.	51. lower limit upper limit	52.
Group 2	53.	54.	55. lower limit upper limit	56.
Group 3	57.	58.	59. lower limit upper limit	60.
Group 4	61.	62.	63. lower limit upper limit	64.

Not applicable

Clear Selection

All outcomes except blood sugar and weight should be recorded here. **(Report results for the most adjusted model.)**

	Number of people included in analysis for each group	**Numerator**	35. Denominator (if person-time used or # events in a certain time per Enter amount of time below and indicate time period here: Days Weeks Months Years Person-years Other (specify:) Not applicable
Group 1	36. List if different from initial N Can't tell N has not changed	37. # with 1 or more events % with 1 or more events Specify other numerator type: Specifiy other numerator value:	38.
Group 2	39. List if different from initial N Can't tell N has not changed	40. # with 1 or more events % with 1 or more events Specify other numerator type: Specifiy other numerator value:	41.
Group 3	42. List if different from initial N Can't tell N has not changed	43. # with 1 or more events % with 1 or more events Specify other numerator type:	44.

☐ Anoxia or acidosis	☐ Clinical diagnosis (criteria not given) ☐ Claims data/ICD-9 ☐ Arterial blood gas from neonate ☐ Cord blood gas ☐ Other (specify): _____ ☐ Not reported
27. ☐ Congenital malformation (specify): _____	28. ☐ Clinical diagnosis (criteria not given) ☐ Claims data/ICD-9 ☐ Other (specify): _____ ☐ Not reported
29. ☐ Respiratory distress syndrome	30. ☐ Clinical diagnosis (criteria not given) ☐ Claims data/ICD-9 ☐ Other (specify): _____ ☐ Not reported
31. ☐ Admission to NICU	NA
32. Mortality ☐ Fetal mortality ☐ Perinatal/neonatal mortality	33. ☐ Death certificate ☐ Clinical diagnosis ☐ Chart review ☐ Other (specify): _____

34. Was this an intention-to-treat analysis?

- ○ Yes
- ○ No
- ○ Not reported

	☐ Not reported
15. ☐ Macrosomia	16. ☐ Birth weight > _____ ☐ Other (specify): _____ ☐ Not reported
17. ☐ Large for gestational age (LGA)	18. ☐ weight (grams) > _____ ☐ percentile weight > _____ ☐ Other (specify:) _____ ☐ Not reported
19. ☐ Small for gestational age (SGA)	20. ☐ weight (grams) < _____ ☐ percentile weight < _____ ☐ Other (specify:) _____ ☐ Not reported
21. ☐ Shoulder dystocia	22. ☐ Clinical diagnosis (criteria not given) ☐ Claims data/ICD-9 _____ ☐ Other (specify): _____ ☐ Not reported
23. Birth trauma ☐ Clavicle bone fracture ☐ Humerus bone fracture ☐ Other bone fracture (specify:) ☐ Nerve palsy ☐ Other (specify:)	24. ☐ Clinical diagnosis (criteria not given) ☐ Claims data/ICD-9 _____ ☐ Other (specify): _____ ☐ Not reported
25.	26.

☐ Postpartum infection	☐ Claims data/ICD-9 ☐ Other (specify): _____ ☐ Not reported
5. Operative vaginal delivery ☐ Forceps use ☐ Vacuum use ☐ Other (specify:) _____	6. ☐ Clinical diagnosis (criteria not given) ☐ Claims data/ICD-9 ☐ Other (specify): _____ ☐ Not reported
7. Perineal tears ☐ 3rd degree tears ☐ 4th degree tears	8. ☐ Clinical diagnosis (criteria not given) ☐ Claims data/ICD-9 ☐ Other (specify): _____ ☐ Not reported
9. Cesarean delivery after failed attempt at vaginal delivery ☐ Failed induction ☐ Protracted labor ☐ Cesarean delivery ☐ Other (specify:) _____	10. TBD ☐ Clinical diagnosis (criteria not given) ☐ Claims data/ICD-9 ☐ Other (specify): _____ ☐ Not reported
Neonatal outcome	**Definition and/or units used (check all that apply)**
11. ☐ Neonatal hypoglycemia	12. ☐ fsg< _____ ☐ symptoms ☐ Other (specify): _____ ☐ Not reported
13. ☐ Hyperbilirubinemia	14. ☐ Serum bilirubin > _____ ☐ Other (specify): _____

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Previewing at Level 21

Reviewer Comments (Add a Comment)

Refid: 1, Geremia, C. and Cianfarani, S., Insulin Sensitivity in Children Born Small for Gestational Age (SGA), *Rev Diabet Stud*, 1(2), 2004, p.58-65
State: Excluded, Level: 2

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KQ2 Outcomes Form
Labor and Postpartum Management of Gestational Diabetes Mellitus

Please complete this form if:

- **Study applies to KQ2**
- **Maternal outcome being reported in hemorrhage, infection, perineal laceration, operative vaginal delivery, or failed attempt at vaginal delivery**
- **Neonatal outcome being reported is hypoglycemia, hyperbilirubinemia, macrosomia, LGA, SGA, shoulder dystocia, birth trauma, anoxia or acidosis, congenital malformations, respiratory distress syndrome, admission to NICU, or mortality.**

Mark outcome of interest and how defined or what units used. **(Check only one outcome per form)**

Maternal outcome	Definition and/or units used (check all that apply)
1. Hemorrhage ☐ Postpartum hemorrhage ☐ Other (specify:)	2. ☐ Clinical diagnosis (criteria not given) ☐ Claims data/ICD-9 ☐ Other (specify): ☐ Not reported
3. Infection ☐ Intrapartum infection	4. TBD ☐ Clinical diagnosis (criteria not given)

- [ ] Glucose: specify glucose measure used (such as mean glucose during pregnancy)
- [ ] Duration of gestational diabetes
- [ ] Duration of treatment for gestational diabetes
- [ ] Gestational age
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Other (specify):

27. Comments:

Enlarge Shrink

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Form took 0.1875 seconds to render

18. Spontaneous labor and vaginal delivery, %					
19. Spontaneous labor and cesarean delivery, N					
20. Spontaneous labor and cesarean delivery, %					
21. Induced labor and vaginal delivery, N					
22. Induced labor and vaginal delivery, %					
23. Induced labor and cesarean delivery, N					
24. Induced labor and cesarean delivery, %					

25. If an **observational study**, were adjustments done?

- ○ Yes
- ○ No
- ○ Not applicable

Clear Selection

26. If yes, what confounders were adjusted for? (check all that apply)

- ☐ Maternal age
- ☐ Race
- ☐ Parity
- ☐ Family History of Diabetes
- ☐ Prior GDM
- ☐ Diagnosed with GDM prior to 24 weeks
- ☐ Pre-pregnancy weight
- ☐ Pre-pregnancy BMI
- ☐ Gestational weight gain
- ☐ Other maternal disease confounders such as thyroid disease, placental abruption, placental previa
- ☐ Multiple gestation
- ☐ Steroid use during pregnancy

- [ ] LMP
- [ ] 1st trimester ultrasound
- [ ] 2nd trimester ultrasound
- [ ] Other

If intrauterine fetal weight or another measure of fetal size (e.g. abdominal circumference) was used to determine timing of delivery, what was the measure for each group? If mean or median of measure provided, please give details (e.g. mean estimated intrauterine fetal weight for group 1).

	Group 1	Group 2	Group 3	Group 4
9. Grams				
10. AC percentile				
11. Other (specify:)				
12. Mean				
13. Median				
14. Standard deviation				

15. What was used to assess the patient's readiness for induction?

- [ ] Bishop's score
- [ ] Fetal fibronectin
- [ ] Other (specify:)

16. What was the method for induction?

- [ ] Mechanical interventions
- [ ] Misoprostil (saline infusion)
- [ ] Monitoring/conservative care
- [ ] Oxytocin
- [ ] Prostaglandin E2 gel
- [ ] Stripping of membranes
- [ ] Other (specify:)

What was the N and % of patients who ultimately had each outcome?

	Group 1	Group 2	Group 3	Group 4	Total
17. Spontaneous labor and vaginal delivery, N					

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Previewing at Level 20

Reviewer Comments (Add a Comment)

Refid: 1, Geremia, C. and Cianfarani, S., Insulin Sensitivity in Children Born Small for Gestational Age (SGA), *Rev Diabet Stud*, 1(2), 2004, p.58-65
State: Excluded, Level: 2

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KQ2 Intervention Form

Labor and Postpartum Management of Gestational Diabetes Mellitus

Please complete this form for studies that apply to KQ2.

What was the initial planned management for each group?

	Group 1	Group 2	Group 3	Group 4
1. Spontaneous labor and vaginal delivery (also termed "expectant management") (could include those augmented with Pitocin)	☐	☐	☐	☐
2. Induced labor and vaginal delivery	☐	☐	☐	☐
3. "Elective" cesarean delivery (also termed "planned" cesarean delivery)	☐	☐	☐	☐
4. Other (specify:)				

If gestational age (weeks) was used to determine timing of delivery, what was the timing (i.e. gestational age) for each group? (Please write in the timing.)

	Group 1	Group 2	Group 3	Group 4
5. Weeks				

If the mean gestational age of delivery for a group is provided, please also include this information.

	Group 1	Group 2	Group 3	Group 4
6. Mean				
7. Standard deviation				

8. How was gestational age determined?

Enlarge Shrink

If study was an RCT, skip Q6-14. For all other study designs, answer Q6-14.

	Yes	No	
7. Are pre-specified hypotheses stated?	◯	◯	Clear
8. Are inclusion and exclusion criteria reported?	◯	◯	Clear

9. How was the study population sampled?

- ☐ Consecutive
- ☐ Random
- ☐ Convenience
- ☐ Other type of sample
- ☐ Not stated

	Yes	No	
10. Were power or sample size calculations used?	◯	◯	Clear
11. Does the article state how the outcome was defined?	◯	◯	Clear

12. What was the loss to follow-up?

- ☐ <10%
- ☐ 10-20%
- ☐ >20%
- ☐ Not reported

13. Do the authors report how loss to follow-up was handled in the analysis?

- ◯ Yes
- ◯ No
- ◯ Not applicable (i.e., no loss to follow-up)

Clear Selection

14. What was the percent of missing data?

- ☐ <10%
- ☐ 10-20%
- ☐ >20%
- ☐ Not reported

15. Do the authors report how missing data was handled in the analysis?

- ◯ Yes
- ◯ No
- ◯ Not applicable (i.e., no missing data)

Clear Selection

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Reviewer Comments (Add a Comment)

Refid: 1, Geremia, C. and Cianfarani, S., Insulin Sensitivity in Children Born Small for Gestational Age (SGA), *Rev Diabet Stud*, 1 (2), 2004, p.58-65
State: Excluded, Level: 2

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KQ1 Quality Form

Labor and Postpartum Management of Gestational Diabetes Mellitus

Please complete this form for studies that apply to KQ1.

1. Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)?

- Yes (1)
- No (0)
- Not Reported/Can't Tell (0)

Clear Selection

2. If yes to q1, was the randomization scheme described AND appropriate?

- Yes: (1) appropriate randomization is if each study participant is allowed to have the same chance of receiving each intervention and the investigators could not predict which treatment was next.
- No: (-1) randomization described AND inappropriate (e.g. methods of allocation using date of birth, date of admission, hospital numbers, or alteration should not be regarded as appropriate)
- No: (0) randomization methods not described

Clear Selection

3. Was the study described as double blind?

- Yes (1)
- No (0)
- Not Reported/Can't Tell (0)

Clear Selection

4. If yes to Q3, was the method of double blinding described AND appropriate?

- Yes: (1) appropriate double blinding is if neither the person doing the assessments nor the study participant could identify the intervention being assessed OR if the use of active placebos, identical placebos or dummies is mentioned
- No: (-1) the study was described as double blind AND inappropriate (e.g. comparison of tablet vs lifestyle with no double dummy or fake tablet given to the lifestyle group)
- No: (0) no description of double blinding available and unable to tell if appropriate or not.

Clear Selection

5. Was there a description of withdrawals and drop-outs?

- Yes: (1) the number and the reasons for withdrawals in each group must be stated or state that there were no withdrawals. If subjects were not included in the analysis, they must state the number and reasons for not including them in the analysis.
- No (0)

Clear Selection

6. Comments:

Group 2			
Group 3	109.	110.	111.
Group 4	112.	113.	114.

115. Comments:

Enlarge Shrink

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Mean difference from placebo/other group (For measures of variability, please record the standard error when available. If the standard error is please record either the 95% confidence interval or the standard deviation. Always record the p-value when available.)

	77. **Point estimate (select one:)** Mean / Median / Other (specify:) Clear Selection	78. **Measure of variability (select one:)** Standard error / Standard deviation / Other (specify:) Clear Selection	79. **(Select one:)** 95% Confidence interval / Interquartile range (IQR) Clear Selection	**N for the analysis**	
Group 1	80.	81.	82. lower limit / upper limit	83.	84.
Group 2	85.	86.	87. lower limit / upper limit	88.	89.
Group 3	90.	91.	92. lower limit / upper limit	93.	94.
Group 4	95.	96.	97. lower limit / upper limit	98.	99.

Other statistics

	100. **Other measure** (specify:)	101. **Other measure** (specify:)	102. **Other measure** (specify:)
Group 1	103.	104.	105.
	106.	107.	108.

			upper limit		
Group 4	49.	50.	51. lower limit upper limit	52.	53.

Mean difference from baseline (For measures of variability, please record the standard error when available. If the standard error is not availab either the 95% confidence interval or the standard deviation. Always record the p-value when available.)

	54. **Point estimate (select one:)**	55. **Measure of variability (select one:)**	56. **(Select one:)**	**N for the analysis**	
	Mean Median Other (specify:) Clear Selection	Standard error Standard deviation Other (specify:) Clear Selection	95% Confidence interval Interquartile range (IQR) Clear Selection		
Group 1	57.	58.	59. lower limit upper limit	60.	61.
Group 2	62.	63.	64. lower limit upper limit	65.	66.
Group 3	67.	68.	69. lower limit upper limit	70.	71.
Group 4	72.	73.	74. lower limit upper limit	75.	76.

Group 2	16.	17.	18. lower limit / upper limit	19.	20.
Group 3	21.	22.	23. lower limit / upper limit	24.	25.
Group 4	26.	27.	28. lower limit / upper limit	29.	30.

Final measures (For measures of variability, please record the standard error when available. If the standard error is not available, please recor confidence interval or the standard deviation. Always record the p-value when available.)

	31. **Point estimate (select one:)**	32. **Measure of variability (select one:)**	33. **(Select one:)**	**N for the analysis**	
	Mean / Median / Other (specify:) Clear Selection	Standard error / Standard deviation / Other (specify:) Clear Selection	95% Confidence interval / Interquartile range (IQR) Clear Selection		
Group 1	34.	35.	36. lower limit / upper limit	37.	38.
Group 2	39.	40.	41. lower limit / upper limit	42.	43.
Group 3	44.	45.	46. lower limit	47.	48.

	☐ pounds ☐ Other (specify:) ☐ Not reported
Neonatal outcome	**Definition and/or units used (check all that apply)**
5. ☐ Birth weight	6. ☐ grams ☐ Other (specify:) ☐ Not reported

7. Was this an intention-to-treat analysis?

- ○ Yes
- ○ No
- ○ Not reported
- ○ Not applicable

Clear Selection

Blood sugar and weight outcomes should be recorded here. **(Report results for the most adjusted model.)**

Baseline measures (For measures of variability, please record the standard error when available. If the standard error is not available, please re confidence interval or the standard deviation. Always record the p-value when available.)

	8. **Point estimate (select one:)**	9. **Measure of variability (select one:)**	10. **(Select one:)**	**N for the analysis**	
	○ Mean ○ Median ○ Other (specify:) Clear Selection	○ Standard error ○ Standard deviation ○ Other (specify:) Clear Selection	○ 95% Confidence interval ○ Interquartile range (IQR) Clear Selection		
Group 1	11.	12.	13. lower limit upper limit	14.	15.

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Reviewer Comments (Add a Comment)

Refid: 1, Geremia, C. and Cianfarani, S., Insulin Sensitivity in Children Born Small for Gestational Age (SGA), *Rev Diabet Stud*, 1(2), 2004, p.58-65
State: Excluded, Level: 2

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KQ1 Outcomes Form
Labor and Postpartum Management of Gestational Diabetes Mellitus

Please complete this form if:

- **Study applies to KQ1**
- **Maternal outcome being reported is glycemic control or maternal weight**
- **Neonatal outcomes being reported is birth weight.**

Mark outcome of interest and how defined or what units used. **(Check only one outcome per form)**

Maternal outcome	Definition and/or units used (check all that apply)
1. Glycemic control during treatment (choose one:) ○ Fasting plasma glucose during pregnancy ○ Pre-prandial glucose during pregnancy ○ 1 hour postprandial glucose during pregnancy ○ 2 hour postprandial glucose during pregnancy ○ Combined glucose during pregnancy ○ Other (specify:) Clear Selection	2. ☐ mmol/L ☐ mg/dL ☐ Other (specify:) ☐ Not reported
3. ☐ Maternal weight	4. ☐ kg

Group 2	84.	85.	86.
Group 3	87.	88.	89.
Group 4	90.	91.	92.

93. Comments:

Enlarge Shrink

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	56. **Point estimate (select one:)** ○ Relative risk ○ Relative hazard ○ Odds ratio ○ Risk difference ○ Other (specify:) Clear Selection	**Indicate reference group**	57. **Measure of variability (select one:)** ○ Standard error ○ Standard deviation ○ Other (specify:) Clear Selection	**95% Confidence interval**	**p-value**
Group 1	58.	59.	60.	61. lower limit / upper limit	62.
Group 2	63.	64.	65.	66. lower limit / upper limit	67.
Group 3	68.	69.	70.	71. lower limit / upper limit	72.
Group 4	73.	74.	75.	76. lower limit / upper limit	77.

Other statistics

	78. **Other measure** (specify:)	79. **Other measure** (specify:)	80. **Other measure** (specify:)
Group 1	81.	82.	83.

Measure of Association (For measures of variability, please record the standard error when available. If the standard error is not available, plea record either the 95% confidence interval or the standard deviation. Always record the p-value when available.)

	34. **Point estimate (select one:)**	**Indicate reference group**	35. **Measure of variability (select one:)**	**95% Confidence interval**	**p-value**
	○ Relative risk ○ Relative hazard ○ Odds ratio ○ Risk difference ○ Other (specify:) Clear Selection		○ Standard error ○ Standard deviation ○ Other (specify:) Clear Selection		
Group 1	36.	37.	38.	39. lower limit / upper limit	40.
Group 2	41.	42.	43.	44. lower limit / upper limit	45.
Group 3	46.	47.	48.	49. lower limit / upper limit	50.
Group 4	51.	52.	53.	54. lower limit / upper limit	55.

Measure of Association (For measures of variability, please record the standard error when available. If the standard error is not available, plea record either the 95% confidence interval or the standard deviation. Always record the p-value when available.)

		Specifiy other numerator value:	
Group 4	14.	15. # with 1 or more events % with 1 or more events Mean # of events Specify other numerator type: Specifiy other numerator value:	16.

Incidence Rate (For measures of variability, please record the standard error when available. If the standard error is not available, please recor either the 95% confidence interval or the standard deviation. Always record the p-value when available.)

	Point Estimate	17. **Measure of variability (select one:)** Standard error Standard deviation Other (specify:) Clear Selection	95% Confidence interval	p-value
Group 1	18.	19.	20. lower limit upper limit	21.
Group 2	22.	23.	24. lower limit upper limit	25.
Group 3	26.	27.	28. lower limit upper limit	29.
Group 4	30.	31.	32. lower limit upper limit	33.

	Number of people included in analysis for each group	Numerator	4. Denominator (if person-time used or # events in a certain time period): Enter amount of time below and indicate time period here:
			☐ Days ☐ Weeks ☐ Months ☐ Years ☐ Person-years ☐ Other (specify:)
Group 1	5.	6. # with 1 or more events % with 1 or more events Mean # of events Specify other numerator type: Specifiy other numerator value:	7.
Group 2	8.	9. # with 1 or more events % with 1 or more events Mean # of events Specify other numerator type: Specifiy other numerator value:	10.
Group 3	11.	12. # with 1 or more events % with 1 or more events Mean # of events Specify other numerator type:	13.

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Previewing at Level 16

Reviewer Comments (Add a Comment)

Refid: 1, Geremia, C. and Cianfarani, S., Insulin Sensitivity in Children Born Small for Gestational Age (SGA), *Rev Diabet Stud*, 1(2), 2004, p.58-65
State: Excluded, Level: 2

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KQ1 Outcomes Form
Labor and Postpartum Management of Gestational Diabetes Mellitus

Please complete this form if:

- **Study applies to KQ1**
- **Maternal outcome being reported is hypoglycemia.**

Mark outcome of interest and how defined or what units used. **(Check only one outcome per form)**

Maternal outcome	Definition and/or units used (check all that apply)
1. ☐ Maternal hypoglycemia	2. ☐ fsg< ☐ symptoms ☐ Other (specify): ☐ Not reported

3. Was this an intention-to-treat analysis?

- ○ Yes
- ○ No
- ○ Not reported
- ○ Not applicable

Clear Selection

All outcomes except blood sugar and weight should be recorded here. **(Report results for the most adjusted model.)**

Other statistics

	109. **Other measure** (specify:)	110. **Other measure** (specify:)	111. **Other measure** (specify:)
Group 1	112.	113.	114.
Group 2	115.	116.	117.
Group 3	118.	119.	120.
Group 4	121.	122.	123.

124. Comments:

Enlarge Shrink

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				limit	

Measure of Association (For measures of variability, please record the standard error when available. If the standard error is not available, plea record either the 95% confidence interval or the standard deviation. Always record the p-value when available.)

	87. **Point estimate (select one:)**	**Indicate reference group**	88. **Measure of variability (select one:)**	**95% Confidence interval**	**p-value**
	○ Relative risk ○ Relative hazard ○ Odds ratio ○ Risk difference ○ Other (specify:) Clear Selection		○ Standard error ○ Standard deviation ○ Other (specify:) Clear Selection		
Group 1	89.	90.	91.	92. lower limit upper limit	93.
Group 2	94.	95.	96.	97. lower limit upper limit	98.
Group 3	99.	100.	101.	102. lower limit upper limit	103.
Group 4	104.	105.	106.	107. lower limit upper limit	108.

Group 4	61.	62.	63. lower limit / upper limit	64.

Measure of Association (For measures of variability, please record the standard error when available. If the standard error is not available, plea record either the 95% confidence interval or the standard deviation. Always record the p-value when available.)

	65. **Point estimate (select one:)**	**Indicate reference group**	66. **Measure of variability (select one:)**	**95% Confidence interval**	**p-value**
	○ Relative risk ○ Relative hazard ○ Odds ratio ○ Risk difference ○ Other (specify:) Clear Selection		○ Standard error ○ Standard deviation ○ Other (specify:) Clear Selection		
Group 1	67.	68.	69.	70. lower limit / upper limit	71.
Group 2	72.	73.	74.	75. lower limit / upper limit	76.
Group 3	77.	78.	79.	80. lower limit / upper limit	81.
Group 4	82.	83.	84.	85. lower limit / upper	86.

	from initial N Can"t tell N has not changed	events % with 1 or more events Specify other numerator type: Specifiy other numerator value:	
Group 4	45. List if different from initial N Can"t tell N has not changed	46. # with 1 or more events % with 1 or more events Specify other numerator type: Specifiy other numerator value:	47.

Incidence Rate (For measures of variability, please record the standard error when available. If the standard error is not available, please recor either the 95% confidence interval or the standard deviation. Always record the p-value when available.)

	Point Estimate	48. **Measure of variability (select one:)** Standard error Standard deviation Other (specify:) Clear Selection	95% Confidence interval	p-value
Group 1	49.	50.	51. lower limit upper limit	52.
Group 2	53.	54.	55. lower limit upper limit	56.
Group 3	57.	58.	59. lower limit upper limit	60.

- Yes
- No
- Not reported
- Not applicable

Clear Selection

All outcomes except blood sugar and weight should be recorded here. **(Report results for the most adjusted model.)**

	Number of people included in analysis for each group	**Numerator**	35. Denominator (if person-time used or # events in a certain time pe Enter amount of time below and indicate time period here:
			☐ Days ☐ Weeks ☐ Months ☐ Years ☐ Person-years ☐ Other (specify:) ☐ Not applicable
Group 1	36. List if different from initial N ☐ Can"t tell ☐ N has not changed	37. # with 1 or more events % with 1 or more events Specify other numerator type: Specifiy other numerator value:	38.
Group 2	39. List if different from initial N ☐ Can"t tell ☐ N has not changed	40. # with 1 or more events % with 1 or more events Specify other numerator type: Specifiy other numerator value:	41.
Group 3	42. List if different	43. # with 1 or more	44.

☐ Other bone fracture (specify:) ☐ Nerve palsy ☐ Other (specify:)	☐ Other (specify): _____ ☐ Not reported
25. ☐ Anoxia or acidosis	26. ☐ Clinical diagnosis (criteria not given) ☐ Claims data/ICD-9 ☐ Arterial blood gas from neonate ☐ Cord blood gas ☐ Other (specify): _____ ☐ Not reported
27. ☐ Congenital malformation (specify): _____	28. ☐ Clinical diagnosis (criteria not given) ☐ Claims data/ICD-9 ☐ Other (specify): _____ ☐ Not reported
29. ☐ Respiratory distress syndrome	30. ☐ Clinical diagnosis (criteria not given) ☐ Claims data/ICD-9 ☐ Other (specify): _____ ☐ Not reported
31. ☐ Admission to NICU	NA
32. Mortality ☐ Fetal mortality ☐ Perinatal/neonatal mortality	33. ☐ Death certificate ☐ Clinical diagnosis ☐ Chart review ☐ Other (specify): _____

34. Was this an intention-to-treat analysis?

	☐ Not reported
13. ☐ Hyperbilirubinemia	14. ☐ Serum bilirubin > _____ ☐ Other (specify): _____ ☐ Not reported
15. ☐ Macrosomia	16. ☐ Birth weight > _____ ☐ Other (specify): _____ ☐ Not reported
17. ☐ Large for gestational age (LGA)	18. ☐ weight (grams) > _____ ☐ percentile weight > _____ ☐ Other (specify:) _____ ☐ Not reported
19. ☐ Small for gestational age (SGA)	20. ☐ weight (grams) < _____ ☐ percentile weight < _____ ☐ Other (specify:) _____ ☐ Not reported
21. ☐ Shoulder dystocia	22. ☐ Clinical diagnosis (criteria not given) ☐ Claims data/ICD-9 ☐ Other (specify): _____ ☐ Not reported
23. Birth trauma ☐ Clavicle bone fracture ☐ Humerus bone fracture	24. ☐ Clinical diagnosis (criteria not given) ☐ Claims data/ICD-9

	☐ Other (specify): ☐ Not reported
3. C-section ☐ Elective C-section ☐ Emergency C-section ☐ Total C-sections ☐ Other (specify:)	4. ☐ Clinical diagnosis (criteria not given) ☐ Claims data/ICD-9 ☐ Other (specify): ☐ Not reported
5. Hemorrhage ☐ Intrapartum hemorrhage ☐ Postpartum hemorrhage ☐ Other (specify:)	6. ☐ Clinical diagnosis (criteria not given) ☐ Claims data/ICD-9 ☐ Other (specify): ☐ Not reported
7. Operative vaginal delivery ☐ Forceps use ☐ Vacuum use ☐ Other (specify:)	8. ☐ Clinical diagnosis (criteria not given) ☐ Claims data/ICD-9 ☐ Other (specify): ☐ Not reported
9. Perineal tears ☐ 3rd degree tears ☐ 4th degree tears	10. ☐ Clinical diagnosis (criteria not given) ☐ Claims data/ICD-9 ☐ Other (specify): ☐ Not reported
Neonatal outcome	**Definition and/or units used (check all that apply)**
11. ☐ Neonatal hypoglycemia	12. ☐ fsg ☐ symptoms ☐ Other (specify):

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Reviewer Comments (Add a Comment)

Refid: 1, Geremia, C. and Cianfarani, S., Insulin Sensitivity in Children Born Small for Gestational Age (SGA), *Rev Diabet Stud*, 1(2), 2004, p.58-65
State: Excluded, Level: 2

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KQ1 Outcomes Form
Labor and Postpartum Management of Gestational Diabetes Mellitus

Please complete this form if:

- **Study applies to KQ1**
- **Maternal outcome being reported is pre-eclampsia, c-section, hemorrhage, operative vaginal delivery perineal tears**
- **Neonatal outcome being reported is hypoglycemia, hyperbilirubinemia, macrosomia, LGA, SGA, shoulder dystocia, birth trauma, anoxia or acidosis, congenital malformations, respiratory distress syndrome, admission to NICU, or mortality.**

Mark outcome of interest and how defined or what units used. **(Check only one outcome per form)**

Maternal outcome	Definition and/or units used (check all that apply)
1. ☐ Pre-eclampsia	2. ☐ Clinical diagnosis (criteria not given) ☐ Claims data/ICD-9 ☐ Blood pressure (specify systolic and/or diastolic): Systolic: Diastolic: ☐ Proteinuria:

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- Yes
- No
- Not applicable

Clear Selection

44. If yes, what confounders were adjusted for? (check all that apply)

- Maternal age
- Race
- Parity
- Family History of Diabetes
- Prior GDM
- Diagnosed with GDM prior to 24 weeks
- Pre-pregnancy weight
- Pre-pregnancy BMI
- Gestational weight gain
- Other maternal disease confounders such as thyroid disease, placental abruption, placental previa
- Multiple gestation
- Steroid use during pregnancy
- Glucose: specify glucose measure used (such as mean glucose during pregnancy)
- Duration of gestational diabetes
- Duration of treatment for gestational diabetes
- Other (specify):
- Other (specify):
- Other (specify):
- Other (specify):
- Other (specify):

45. Please write in any additional comments regarding key question 1

If escalated, what were the mean and max dose of medication for each group (if applicable)?

	Group 1	Group 2	Group 3	Group 4
34. Mean				
35. Max				

	Group 1	Group 2	Group 3	Group 4
36. What were the **target glucose values** for each group? **(Enter NR if not reported.)**				

37. What was the unit for the target glucose values in above question?

- mmol/l
- mg/dL
- other: specify

Clear Selection

38. Are the target glucose values in **Q36**:

- Fasting glucose
- 1 hour postprandial glucose
- 2 hour postprandial glucose
- Not specified

Clear Selection

(If assignment to treatment was non-randomized, answer:)

39. Were there different cut-points in glucose used for assigning subjects to each treatment group?

- Yes
- No
- Not applicable

Clear Selection

	Group 1	Group 2	Group 3	Group 4	rep
40. At what **level** of glucose was the decision made to add insulin, switch to insulin or add oral?					

For each group, report the number and/or percent of participants who added insulin to their regimen, switched their regimen to insulin or added oral to their regimen.

	Group 1	Group 2	Group 3	Group 4	Total
41. Number					
42. Percent					

43. If an **observational study**, were adjustments done?

12. Insulin switched to oral	☐	☐	☐	☐
13. Insulin added to diet	☐	☐	☐	☐
14. Insulin added to oral	☐	☐	☐	☐
15. Oral added to diet	☐	☐	☐	☐
16. Oral added to insulin	☐	☐	☐	☐
17. Other (Specify):				

What were the **starting dose**, **units**, and **number of times a day** for each group (if applicable)?

	Group 1	Group 2	Group 3	Group 4
Dose	18.	19.	20.	21.
Unit	22. ☐ mg ☐ grams ☐ IU ☐ Units/kg ☐ Other (specify):	23. ☐ mg ☐ grams ☐ IU ☐ Units/kg ☐ Other (specify):	24. ☐ mg ☐ grams ☐ IU ☐ Units/kg ☐ Other (specify):	25. ☐ mg ☐ grams ☐ IU ☐ Units/kg ☐ Other (specify):
# times per day	26.	27.	28.	29.

Was the dose of drug **fixed** or **escalated** for each group (if applicable)?

	Group 1	Group 2	Group 3	Group 4
30. Fixed	☐	☐	☐	☐
31. Escalated	☐	☐	☐	☐
32. Not Specified	☐	☐	☐	☐
33. Other (Specify):				

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Reviewer Comments (Add a Comment)

Refid: 1, Geremia, C. and Cianfarani, S., Insulin Sensitivity in Children Born Small for Gestational Age (SGA), *Rev Diabet Stud*, 1(2), 2004, p.58-65
State: Excluded, Level: 2

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KQ1 Intervention Form

Labor and Postpartum Management of Gestational Diabetes Mellitus

Please complete this form for studies that apply to KQ1.

Select the intervention at baseline for each group. (Check all that apply)

	Group 1	Group 2	Group 3	Group 4
1. Diet	☐	☐	☐	☐
2. NPH Insulin	☐	☐	☐	☐
3. Regular insulin	☐	☐	☐	☐
4. Lispro insulin	☐	☐	☐	☐
5. Insulin pump	☐	☐	☐	☐
6. Metformin	☐	☐	☐	☐
7. Sulfonylurea	☐	☐	☐	☐
8. Placebo	☐	☐	☐	☐
9. Diet switched to oral (either metformin or sulfonylurea)	☐	☐	☐	☐
10. Diet switched to insulin	☐	☐	☐	☐
11. Oral switched to insulin	☐	☐	☐	☐

☐ Gestational age at test is not reported

For the test used, enter the mean or median glucose values of the results of the test.

	Group 1	Group 2	Group 3	Group 4	Total
50g					
3 hour, 100g OGTT Fasting					
1 hr					
2 hr					
3 hr					
2 hour, 75g OGTT Fasting					
1 hr					
2 hr					

Values are:

☐ Mean

☐ Median

☐ Range

☐ Other measure (specify)

☐ Glucose values are not reported

77. Comments:

Enlarge Shrink

Save to finish later | Submit Data

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☐ 100g, O'Sullivan or NDDG (National Diabetes Data Group	105 mg/dL or 5.8 mmol/L	190 mg/dL or 10.6 mmol/L	165 mg/dL or 9.2 mmol/L	1 8
☐ 75g, WHO (World Health Organization)	126 mg/dL or 7.0 mmol/L	n/a	140 mg/dL or 7.8 mmol/L	
☐ 75g, ADA (American Diabetes Association)	95 mg/dL or 5.3 mmol/L	180 mg/dL or 10.0 mmol/L	155 mg/dL or 8.6 mmol/L	
☐ 75g, CDA (Canadian Diabetes Association)	95 mg/dL or 5.3 mmol/L	190 mg/dL or 10.6 mmol/L	160 mg/dL or 8.9 mmol/L	
☐ Other test used (specify name of test here and enter threshold values for the appropriate times)	mg/dL mmol/L	mg/dL mmol/L	mg/dL mmol/L	mg/dL mmol/L
☐ 75g OGTT, threshold value not specified	n/a	n/a	n/a	
☐ 100g OGTT, threshold value not specified	n/a	n/a	n/a	

For the test used, enter the mean, median or range of gestational age when the test was conducted.

66. Gestational age at test, mean, median or range in weeks	67. Values are:
50g	☐ Mean
3 hour, 100g OGTT	☐ Median
2 hour, 75g OGTT	☐ Range
Other test	☐ Other measure (specify)

	Group 1	Group 2	Group 3	Group 4	Total
39. Diet, n					
40. Diet, %					
41. Oral hypoglycemics, n					
42. Oral hypoglycemics, %					
43. Insulin, n					
44. Insulin, %					

	Specify management method	Group 1	Group 2	Group 3	Group 4
45. Other method of management, n					
46. Other method of management, %					
47. Other method of management, n					
48. Other method of management, %					
49. Other method of management, n					
50. Other method of management, %					

Other population characteristics

(Only include other population characteristics that either are statistically significant or considered a confounder.)

	Other	Group 1	Group 2	Group 3	Group 4
51. Other (specify)					
52. Other (specify)					
53. Other (specify)					

OGTT

What was the threshold value for the OGTT?

	Fasting	1 hour	2 hour	
100g, Carpenter and Coustan criteria	95 mg/dL or 5.3 mmol/L	180 mg/dL or 10.0 mmol/L	155 mg/dL or 8.6 mmol/L	1 7

- Mean
- Median
- Range
- Other
- Not reported

Clear Selection

	Group 1	Group 2	Group 3	Group 4	Total
24. Pre-pregnancy weight					
25. First trimester weight					
26. Pregnancy weight gain					
27. Postpartum weight					
28. Pre-pregnancy BMI					
29. Pregnancy BMI at delivery					
30. Postpartum BMI					

Previous pregnancies/live births

	Group 1	Group 2	Group 3	Group 4	
31. Number of previous pregnancies, mean (gravida)					
32. Number of previous live births, mean (parity)					

	Specify parity category	Group 1	Group 2	Group 3	Group 4	
33. Other parity						
34. Other parity						
35. Other parity						
36. Other parity						

Gestational age at time of enrollment

	Group 1	Group 2	Group 3	Group 4	
37. Gestational age at time of enrollment, mean weeks					
38. Gestational age at time of enrollment, range in weeks					

Method of GDM management during pregnancy

Age

	Group 1	Group 2	Group 3	Group 4	Total
4. Mean age					
5. Age range					

	Specify age category	Group 1	Group 2	Group 3	Group 4	
6. Other age						
7. Other age						
8. Other age						
9. Other age						

Race

	Group 1	Group 2	Group 3	Group 4	Total
10. African American, n					
11. African American, %					
12. Caucasian, n					
13. Caucasian, %					
14. Asian/Asian American, n					
15. Asian/Asian American, %					
16. Hispanic/Latino, n					
17. Hispanic/Latino, %					

	Specify race	Group 1	Group 2	Group 3	Group 4	
18. Other race, n						
19. Other race, %						
20. Other race, n						
21. Other race, %						

22.

☐ Race not reported

Weight/BMI

23. Weight/BMI values are:

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Previewing at Level 5

Reviewer Comments (Add a Comment)

Refid: 1, Geremia, C. and Cianfarani, S., Insulin Sensitivity in Children Born Small for Gestational Age (SGA), *Rev Diabet Stud*, 1(2), 2004, p.58-65
State: Excluded, Level: 2

Save to finish later | Submit Data

General Form - Part 2
Labor and Postpartum Management of Gestational Diabetes Mellitus

Please complete this form for ALL included studies.

Please respond to the following questions for the **ENTIRE** study.

Study Population Characteristics

1. Does the study include more than 1 group?

- Yes, specify number of groups
- No ->**FILL IN TOTAL COLUMN FOR Q4-Q39.**

Clear Selection

Please fill in the study population characteristics below. **(Enter data only for relevant groups.) (You do NOT need to enter the standard deviation or standard errors for these m "Total" column only if there are no study groups.) (For KQ4, include the data for the total sample under the total column.)**

	Group 1	Group 2	Group 3	Group 4
2. Please provide a one word name for each group indicated in question above. List groups in order of increasing dosage of the intervention, e.g. for KQ1, group 1= placebo (or control), group 2 = 0.7 U/Kg Insulin, group 3 = 2.5 mg glyburide, group 4 = 425mg metformin; e.g., for KQ2, expectant management = group 1.				
3. N enrolled				

Early diagnosis of GDM (1st trimester) Fasting plasma glucose at time of diagnosis Temporal pattern of hyperglycemia Method of glucose control Poor glycemic control **Characteristics of delivery** Preterm labor Macrosomia LGA SGA	Pre-pregnancy weight Pregnancy weight gain High saturated fat diet Physical activity level **Postpartum factors** Postpartum weight loss Postpartum weight retention Postpartum BMI Breastfeeding Contraceptive use Postpartum depression Psychological characteristics	Insulin antibodies Anti-islet cell anti-GAD C-peptide Pro-insulin

8. KEY QUESTION 4: What are the performance characteristics (sensitivity, specificity, and reproducibility) of tests for diagnosing diabetes when conducted in postpartum GDM patients after pregnancy? Are there differences in the performance characteristics of the test results based on sub-group analysis?

☐ Applies to KQ 4

9. Reviewer comments:

Enlarge Shrink

10. Reviewer initials (only enter if sharing a user id).

Enlarge Shrink

11. Applies to KQ3, diabetes only AND:

○ Reports relative measure

○ Does not report relative measure

Clear Selection

12. Observational study that applies to KQ1 and:

☐ compares glyburide/glibenclamide to insulin

☐ compares insulin to another insulin

☐ has another relevant comparison

☐ does not have a comparison of interest

Save to finish later Submit Data

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☐ Applies to KQ 2b: What is the evidence for vaginal labor induction at 40 weeks compared to labor induction at an earlier gestational age (<40 weeks) or spontaneous labor in the pregnancy of gestational diabetes mellitus?
i. labor induction at <40 weeks v labor induction at 40 weeks
ii. labor induction at 40 weeks v spontaneous labor
iii. labor induction at <40 weeks v spontaneous labor

☐ Applies to KQ 2c: How is the estimated intrauterine fetal weight related to outcomes of management of GDM with medically indicated cesarean delivery or timing (i.e., gestational age range) of labor induction?

☐ Applies to KQ 2d: How is gestational age related to outcomes of management of GDM with medically indicated cesarean delivery or choice of timing of induction (i.e. gestational age range) of labor induction?

Maternal Outcomes:	**Neonatal Outcomes:**
· postpartum hemorrhage, · intrapartum infection, · postpartum infection, · third or fourth degree lacerations or any other perineal laceration and episiotomy, · operative vaginal delivery · cesarean delivery after failed attempt at vaginal delivery (e.g., failed induction, protracted labor)	· macrosomia, · LGA or SGA, · respiratory distress syndrome, · birth weight, · shoulder dsytocia, · birth trauma, · nerve palsy and fracture, · anoxia or acidosis, · hypoglycemia, and hyperbilirubinemia, · neonatal intensive care admissions, · congenital malformations, · mortality

6. KEY QUESTION 3: What risk factors are associated with short-term and long-term development of 1) impaired glucose tolerance, and/or 2) type 2 diabetes mellitus following a pregnancy with GDM? (choose all that apply)
Note: If the study DOES NOT use an accepted diagnostic method (FBS > 125 mg/dl; 75g OGTT, 2-hour glusose ≥ 200 mg/dl; random glucose ≥ 200 mg/dl; self-reported type 2 diabetes mellitus; current use of an antidiabetic medication) for type 2 diabetes mellitus it is not eligible for Q3

(Note: exclude if evaluates risk factors for only impaired glucose tolerance)

☐ Applies to KQ3 for type 2 diabetes mellitus only or has a separate analysis for type 2 diabetes mellitus only

☐ Applies to KQ3 for impaired glucose tolerance and type 2 diabetes combined

7. For studies that apply to KQ3, was a multivariate analysis reported?

○ Multivariate analysis reported

○ Multivariate analysis not reported

Clear Selection

Risk Factors for KQ3		
Demographics	**Cumulative pregnancy-related factors**	**Additional factors**
Age	Parity	Waist-to-hip ratio
Race	# of prior GDM pregnancies	Waist circumference
Income/Eductation/SES	# prior macrosomic infants	**Clinical measures**
Pregnancy Characteristics	**Maternal lifestyle**	Insulin

☐ other: specify

2. UNCLEAR

○ unclear (can not determine from abstract alone OR no abstract available)--move to Article Review without identifying a Key Question

Clear Selection

This article may apply to one of the following Key Questions (KQ)--choose all that apply.

3. KEY QUESTION 1: What is the evidence for the risks and benefits of FDA approved oral hypoglycemic agents (glyburide) to treat GDM and metformin (although not officially approved, it is used in certain clinical situations) compared to all types of insulin approved by the FDA for use in pregnancy for both the mother and neonate?
Note: If the study DOES NOT contain an appropriate comparison group (see listing of appropriate comparisons below) it is not eligible for Q1.
Note: FDA approved insulins for use during pregnancy: lispro, aspart, regular, nph, and the insulin pump that includes lispro or aspart

☐ Applies to KQ 1

4. For studies that apply to KQ1, indicate the study design:

○ RCTs

○ Observational study or other study type

Clear Selection

Comparisons:	**Maternal Outcomes:**	**Neonatal Outcomes:**
i. diet v approved insulin ii. diet v metformin iii. diet v gliburide iv. metformin v approved insulin v. metformin v gliburide vi. gliburide v insulin vii. approved insulin v approved insulin viii. metformin v placebo ix. gliburide v placebo x. insulin v placebo	· hypoglycemia, · glycemic control (Note: studies measuring glycemic control should report specific measures (e.g., fasting blood sugar, 1 hour and 2 hour post prandial glucose)), · cesarean delivery, · pre-eclampsia, and postpartum hemorrhage · maternal weight, · perineal lacerations, · operative vaginal delivery	· macrosomia, · LGA or SGA, · respiratory distress syndrome, · birth weight, · shoulder dsytocia, · birth trauma, · nerve palsy and fracture, · anoxia or acidosis, · hypoglycemia, and hyperbilirubinemia, · neonatal intensive care admissions, · congenital malformations, · mortality

5. KEY QUESTION 2: What is the evidence that medically indicated cesarean delivery or choice of timing of induction result in beneficial or harmful neonatal outcomes in GDM (as outlined above for Key Question #1) and maternal outcomes?
Note: intended method of delivery should be clearly defined (e.g., for cesarean delivery, groups must be defined as either elective cesarean or cesarean following labor)
Note: studies should report a measure of gestational age at induction for KQ2b
Note: studies should only be included for KQ2c if intrauterine fetal weight was measured using ultrasound

☐ Applies to KQ 2a: What is the evidence for elective cesarean delivery at term compared to an attempt at vaginal delivery (spontaneous or induced) at term?
i. cesarean v spontaneous labor and vaginal delivery at term
ii. cesarean v induced labor and vaginal delivery at term
iii. cesarean v any attempt at vaginal delivery at term

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Previewing at Level 3

Reviewer Comments (Add a Comment)

Refid: 1, Geremia, C. and Cianfarani, S., Insulin Sensitivity in Children Born Small for Gestational Age (SGA), *Rev Diabet Stud*, 1(2), 2004, p.58-65
State: Excluded, Level: 2

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ARTICLE Review Form

Does this article POTENTIALLY apply to any of the key questions?

1. NO, this article does not apply to any of our Key Questions

- ☐ not written in English
- ☐ study evaluates outcomes in animals only (no humans evaluated)
- ☐ not evaluating people with gestational diabetes (Note: Exclude if there is not a separate analysis for gestational diabetes AND if less than 90% of total sample has gestational diabetes.)
- ☐ does not include original data (e.g., is a meeting abstract, review, commentary, letter, editorial)
- ☐ case report or case series of less than 50 cases (Note: there is no sample size criteria for studies with a comparison group)
- ☐ diagnosis of GDM NOT confirmed using either a 3-hr 100g OGTT or a 2-hr 75g OGTT for a majority of patients (Note: WHO, NDDG, and International Workshop Conference are acceptable diagnostic protocols)
- ☐ evaluates a maternal or fetal outcome NOT being evaluated in our report
- ☐ does not include a medication of interest for Key Questsion 1
- ☐ no appropriate comparison group for Key Questions 1, 2a or 2b (Note: there cannot be a historical comparison group for KQ1)
- ☐ no relevant risk factor for Key Question 3
- ☐ does not apply to any of the key questions
- ☐ review article—may include important information—pull for hand searching
- ☐ review article that does not apply to any of the key questions

cesarean delivery or choice of timing of induction (i.e. gestational age range) of labor induction?

5. KEY QUESTION 3: What risk factors are associated with short-term and long-term development of 1) impaired glucose tolerance, and/or 2) type 2 diabetes mellitus following a pregnancy with GDM?(choose all that applly)
Note: If the study DOES NOT use an accepted diagnostic method (FBS > 125 mg/dl; 75g OGTT, 2-hour glusose ≥ 200 mg/dl; random glucose ≥ 200 mg/dl; self-reported type 2 diabetes mellitus; current use of an antidiabetic medication) for type 2 diabetes mellitus it is not eligible for Q3

- [ ] Applies to KQ3 for type 2 diabetes mellitus
- [ ] Applies to KQ3 for impaired glucose tolerance

6. KEY QUESTION 4: What are the performance characteristics (sensitivity, specificity, and reproducibility) of tests for diagnosing diabetes when conducted in postpartum GDM patients after pregnancy? Are there differences in the performance characteristics of the test results based on sub-group analysis?

- [ ] Applies to KQ 4

7. Reviewer initials (only enter if sharing a user id).

Enlarge Shrink

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Form took 0.515625 seconds to render

2. UNCLEAR

unclear (can not determine from abstract alone OR no abstract available)--move to Article Review without identifying a Key Question

Clear Selection

This article may apply to one of the following Key Questions (KQ)--choose all that apply.

3. KEY QUESTION 1: What is the evidence for the risks and benefits of FDA approved oral hypoglycemic agents (glyburide) to treat GDM and metformin (although not officially approved, it is used in certain clinical situations) compared to all types of insulin approved by the FDA for use in pregnancy for both the mother and neonate?
Note: If the study DOES NOT contain an appropriate comparison group (see listing of appropriate comparisons below) it is not eligible for Q1.
Note: FDA approved insulins for use during pregnancy: lispro, aspart, regular, nph, and the insulin pump that includes lispro or aspart

Applies to KQ 1

Comparisons:	**Maternal Outcomes:**	**Neonatal Outcomes:**
i. diet v approved insulin ii. diet v metformin iii. diet v gliburide iv. metformin v approved insulin v. metformin v gliburide vi. gliburide v insulin vii. approved insulin v approved insulin viii. metformin v placebo ix. gliburide v placebo x. insulin v placebo	· hypoglycemia, · glycemic control (fasting blood sugar, 1 hour and 2 hour post prandial glucose), · cesarean delivery, · pre-eclampsia, and postpartum hemorrhage · maternal weight, · perineal lacerations, · operative vaginal delivery	· macrosomia, · birth weight, · shoulder dsytocia, · birth trauma, · nerve palsy and fracture, · anoxia or acidosis, · hypoglycemia, and hyperbilirubinemia, · neonatal intensive care admissions, · congenital malformations · mortality

4. KEY QUESTION 2: What is the evidence that medically indicated cesarean delivery or choice of timing of induction result in beneficial or harmful neonatal outcomes in GDM (as outlined above for Key Question #1)?

Applies to KQ 2a: What is the evidence for elective cesarean delivery at term compared to an attempt at vaginal delivery (spontaneous or induced) at term?
i. cesarean v spontaneous labor and vaginal delivery at term
ii. cesarean v induced labor and vaginal delivery at term
iii. cesarean v any attempt at vaginal delivery at term

Applies to KQ 2b: What is the evidence for vaginal labor induction at 40 weeks compared to labor induction at an earlier gestational age (<40 weeks) or spontaneous labor in the pregnancy of gestational diabetes mellitus?
i. labor induction at <40 weeks v labor induction at 40 weeks
ii. labor induction at 40 weeks v spontaneous labor
iii. labor induction at <40 weeks v spontaneous labor

Applies to KQ 2c: How is the estimated intrauterine fetal weight related to outcomes of management of GDM with medically indicated cesarean delivery or timing (i.e., gestational age range) of labor induction?

Applies to KQ 2d: How is gestational age related to outcomes of management of GDM with medically indicated

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Previewing at Level 2

Reviewer Comments (Add a Comment)

Refid: 1, Geremia, C. and Cianfarani, S., Insulin Sensitivity in Children Born Small for Gestational Age (SGA), *Rev Diabet Stud*, 1(2), 2004, p.58-65
State: Excluded, Level: 2

Keywords:
No keywords available

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Abstract:
In the past decade, several epidemiological studies have shown a relationship between intrauterine growth retardation and insulin resistance, type 2 diabetes and cardiovascular disease in adulthood. Although the biological mechanisms underlying this association are still largely unknown, different explanatory hypotheses have been proposed. It seems likely that the various pathways may interact with each other, all contributing at different degrees to the development of the metabolic disturbances.

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ABSTRACT Review Form

Does this article POTENTIALLY apply to any of the key questions?

1. NO, this article does not apply to any of our Key Questions

- [ ] not written in English
- [ ] study evaluates outcomes in animals only (no humans evaluated)
- [ ] not evaluating ANY people with gestational diabetes (exclude even if our list of maternal and fetal outcomes are evaluated)
- [ ] does not include original data (e.g., is a meeting abstract, review, commentary, letter, editorial)
- [ ] case report or case series of less than 50 cases
- [ ] diagnosis of GDM NOT based on either a 3-hr 100g OGTT, or a 2-hr 75g OGTT for a majority of patients
- [ ] evaluates a maternal or fetal outcome NOT being evaluated in our report
- [x] does not include a medication of interest for Key Questsion 1
- [ ] no appropriate comparison group for Key Questions 1, 2a or 2b
- [x] does not apply to any of the key questions
- [ ] review article—may include important information—pull for hand searching
- [ ] other: specify

	Yes	No	
11. Were confidence intervals or standard errors reported for point estimates?	○	○	Clear
12. Were estimates reported for demographic or clinical subgroups?	○	○	Clear
13. Did the authors provide a description of participants that were loss to follow-up?	○	○	Clear
14. Was a cross tabulation of the screening test with the reference test included (e.g. are you able to recreate the contingency tables from the data provided)?	○	○	Clear

15. Comments:

Enlarge Shrink

	Yes	No	Not reported	
16. Was the screening test(s) interpreted independently (i.e., evaluated without knowledge) of the results of the reference test?	○	○	○	Clear
17. Was the reference test interpreted independently (i.e., evaluated without knowledge) of the results of the screening test?	○	○	○	Clear

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Evidence Table 1. Characteristics of studies reporting on the effects of oral hypoglycemic agents or insulin on maternal and neonatal outcomes: randomized controlled trials

Author, year Country Study design	Time period	OGTT GA at diagnosis (in weeks)	OGTT results (in mg/dL)	Mean age (in years) (Age range)	Race, n (%)	Weight (in kg) / BMI (in kg/m^2), mean	Gravida/ parity, mean	Treatment, N	Initial dose (fixed or escalated) Maximum dose Mean dose
Insulin versus glyburide									
Anjalakshi, 2006[33] India RCT	NR	75-gm WHO G1: 22.62	G1: 2hr: 174.92	G1: 27.46	G1: Asian: 13 (100)	G1: Pre-pregnancy BMI: 25.32	G1: NR	G1: Insulin, 13	G1: Initial dose: 0.1 units/kg (esc) Max dose: NR Mean dose: NR
		G2: 22.5	G2: 2hr: 167.1*	G2: 24.9	G2: Asian: 10 (100)	G2: Pre-pregnancy BMI: 22.82	G2: NR	G2: Glibenclamide, 10	G2: Initial dose: 0.625 mg (esc) Max dose: NR Mean dose: NR
Bertini, 2005[37] Brazil RCT	Start year: October 1, 2003 End year: July 1, 2004 Planned study period: 8 months	75-gm WHO and the Brazilian Health Ministry F: 110 mg/dL 2hr: 140 mg/dL G1: NR	G1: NR	G1: 28.7	G1: NR	G1: Pre-pregnancy BMI: 27	G1: Gravida: 2.5	G1: Insulin, 27	G1: Initial dose: 0.7 units/kg in the 1st trimester, 0.8 in the second, 0.9 in the third, 4 times per day (esc) Max dose: NR Mean dose: NR
		G2: NR	G2: NR	G2: 31.2	G2: NR	G2: Pre-pregnancy BMI: 27.5	G2: Gravida: 3.2	G2: Glyburide, 24	G2: Initial dose: 5 mg, 1 time per day (esc) Max dose: 20mg/day Mean dose: NR
		G3: NR	G3: NR	G3: 31.5	G3: NR	G3: Pre-pregnancy BMI: 25.7	G3: Gravida: 2.9	G3: Acarbose, 19	G3: Initial dose: 50 mg, 3 times per day (esc) Max dose: 300mg/day Mean dose: NR
Langer, 2000[32 107] US RCT	NR	3hr 100-gm OGTT[†] F: 95 mg/dL G1: 25	G1: F: 98 1hr: 201 2hr: 174 3hr: 134	G1: 30	G1: NR	G1: Pre-pregnancy BMI (n, % with BMI>=27.3): 132 (65)	G1: (Number of nulliparity: 59)	G1: Insulin, 203	G1: Initial dose: 0.7 units/kg, 3 times per day (esc) Max dose: no max dose Mean dose: 85 units/day
		G2: 24	G2: F: 97 1hr: 197 2hr: 174 3hr: 140	G2: 29	G2: NR	G2: Pre-pregnancy BMI (n, % with BMI>=27.3): 141 (70)	G2: (Number of nulliparity: 56)	G2: Glyburide, 201	G2: Initial dose: 2.5 mg, 1 time per day (esc) Max dose: 20 mg/day Mean dose: 9 mg/day

Evidence Table 1. Characteristics of studies reporting on the effects of oral hypoglycemic agents or insulin on maternal and neonatal outcomes: randomized controlled trials (continued)

Author, year Country Study design	Time period	OGTT GA at diagnosis (in weeks)	OGTT results (in mg/dL)	Mean age (in years) (Age range)	Race, n (%)	Weight (in kg) / BMI (in kg/m^2), mean	Gravida/ parity, mean	Treatment, N	Initial dose (fixed or escalated) Maximum dose Mean dose
Insulin versus insulin lispro									
Jovanovic, 1999[36] US RCT	NR	100-gm, Carpenter and Coustan criteria G1: 25.6	G1: NR	G1: 29.8	G1: C: 0 (0) Hisp: 23 (100)	G1: Pre-pregnancy weight: 78.5 Pre-pregnancy BMI: 33.3	G1: Gravida: 2.4 Parity: 1.7	G1: Regular human insulin, 23	G1: Initial dose: 0.7 units/kg, 3 + 2 NPH times per day (esc) Max dose: NR Mean dose: NR
		G2: 27.3	G2: NR	G2: 34.2	G2: C: 2 (11) Hisp: 17 (89)	G2: Pre-pregnancy weight: 76.3 Pre-pregnancy BMI: 31.5	G2: Gravida: 1.8 Parity: 1.4	G2: Insulin lispro, 19	G2: Initial dose: 0.7 units/kg, 3 + 2 NPH times per day (esc) Max dose: NR Mean dose: NR
Mecacci, 2003[34] Italy RCT	Start year: June 1999 End year: Dec 2000	100-gm, Carpenter and Coustan criteria G1: median 28 (26-32)	G1: F: 91 1hr: 197 2hr: 189 3hr: 138	G1: (28-41) (median 35)	G1: C: 24 (100)	G1: Pre-pregnancy weight: (Median: 60.5) Pre-pregnancy BMI: (Median: 22.3)	G1: Parity: (median 1 (range 0-1))	G1: Regular human insulin, 24	G1: Initial dose: 1 unit/10 gms of carbohydrate in each meal, 3 times per day (esc) Max dose: NR Mean dose: 34.3 units/day
		G2: median 28 (25-32)	G2: F: 92 1hr: 193 2hr: 170 3hr: 126	G2: (24-40) (median 34.5)	G2: C: 25 (100)	G2: Pre-pregnancy weight: (Median: 61.4) Pre-pregnancy BMI: (Median: 21.5)	G2: Parity: (median 1 (range 0-2))	G2: Insulin lispro, 25	G2: Initial dose: 1 unit/10 gms of carbohydrate in each meal, 3 times per day (esc) Max dose: NR Mean dose: 35.1 units/day
Insulin versus insulin									
Nachum, 1999[35] Israel RCT	Start year: 1993 End year: 1997 Planned study period: 48 months	100-gm, O'Sullivan or NDDG G1: 28	G1: NR	G1: 33	G1: NR	G1: Pre-pregnancy weight: 72 Pre-pregnancy BMI: 27.8	G1: Gravida: 3.4	G1: Insulin twice daily, 136	G1: Initial dose: NR, 2 times per day Max dose: NR Mean dose: NR
		G2: 27.4	G2: NR	G2: 33	G2: NR	G2: Pre-pregnancy weight: 73 Pre-pregnancy BMI: 27.9	G2: Gravida: 3.5	G2: Insulin four times daily, 138	G2: Initial dose: NR, 4 times per day Max dose: NR Mean dose: NR

Evidence Table 1. Characteristics of studies reporting on the effects of oral hypoglycemic agents or insulin on maternal and neonatal outcomes: randomized controlled trials (continued)

Author, year Country Study design	Time period	OGTT GA at diagnosis (in weeks)	OGTT results (in mg/dL)	Mean age (in years) (Age range)	Race, n (%)	Weight (in kg) / BMI (in kg/m^2), mean	Gravida/ parity, mean	Treatment, N	Initial dose (fixed or escalated) Maximum dose Mean dose
Poyhonen-Alho, 2002[31] Finland RCT	NR	2hr, 75-gm F: 4.8 mmol/L 1hr: 10 mmol/L 2hr: 8.7 mmol/L G1: (24-28)	G1: NR	G1: NR	G1: NR	G1: NR	G1: NR	G1: Short-acting insulin, 11	G1: Initial dose: 4+6+4 IU, 3 times per day (before breakfast, lunch, dinner) (esc) Max dose: 16.8 Mean dose: NR
		G2: NR	G2: NR	G2: NR	G2: NR	G2: NR	G2: NR	G2: Long-acting insulin, 12	G2: Initial dose: 14 IU, 1 time per day (morning) (esc) Max dose: 19.5 Mean dose: NR
Diet versus insulin									
Thompson, 1990[30] US RCT	Start year: 1985 End year: 1988	100-gm, O'Sullivan or NDDG G1: NR	G1: F: 101	G1: 26	G1: NR	G1: Post-pregnancy weight: 200 lb	G1: Gravida: 2.5 Parity: 1.3	G1: Diet, 50	G1: Initial dose: 35 kilocalories/kg ideal body weight
		G2: NR	G2: F: 101	G2: 27	G2: NR	G2: Post-pregnancy weight: 192 lb	G2: Gravida: 3 Parity: 1.4	G2: Diet and insulin, 45	G2: Initial dose: 20 units NPH + 10 units RI units, 1 time per day (fixed) Max dose: NR Mean dose: NR

* This is the 2 hr PG status after 2 weeks of diet, not the 2hr PG after 75-gm OGTT.
† Only used FBG to determine treatment and eligibility for study.

Asian = Asian or Asian American; BMI = body mass index; C = Caucasian; dL = deciliter; esc = escalated; F = fasting; FBG = fasting blood glucose; G = group; GA = gestational age; gm = gram; Hisp = Hispanic; hr = hour; IU = international units; kg = kilogram; L = liter; lb = pound; m = meter; mg = milligram; mmol = millimole; NDDG = National Diabetes Data Group; NPH = neutral protamine Hagedorn; NR = not reported; OGTT = oral glucose tolerance test; PG = plasma glucose; RCT = randomized controlled trial; RI = regular insulin; US = United States; WHO = World Health Organization

Evidence Table 1. Characteristics of studies reporting on the effects of oral hypoglycemic agents or insulin on maternal and neonatal outcomes: randomized controlled trials (continued)

Author, year Country Study design	Time period	OGTT GA at diagnosis (in weeks)	OGTT results (in mg/dL)	Mean age (in years) (Age range)	Race, n (%)	Weight (in kg) / BMI (in kg/m^2), mean	Gravida/ parity, mean	Treatment, N	Initial dose (fixed or escalated) Maximum dose Mean dose
Insulin versus insulin lispro									
Jovanovic, 1999[36] US RCT	NR	100-gm, Carpenter and Coustan criteria G1: 25.6	G1: NR	G1: 29.8	G1: C: 0 (0) Hisp: 23 (100)	G1: Pre-pregnancy weight: 78.5 Pre-pregnancy BMI: 33.3	G1: Gravida: 2.4 Parity: 1.7	G1: Regular human insulin, 23	G1: Initial dose: 0.7 units/kg, 3 + 2 NPH times per day (esc) Max dose: NR Mean dose: NR
		G2: 27.3	G2: NR	G2: 34.2	G2: C: 2 (11) Hisp: 17 (89)	G2: Pre-pregnancy weight: 76.3 Pre-pregnancy BMI: 31.5	G2: Gravida: 1.8 Parity: 1.4	G2: Insulin lispro, 19	G2: Initial dose: 0.7 units/kg, 3 + 2 NPH times per day (esc) Max dose: NR Mean dose: NR
Mecacci, 2003[34] Italy RCT	Start year: June 1999 End year: Dec 2000	100-gm, Carpenter and Coustan criteria G1: median 28 (26-32)	G1: F: 91 1hr: 197 2hr: 189 3hr: 138	G1: (28-41) (median 35)	G1: C: 24 (100)	G1: Pre-pregnancy weight: (Median: 60.5) Pre-pregnancy BMI: (Median: 22.3)	G1: Parity: (median 1 (range 0-1))	G1: Regular human insulin, 24	G1: Initial dose: 1 unit/10 gms of carbohydrate in each meal, 3 times per day (esc) Max dose: NR Mean dose: 34.3 units/day
		G2: median 28 (25-32)	G2: F: 92 1hr: 193 2hr: 170 3hr: 126	G2: (24-40) (median 34.5)	G2: C: 25 (100)	G2: Pre-pregnancy weight: (Median: 61.4) Pre-pregnancy BMI: (Median: 21.5)	G2: Parity: (median 1 (range 0-2))	G2: Insulin lispro, 25	G2: Initial dose: 1 unit/10 gms of carbohydrate in each meal, 3 times per day (esc) Max dose: NR Mean dose: 35.1 units/day
Insulin versus insulin									
Nachum, 1999[35] Israel RCT	Start year: 1993 End year: 1997 Planned study period: 48 months	100-gm, O'Sullivan or NDDG G1: 28	G1: NR	G1: 33	G1: NR	G1: Pre-pregnancy weight: 72 Pre-pregnancy BMI: 27.8	G1: Gravida: 3.4	G1: Insulin twice daily, 136	G1: Initial dose: NR, 2 times per day Max dose: NR Mean dose: NR
		G2: 27.4	G2: NR	G2: 33	G2: NR	G2: Pre-pregnancy weight: 73 Pre-pregnancy BMI: 27.9	G2: Gravida: 3.5	G2: Insulin four times daily, 138	G2: Initial dose: NR, 4 times per day Max dose: NR Mean dose: NR

Evidence Table 1. Characteristics of studies reporting on the effects of oral hypoglycemic agents or insulin on maternal and neonatal outcomes: randomized controlled trials (continued)

Author, year Country Study design	Time period	OGTT GA at diagnosis (in weeks)	OGTT results (in mg/dL)	Mean age (in years) (Age range)	Race, n (%)	Weight (in kg) / BMI (in kg/m^2), mean	Gravida/ parity, mean	Treatment, N	Initial dose (fixed or escalated) Maximum dose Mean dose
Poyhonen-Alho, 2002[31] Finland RCT	NR	2hr, 75-gm F: 4.8 mmol/L 1hr: 10 mmol/L 2hr: 8.7 mmol/L G1: (24-28)	G1: NR	G1: NR	G1: NR	G1: NR	G1: NR	G1: Short-acting insulin, 11	G1: Initial dose: 4+6+4 IU, 3 times per day (before breakfast, lunch, dinner) (esc) Max dose: 16.8 Mean dose: NR
		G2: NR	G2: NR	G2: NR	G2: NR	G2: NR	G2: NR	G2: Long-acting insulin, 12	G2: Initial dose: 14 IU, 1 time per day (morning) (esc) Max dose: 19.5 Mean dose: NR
Diet versus insulin									
Thompson, 1990[30] US RCT	Start year: 1985 End year: 1988	100-gm, O'Sullivan or NDDG G1: NR	G1: F: 101	G1: 26	G1: NR	G1: Post-pregnancy weight: 200 lb	G1: Gravida: 2.5 Parity: 1.3	G1: Diet, 50	G1: Initial dose: 35 kilocalories/kg ideal body weight
		G2: NR	G2: F: 101	G2: 27	G2: NR	G2: Post-pregnancy weight: 192 lb	G2: Gravida: 3 Parity: 1.4	G2: Diet and insulin, 45	G2: Initial dose: 20 units NPH + 10 units RI units, 1 time per day (fixed) Max dose: NR Mean dose: NR

* This is the 2 hr PG status after 2 weeks of diet, not the 2hr PG after 75-gm OGTT.
† Only used FBG to determine treatment and eligibility for study.

Asian = Asian or Asian American; BMI = body mass index; C = Caucasian; dL = deciliter; esc = escalated; F = fasting; FBG = fasting blood glucose; G = group; GA = gestational age; gm = gram; Hisp = Hispanic; hr = hour; IU = international units; kg = kilogram; L = liter; lb = pound; m = meter; mg = milligram; mmol = millimole; NDDG = National Diabetes Data Group; NPH = neutral protamine Hagedorn; NR = not reported; OGTT = oral glucose tolerance test; PG = plasma glucose; RCT = randomized controlled trial; RI = regular insulin; US = United States; WHO = World Health Organization

Evidence Table 2. Effects of oral hypoglycemic agents or insulin on maternal outcomes: randomized controlled trials

Author, year	Treatment, N	Operative vaginal delivery, n (%)	Pre-eclampsia, n (%)	Cesarean delivery, n (%)	Weight, mean	Glycemic control during pregnancy, mean	Hypoglycemia, n (%)	Intention to treat analysis
Insulin versus glyburide								
Anjalakshi, 2006[33]	G1: Insulin, 13					2 hr PG at entry and before confinement (mg/dL) Baseline: 174.92 (sd: 31.05) Final: 93 (sd: 9.75)		NR
	G2: Glibenclamide, 10					2 hr PG at entry and before confinement (mg/dL) Baseline: 167.1 (sd: 22.97) Final: 95.29 (sd: 7.41)		
Bertini, 2005[37]	G1: Insulin, 27			Total cesarean deliveries: 12 (44)	Maternal weight (kg) Mean difference from baseline: 11.5 (sd: 3.8)		Requiring hospital admission: 0 (0)	Y
	G2: Glyburide, 24			Total cesarean deliveries: 12 (50)	Maternal weight (kg) Mean difference from baseline: 10 (sd: 5.2)		Requiring hospital admission: 0 (0)	
	G3: Acarbose, 19			Total cesarean deliveries: 10 (52)	Maternal weight (kg) Mean difference from baseline: 10.6 (sd: 3.2) p = 0.46*		Requiring hospital admission: 0 (0)	

Evidence Table 2. Effects of oral hypoglycemic agents or insulin on maternal outcomes: randomized controlled trials (continued)

Author, year	Treatment, N	Operative vaginal delivery, n (%)	Pre-eclampsia, n (%)	Cesarean delivery, n (%)	Weight, mean	Glycemic control during pregnancy, mean	Hypoglycemia, n (%)	Intention to treat analysis
Langer, 2000 [32]	G1: Insulin, 203		12 (6)	Total cesarean deliveries: 49 (24)		FBG (mg/dL) Baseline: 108 (sd: 26) Final: 96† (sd: 16) Pre-prandial glucose (mg/dL) Baseline: 107 (sd: 23) Final: 97† (sd: 14) 2 hr PPG (mg/dL) Baseline: 129 (sd: 27) Final: 112† (sd: 15) Combined glucose (mg/dL) Baseline: 116‡ (sd: 22) Final: 105 (sd: 18)	Fsg < 40 mg/dL: 41 (20)	Y
	G2: Glyburide, 201		12 (6)	Total cesarean deliveries: 46 (23)		FBG (mg/dL) Baseline: 104 (sd: 25) p = 0.12¶ Final: 98† (sd: 13) p = 0.17¶ Pre-prandial glucose (mg/dL) Baseline: 104 (sd: 20) p = 0.16¶ Final: 95† (sd: 15) p = 0.17¶ 2 hr PPG (mg/dL) Baseline: 130 (sd: 25) p = 0.69¶ Final: 113† (sd: 22) p = 0.6¶ Combined glucose (mg/dL) Baseline: 114‡ (sd: 19) p = 0.33¶ Final: 105 (sd: 16) p = 0.99¶	Fsg < 40 mg/dL: 4 (2) p = 0.03¶	

Evidence Table 2. Effects of oral hypoglycemic agents or insulin on maternal outcomes: randomized controlled trials (continued)

Author, year	Treatment, N	Operative vaginal delivery, n (%)	Pre-eclampsia, n (%)	Cesarean delivery, n (%)	Weight, mean	Glycemic control during pregnancy, mean	Hypoglycemia, n (%)	Intention to treat analysis
Insulin versus insulin lispro								
Jovanovic, 1999 [36]	G1: Regular human insulin, 23			Total cesarean deliveries: 6 (27.27)		HbA1c (%) Baseline: 5.24 (sd: 0.09) Final: 5.16 (sd: 0.12) Mean difference from baseline: 0.07	Fsg < 55 mg/dL: mean % hypoglycemic episodes of all blood glucose determinations: 2.2	NR
	G2: Insulin lispro, 19			Total cesarean deliveries: 7 (36.84)		HbA1c (%) Baseline: 5.47 (sd: 0.09) Final: 5.12 (sd: 0.11) Mean difference from baseline: 0.35	Fsg < 55 mg/dL: mean % hypoglycemic episodes of all blood glucose determinations: 0.88	
Mecacci, 2003 [34]	G1: Regular human insulin, 24			Cesarean delivery for CPD: 2 (8) Total cesarean deliveries: 6 (25)		Pre-prandial glucose (mg/dL) Mean: 74.3[§] (sd: 8.6) 1 hour PPG (mg/dL) Mean: 88[§] (sd: 11) 2 hour PPG (mg/dL) Mean: 97.9[§] (sd: 12.5)		N
	G2: Insulin lispro, 25			Cesarean delivery for CPD: 1 (4) p > 0.05[‖] Total cesarean deliveries: 7 (28) p > 0.05[‖]		Pre-prandial glucose (mg/dL) Mean: 73.4[§] (sd: 8.1) p > 0.05[‖] 1 hour PPG (mg/dL) Mean: 108.4[§] (sd: 10.7) p < 0.001[‖] 2 hour PPG (mg/dL) Mean: 93.6[§] (sd: 11.1) p > 0.05[‖]		

Evidence Table 2. Effects of oral hypoglycemic agents or insulin on maternal outcomes: randomized controlled trials (continued)

Author, year	Treatment, N	Operative vaginal delivery, n (%)	Pre-eclampsia, n (%)	Cesarean delivery, n (%)	Weight, mean	Glycemic control during pregnancy, mean	Hypoglycemia, n (%)	Intention to treat analysis
Insulin versus insulin								
Nachum, 1999 [35]	G1: Insulin twice daily, 136			Total cesarean deliveries: 52 (38)	Maternal weight gain (kg) Mean difference from baseline: 11.4 (sd: 3.5)	Combined glucose (mmol/L) Final mean: 5.6 (sd: 0.48) HbA1c (%) Final: 5.8 (sd: 1)	Severe hypoglycemia requiring help from another person: 1 (0.7)	NR
	G2: Insulin four times daily, 138			Total cesarean deliveries: 54 (39) Risk difference: 0	Maternal weight gain (kg) Mean difference from baseline: 10.7 (sd: 3.6)	Combined glucose (mmol/L) Final: 5.42 (sd: 0.54) HbA1c (%) Final: 5.5 (sd: 1)	Severe hypoglycemia requiring help from another person: 1 (0.7)	
Diet versus insulin								
Thompson, 1990 [30]	G1: Diet, 50			Total cesarean deliveries: 8 (23.53)		FBG (mg/dL) Baseline: 95 (sd: 13) Final: 79.7 (sd: 11)		NR
	G2: Diet and insulin, 45			Total cesarean deliveries: 8 (23.53)		FBG (mg/dL) Baseline: 96 (sd: 12) Final: 81.3 (sd: 8)		

* Comparing G1 to G2 to G3.
† Mean values throughout pregnancy.
‡ Mean glucose 1 week prior to treatment assignment.
¶ Comparing G1 to G2.
§ Mean from diagnosis of GDM to 38 weeks.
‖ Comparing G1 to G2 to G3, where G3 is a nondiabetic control group whose data is not shown.

CPD = cephalopelvic disproportion; dL = deciliter; FBG = fasting blood glucose; fsg = finger stick glucose; G = group; HbA1c = Hemoglobin A1c; hr = hour; kg = kilograms; mg = milligrams; N = no; NR = not reported; PG = plasma glucose; PPG = postprandial glucose; sd = standard deviation; Y = yes

Evidence Table 3. Grading of the body of evidence of the effects of oral hypoglycemic agents or insulin on maternal or neonatal outcomes (KQ1)

	Maternal outcomes		
	Insulin versus glyburide	**Insulin versus insulin lispro**	**Diet or insulin versus insulin**
Quantity of evidence: Number of studies	7	2	3
Total number of patients studied	1310	91	392
Quality and consistency of evidence: Were study designs mostly randomized trials (high quality), non-randomized controlled trials (medium quality), observational studies (low quality), or about a 50:50 mix of experimental and observational (medium quality)?	Medium	High	High
Did the studies have serious (-1) or very serious (-2) limitations in quality? (Enter 0 if none)	-2	-2	-2
Did the studies have important inconsistency? (-1)	-1	-1	-1
Was there some (-1) or major (-2) uncertainty about the directness (i.e. extent to which the people, interventions and outcomes are similar to those of interest)? Reminder: we're looking for head to head comparisons of different diabetes meds to get full credit for directness in addressing our question.	-1	-1	-1
Were data imprecise or sparse? (-1) (i.e. lack of data or very wide confidence intervals that may change conclusions)	-1	-1	-1
Did the studies have high probability of reporting bias? (-1)	-1	0	0
Did the studies show strong evidence of association between intervention and outcome? ("strong" if significant relative risk or odds ratio > 2 based on consistent evidence from 2 or more studies with no plausible confounders (+1); "very strong" if significant relative risk or odds ratio > 5 based on direct evidence with no major threats to validity (+2)) - use your clinical judgment for absolute differences.	0	0	0
Did the studies have evidence of a dose-response gradient? (+1)	0	0	0
Did the studies have unmeasured plausible confounders that most likely reduced the magnitude of the observed association? (+1)	+1	+1	+1
Overall grade of evidence (high, moderate, low, very low)	Very low	Very low	Very low

High = further research is very unlikely to change our confidence in the estimates; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low = any estimate of effect is very uncertain.

Evidence Table 3. Grading of the body of evidence of the effects of oral hypoglycemic agents or insulin on maternal or neonatal outcomes (KQ1) (continued)

	Neonatal outcomes		
	Insulin versus glyburide	**Insulin versus insulin lispro**	**Diet or insulin versus insulin**
Quantity of evidence: Number of studies	7	2	3
Total number of patients studied	1310	91	392
Quality and consistency of evidence: Were study designs mostly randomized trials (high quality), non-randomized controlled trials (medium quality), observational studies (low quality), or about a 50:50 mix of experimental and observational (medium quality)?	Medium	High	High
Did the studies have serious (-1) or very serious (-2) limitations in quality? (Enter 0 if none)	-2	-2	-2
Did the studies have important inconsistency? (-1)	-1	-1	-1
Was there some (-1) or major (-2) uncertainty about the directness (i.e. extent to which the people, interventions and outcomes are similar to those of interest)? Reminder: we're looking for head to head comparisons of different diabetes meds to get full credit for directness in addressing our question.	-1	-1	-1
Were data imprecise or sparse? (-1) (i.e. lack of data or very wide confidence intervals that may change conclusions)	-1	-1	-1
Did the studies have high probability of reporting bias? (-1)	0/-1	0	0
Did the studies show strong evidence of association between intervention and outcome? ("strong" if significant relative risk or odds ratio > 2 based on consistent evidence from 2 or more studies with no plausible confounders (+1); "very strong" if significant relative risk or odds ratio > 5 based on direct evidence with no major threats to validity (+2))- use your clinical judgment for absolute differences.	0	0	0
Did the studies have evidence of a dose-response gradient? (+1)	0	0	0
Did the studies have unmeasured plausible confounders that most likely reduced the magnitude of the observed association? (+1)	+1	+1	+1
Overall grade of evidence (high, moderate, low, very low)	Very low	Very low	Very low

High = further research is very unlikely to change our confidence in the estimates; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low = any estimate of effect is very uncertain.

Evidence Table 4. Effects of oral hypoglycemic agents or insulin on neonatal outcomes: randomized controlled trials

Author, year	Treatment, N	Hypo-glycemia, n (%)	Hyper-bilirubinemia, n (%)	Macrosomia, n (%)	LGA, n (%)	SGA, n (%)	Mortality, n (%)	Other outcome, n (%)	Birth weight, mean
Insulin versus glyburide									
Anjalakshi, 2006[33]	G1: Insulin, 13								2.6 kg (sd: 0.43)
	G2: Glibenclamide, 10								2.72 kg (sd: 0.34
Bertini, 2005[37]	G1: Insulin, 27	Capillary glucose < 40 mg/dL: 1 (4)		Birth weight > 4000 gm: 0 (0)	Percentile weight > 90: 1 (4)	Criteria NR: 2 (7)	Perinatal mortality: 0 (0)		3151.2 gm (sd: 407.2)
	G2: Glyburide, 24	Capillary glucose < 40 mg/dL: 8 (33)		Birth weight > 4000 gm: 4 (16)	Percentile weight > 90: 6 (25)	Criteria NR: 0 (0)	Perinatal mortality: 0 (0)		3395.6 gm (sd: 524.4)
	G3: Acarbose, 19	Capillary glucose < 40 mg/dL: 1 (5) p = 0.006*		Birth weight > 4000 gm: 0 (0)	Percentile weight > 90: 2 (10) p = 0.073*	Criteria NR: 0 (0)	Perinatal mortality: 0 (0)		3242.6 gm (sd: 400.6) p = 0.15*
Langer, 2000 [32]	G1: Insulin, 203	Two consecutive blood glucose < 40 mg/dL: 12 (6)	Serum bilirubin > 12 mg/dL: 8 (4)	Birth weight > 4000 gm: 9 (4)	Percentile weight > 90: 26 (13)		Perinatal mortality: 2 (1)	Congenital malformation: 4 (2) NICU admission: 14 (7)	3194 gm (sd: 598)
	G2: Glyburide, 201	Two consecutive blood glucose < 40 mg/dL: 18 (9) p = 0.25†	Serum bilirubin > 12 mg/dL: 12 (6) p = 0.36†	Birth weight > 4000 gm: 14 (7) p = 0.26†	Percentile weight > 90: 24 (12) p = 0.76†		Perinatal mortality: 2 (1) p = 0.99†	Congenital malformation: 5 (2) p = 0.74† NICU admission: 12 (6) p = 0.68†	3256 gm (sd: 543) p = 0.28†

Evidence Table 4. Effects of oral hypoglycemic agents or insulin on neonatal outcomes: randomized controlled trials (continued)

Author, year	Treatment, N	Hypo-glycemia, n (%)	Hyper-bilirubinemia, n (%)	Macrosomia, n (%)	LGA, n (%)	SGA, n (%)	Mortality, n (%)	Other outcome, n (%)	Birth weight, mean
Insulin versus insulin lispro									
Jovanovic, 1999 [36]	G1: Regular human insulin, 23								3169 gm (se: 78)
	G2: Insulin lispro, 19								3098 gm (se: 202)
Mecacci, 2003 [34]	G1: Regular human insulin, 24				Percentile weight >= 90: 3 (12)	Percentile weight <= 10: 1 (4)			3270.8 gm (sd: 389.2)
	G2: Insulin lispro, 25				Percentile weight >= 90: 2 (8) p > 0.05‡	Percentile weight <= 10: 1 (4) p > 0.05‡			3320.8 gm (sd: 246.6) p > 0.05†

Evidence Table 4. Effects of oral hypoglycemic agents or insulin on neonatal outcomes: randomized controlled trials (continued)

Author, year	Treatment, N	Hypo-glycemia, n (%)	Hyper-bilirubinemia, n (%)	Macrosomia, n (%)	LGA, n (%)	SGA, n (%)	Mortality, n (%)	Other outcome, n (%)	Birth weight, mean
Insulin versus insulin									
Nachum, 1999 [35]	G1: Insulin twice daily, 136	Plasma glucose < 1.9 mmol/l in term infants or < 1.4 mmol/l in preterm infants at least on two different occasions during first 48 hours of life: 8 (6)	Serum bilirubin > 205 mmol/l at >= 34 weeks of gestation or > 137 mmol/l at < 34 weeks of gestation: 29 (21)	Birth weight > 4000 gm: 26 (19)	Percentile weight > 90: 41 (30)	Percentile weight < 10: 7 (5)	Perinatal mortality: 1 (1)	Congenital malformation, fatal, requiring surgery, or having significant psychological effects on fetus in later life: 2 (2) RDS, hyaline membrane disease: 0 (0.00) birth trauma, peripheral nerve injury or bone fracture: 3 (2)	
	G2: Insulin four times daily, 138	Plasma glucose < 1.9 mmol/l in term infants or < 1.4 mmol/l in preterm infants at least on two different occasions during first 48 hours of life: 1 (1)	Serum bilirubin > 205mmol/l at >= 34 weeks of gestation or > 137 mmol/l at < 34 weeks of gestation: 15 (11)	Birth weight > 4000 gm: 22 (16)	Percentile weight > 90: 36 (26)	Percentile weight < 10: 4 (3)	Perinatal mortality: 0 (0.00)	Congenital malformation, fatal, requiring surgery, or having significant psychological effects on fetus in later life: 1 (1) RDS, hyaline membrane disease: 1 (1) birth trauma, peripheral nerve injury or bone fracture: 2 (1)	

Evidence Table 4. Effects of oral hypoglycemic agents or insulin on neonatal outcomes: randomized controlled trials (continued)

Author, year	Treatment, N	Hypo-glycemia, n (%)	Hyper-bilirubinemia, n (%)	Macrosomia, n (%)	LGA, n (%)	SGA, n (%)	Mortality, n (%)	Other outcome, n (%)	Birth weight, mean
Poyhonen-Alho, 2002 [31]	G1: Short-acting insulin, 11	NR: 0 (0.00)	NR: 3 (27.27)	(Greater than 2 sd of the mean birth weight = 3079 ± 722): 0 (0.00)				Birth trauma (nerve palsy): 0 (0.00)	
	G2: Long-acting insulin, 12	NR: 1 (8.33)	NR: 3 (25.00)	(Greater than 2 sd of the mean birth weight = 3079 ± 722): 4 (33.33) p: 0.05[†]				Birth trauma (nerve palsy): 1 (8.33)	
Diet versus insulin									
Thompson, 1990 [30]	G1: Diet, 50	Plasma glucose < 30 mg/dL: 5 (14.71)	Serum bilirubin > 10 mg/dL: 0 (0.00)	Birth weight > 4000 gm: 9 (26.47)[¶]					3584 gm (sd: 543)
	G2: Diet and insulin, 45	Plasma glucose < 30 mg/dL: 6 (17.65)	Serum bilirubin > 10 mg/dL: 0 (0.00)	Birth weight > 4000 gm: 2 (5.88)[§]					3170 gm (sd: 522)

* Comparing G1 to G2 to G3.
† Comparing G1 to G2.
‡ Comparing G1 to G2 to G3, where G3 is a nondiabetic control group, whose data is not shown.
¶ Macrosomia in mothers with delivery weight<200lb (N=22 in both groups): 0. Macrosomia in mothers with delivery weight>=200lb (N=12 in both groups): 9.
§ Macrosomia in mothers with delivery weight<200lb (N=22 in both groups): 0. Macrosomia in mothers with delivery weight>=200lb (N=12 in both groups): 2.

dL = deciliter; G = group; gm = gram; kg = kilogram; l = liter; LGA = large for gestational age; mg = milligram; mmol = millimole; NICU = neonatal intensive care unit; NR = not reported; RDS = respiratory distress syndrome; SGA = small for gestational age; sd = standard deviation

Evidence Table 5. Quality of the studies reporting on the effects of oral hypoglycemic agents or insulin on maternal and neonatal outcomes: randomized controlled trials

Author, year	Randomized	Randomization scheme described	Double blinded	Blinding described	Withdrawals described	Quality score*
Anjalakshi, 2006[33]	●					1
Bertini, 2005[37]	●	●			●	3
Langer, 2000[32]	●	●				2
Jovanovic, 1999[36]	●	●			●	3
Mecacci, 2003[34]	●				●	2
Nachum, 1999[35]	●	●				2
Poyhonen-Alho, 2002[31]	●					1
Thompson, 1990[30]	●	●			●	3

● = Yes; blank space = No/Not reported
*Total quality score calculated using the Jadad[22] criteria.

Evidence Table 6. Characteristics of studies reporting on the effects of oral hypoglycemic agents or insulin on maternal and neonatal outcomes: non-randomized controlled trials and observational studies

Author, year Country Study design	Time period	OGTT GA at diagnosis (in weeks)	OGTT results (in mg/dL)	Mean age (in years) (Age range)	Race, n (%)	Weight (in kg) / BMI (in kg/m^2), mean	Gravida/ parity, mean	Treatment, N	Initial dose (fixed or escalated) Maximum dose Mean dose
Jacobson, 2005[48] US Cohort	Start year: 1999 End year: 2002	100-gm O'Sullivan or NDDG G1: 26.3	G1: F: 105 1hr: 223 2hr: 197 3hr: 140	G1: 32.1	G1: AA: 10 (4) C: 116 (43) Asian: 64 (24) Hisp: 66 (25)	G1: 1st documented BMI during pregnancy: 31.9	G1: (number of nulliparous women: 91 (34%))	G1: Insulin in 1999-2000, 268	G1: Initial dose: NR (esc) Max dose: no maximum Mean dose: 34.4 units*
		G2: 25.5	G2: F: 102 1hr: 220 2hr: 195 3hr: 137	G2: 32.8	G2: AA: 9 (4) C: 65 (28) Asian: 88 (37) Hisp: 56 (24)	G2: 1st documented BMI during pregnancy: 30.6	G2: (number of nulliparous women: 78 (33%))	G2: Glyburide in 2001-2002, 236	G2: Initial dose: 2.5 mg, 1 time per day (esc) Max dose: 20 mg/day Mean dose: 5.6 mg†
		G3: stated similar to G2	G3: F: 109 1hr: NR 2hr: NR 3hr: NR	G3: stated similar to G2	G3: AA: stated similar to G2 C: stated similar to G2 Asian: NR (24) Hisp: stated similar to G2	G3: 1st documented BMI during pregnancy: 33.9	G3: (number of nulliparous women: stated similar to G2)	G3: Insulin in 2001-2002, 80	G3: Initial dose: NR (esc) Max dose: no maximum Mean dose: NR
Conway, 2004[47] US Cohort	Start year: Dec 2000 End year: July 2003	100-gm OGTT using 2003 ADA criteria F: 95 mg/dL 1hr: 180 mg/dL 2hr: 155 mg/dL 3hr: 140 mg/dL G1: 20; 23.3 (at time of initiation of glyburide)	G1: F: 115 1hr: 230 2hr: 204 3hr: 176	G1: 30.3	G1: NR	G1: Pre-pregnancy BMI: NR (stated similar between groups)	G1: Parity: 2.2	G1: Glyburide failure, 12	G1: Initial dose: same for glyburide as G2; for insulin was 0.7 to 1.0 (esc) Max dose: no maximum for insulin, max glyburide dose was 20 mg Mean dose: NR
		G2: 18.4; 28.7 (at initiation of glyburide- p < 0.05)	G2: F: 102 1hr: 205 2hr: 169 3hr: 133	G2: 31.3	G2: NR	G2: Pre-pregnancy BMI: NR (stated similar between groups)	G2: Parity: 1.8	G2: Glyburide success, 63	G2: Initial dose: 2.5 mg, 1 time per day (esc) Max dose: 20 mg (10 mg bid) Mean dose: NR

Evidence Table 6. Characteristics of studies reporting on the effects of oral hypoglycemic agents or insulin on maternal and neonatal outcomes: non-randomized controlled trials and observational studies (continued)

Author, year Country Study design	Time period	OGTT GA at diagnosis (in weeks)	OGTT results (in mg/dL)	Mean age (in years) (Age range)	Race, n (%)	Weight (in kg) / BMI (in kg/m^2), mean	Gravida/ parity, mean	Treatment, N	Initial dose (fixed or escalated) Maximum dose Mean dose
Chmait, 2004[45] US Cohort	Start year: 2000 End year: 2002	100-gm Carpenter and Coustan criteria G1: 20	G1: F: 105 1hr: 206 2hr: 192 3hr: 128	G1: 31	G1: Hisp: 9 (69) non-Hispanic: 4 (31)	G1: NR	G1: (Nulliparity: 1 (7.7%))	G1: glyburide failure (glyburide + diet + insulin OR insulin + diet), 13	G1: Initial dose: glyburide starting dose same as G2; insulin dosing based on weeks of gestation;‡ 3 times per day (esc) Max dose: no maximum on insulin, max of 20 mg daily (10 mg bid of glyburide) Mean dose: NR
		G2: 27.3	G2: F: 94 1hr: 199 2hr: 169 3hr: 126	G2: 32	G2: Hisp: 51 (91) non-Hispanic: 5 (9)	G2: NR	G2: (Nulliparity: 8 (14.3%))	G2: glyburide success (glyburide + diet), 56	G2: Initial dose: 2.5 to 5 mg, 1 time per day (esc) Max dose: 20 mg daily (10 mg bid) Mean dose: NR
Yogev, 2004[46] US Non-RCT	Start year: 2001 End year: 2003 Planned study period: 2 years	100-gm Carpenter and Coustan criteria G1: NR	G1: F: 96	G1: 26.4	G1: NR	G1: Pre-pregnancy BMI: 26	G1: (Nulliparity: 9 (33%))	G1: Diet, 27	G1:NA
		G2: NR	G2: F: 99	G2: 28.1	G2: NR	G2: Pre-pregnancy BMI: 27.6	G2: (Nulliparity: 8 (27%))	G2: Insulin, 30	G2: Initial dose: 0.7 units/kg, 3 times per day (esc) Mean dose: 72 units/day
		G3: NR	G3: F: 98	G3: 28.3	G3: NR	G3: Pre-pregnancy BMI: 27.5	G3: (Nulliparity: 7 (28%))	G3: Glyburide, 25	G3: Initial dose: 2.5 mg, 1 time per day (esc) Max dose: 20 mg Mean dose: 8 mg/day

Evidence Table 6. Characteristics of studies reporting on the effects of oral hypoglycemic agents or insulin on maternal and neonatal outcomes: non-randomized controlled trials and observational studies (continued)

Author, year Country Study design	Time period	OGTT GA at diagnosis (in weeks)	OGTT results (in mg/dL)	Mean age (in years) (Age range)	Race, n (%)	Weight (in kg) / BMI (in kg/m^2), mean	Gravida/ parity, mean	Treatment, N	Initial dose (fixed or escalated) Maximum dose Mean dose
Rochon, 2006[49] US Cohort	Start year: 2002 End year: 2005 Planned study period: 30 months	100-gm Carpenter and Coustan criteria G1: 24	G1: F: 107 1hr: 223 2hr: 189 3hr: 114	G1: 31.3	G1: AA: 6 (29) C: 1 (5) Asian: 2 (10) Hisp: 12 (57)	G1: BMI at 1st prenatal visit: 32.2	G1: (Multiparous: 18 (86%))	G1: Glyburide failure (NPH and regular insulin), 21	G1: Initial dose: glyburide starting dose same as G2; starting dose for insulin not reported, 3 times per day (esc) Mean dose: NR
		G2: 26	G2: F: 102 1hr: 200 2hr: 179 3hr: 138	G2: 30.5	G2: AA: 24 (30) C: 1 (1) Asian: 8 (10) Hisp: 47 (59)	G2: BMI at 1st prenatal visit: 31.5	G2: (Multiparous: 56 (70%)	G2: Glyburide success (glyburide + diet), 80	G2: Initial dose 2.5 to 5 mg, 1 time per day (esc) Max dose: 20 mg daily (10 mg bid) Mean dose: NR

*Only available for 249 women

†Only available for 229 women

‡ Insulin dose for 1 to 18 weeks gestation was 0.7 units/kg; for 18 to 26 weeks gestation was 0.8 units/kg; for 26 to 36 weeks gestation used 0.9 units/kg; and for 36 to 40 weeks gestation was 1.0 units/kg.

AA = African American; ADA = American Diabetes Association; Asian = Asian or Asian American; bid = twice daily; BMI = body mass index; C = Caucasian; dL = deciliter; esc = escalated; F = fasting; G = group; GA = gestational age; gm = gram; Hisp. = Hispanic; hr = hour; kg = kilogram; mg = milligram; NA = not applicable; NDDG = National Diabetes Data Group; NR = not reported; OGTT = oral glucose tolerance test; RCT = randomized controlled trial; US = United States

Evidence Table 7. Effects of oral hypoglycemic agents or insulin on maternal outcomes: non-randomized controlled trials and observational studies

Author, year	Treatment, N	Operative vaginal delivery, n (%)	Pre-eclampsia, n (%)	Cesarean delivery, n (%)	Weight, mean	Glycemic control during pregnancy, mean	Hypoglycemia, n (%)
Jacobson, 2005[48]	G1: Insulin in 1999-2000, 268	15 (6)	16 (6) OR: ref	Total cesarean deliveries: 94 (36)		FBG (mg/dL) Baseline: 105.4 (sd: 12.9) Final: 97.7 (sd: 12.2) 1 hour PPG (mg/dL) Baseline: 222.8 (sd: 28.9) Final: 137.8 (sd: 23.6) 2 hour PPG (mg/dL) Baseline: 197.4 (sd: 33.6) Final: 118.8 (sd: 19.6)	Fsg < 60 mg/dL: Mean #: 19 Total number of plasma glucose values measured: 22764
	G2: Glyburide in 2001-2002, 236	12 (5)	28 (12) OR: 2.32 (95% CI: 1.17-4.63)	Total cesarean deliveries: 91 (39)		FBG (mg/dL) Baseline: 102.4 (sd: 14.2) p = 0.005* Final: 90.2 (sd: 12.7) p < 0.001* 1 hour PPG (mg/dL) Baseline: 220 (sd: 27.2) p = 0.48* Final: 131.4 (sd: 23.3) p < 0.001* 2 hour PPG (mg/dL) Baseline: 194.7 (sd: 32.1) p = 0.44* Final: 117.6 (sd: 23.2) p < 0.05*	Fsg < 60 mg/dL: Mean #: 50 Total number of plasma glucose values measured: 24975
Chmait, 2004[45]	G1: glyburide failure (glyburide + diet + insulin OR insulin + diet), 13			Elective cesarean delivery: 1 (7.69) total cesarean deliveries: 5 (38)		Fasting glucose† (mg/dL) Mean: 114 (sd: 17) 1 hour PPG† (mg/dL) Mean: 145 (sd: 20)	
	G2: glyburide success (glyburide + diet), 56			Elective cesarean delivery: 4 (7.14) total cesarean deliveries: 19 (34) p > 0.05*		Fasting glucose† (mg/dL) Mean: 88 (sd: 11) p < 0.001* 1 hour PPG† (mg/dL) Mean: 124 (sd: 12) p < 0.001*	

Evidence Table 7. Effects of oral hypoglycemic agents or insulin on maternal outcomes: non-randomized controlled trials and observational studies (continued)

Author, year	Treatment, N	Operative vaginal delivery, n (%)	Pre-eclampsia, n (%)	Cesarean delivery, n (%)	Weight, mean	Glycemic control during pregnancy, mean	Hypoglycemia, n (%)
Yogev, 2004[46]	G1: Diet, 27					FBG (mg/dL) Baseline: 96 (sd: 21) Final: 99 (sd: 13)	Fsg < 50 mg/dL, symptoms, 30 or more consecutive minutes of glucose determination less than 50 mg/dL, detected only by the CGMS without patient awareness: 0 (0)
	G2: Insulin, 30					FBG (mg/dL) Baseline: 99 (sd: 23) Final: 104 (sd: 15)	Fsg < 50 mg/dL, symptoms, 30 or more consecutive minutes of glucose determination less than 50 mg/dL, detected only by the CGMS without patient awareness: 19 (63) OR: 4.4 (95% CI: 1.4-13.9) p = 0.009‡
	G3: Glyburide, 25					FBG (mg/dL) Baseline: 98 (sd: 27) p = 0.17¶ Final: 105 (sd: 14) p = 0.24¶	Fsg < 50 mg/dL, symptoms, 30 or more consecutive minutes of glucose determination less than 50 mg/dL, detected only by the CGMS without patient awareness: 7 (28) OR: ref

Evidence Table 7. Effects of oral hypoglycemic agents or insulin on maternal outcomes: non-randomized controlled trials and observational studies (continued)

Author, year	Treatment, N	Operative vaginal delivery, n (%)	Pre-eclampsia, n (%)	Cesarean delivery, n (%)	Weight, mean	Glycemic control during pregnancy, mean	Hypoglycemia, n (%)
Rochon, 2006[49]	G1: Glyburide failure (NPH and regular insulin), 21			9 (43)			
	G2: Glyburide success (glyburide + diet), 80			30 (38)			

* Comparing G1 to G2
† During treatment with glyburide
‡ Comparing G1 to G2 to G3
¶ Comparing G2 to G3

CGMS = continuous glucose monitoring system; CI = confidence interval; dL = deciliter; FBG = fasting blood glucose; fsg = finger stick glucose; G = group; mg = milligrams; NPH = Neutral Protamine Hagedorn; OR = odds ratio; PPG = postprandial glucose; ref = reference group; sd = standard deviation

Evidence Table 8. Effects of oral hypoglycemic agents or insulin on neonatal outcomes: non-randomized controlled trials and observational studies

Author, year	Treatment, N	Hypo-glycemia, n (%)	Hyper-bilirubinemia, n (%)	Macrosomia, n (%)	LGA, n (%)	SGA, n (%)	Mortality, n (%)	Other outcome, n (%)	Birth weight, mean
Jacobson, 2005[48]	G1: Insulin in 1999-2000, 268	ICD-9-CM codes: 73 (27) OR: ref	Serum bilirubin > 12 mg/dL within first 7 days of birth: 58 (22) OR: ref	Birth weight > 4000 gm: 64 (24) OR: ref	Percentile weight > 90: 63 (24) OR: ref	Percentile weight < 10: 18 (7) OR: ref		NICU admission: 65 (24) OR: ref birth trauma, claims data/ICD-9 codes, total birth injuries: 3 (1) congenital malformation, claims data/ICD-9 codes: 4 (2)	3599 gm (sd: 650)
	G2: Glyburide in 2001-2002, 236	ICD-9-CM codes: 72 (31) OR: 1.27 (95% CI: 0.84-1.94)	Serum bilirubin > 12 mg/dL within first 7 days of birth: 59 (25) OR: 1.18 (95% CI: 0.75-1.85)	Birth weight > 4000 gm: 60 (25) OR: 1.28 (95% CI: 0.82-2)	Percentile weight > 90: 60 (25) OR: 1.44 (95% CI: 0.91-2.27)	Percentile weight < 10: 12 (6) OR: 0.62 (95% CI: 0.26-1.43)		NICU admission: 35 (15) OR: 0.57 (95% CI: 0.34-0.93) birth trauma, claims data/ICD-9 codes total birth injuries: 8 (3) congenital malformation, claims data/ICD-9 codes: 4 (2)	3661 gm (sd: 629) p = 0.28*
Conway, 2004[47]	G1: glyburide failure, 12			Birth weight > 4000 gm: 1 (8)					3327 gm (sd: 634)
	G2: glyburide success, 63			Birth weight > 4000 gm: 7 (11) p = 1.0*					3267 gm (sd: 815) p = 0.78*

Evidence Table 8. Effects of oral hypoglycemic agents or insulin on neonatal outcomes: non-randomized controlled trials and observational studies (continued)

Author, year	Treatment, N	Hypo-glycemia, n (%)	Hyper-bilirubinemia, n (%)	Macrosomia, n (%)	LGA, n (%)	SGA, n (%)	Mortality, n (%)	Other outcome, n (%)	Birth weight, mean
Chmait, 2004[45]	G1: glyburide failure (glyburide + diet + insulin OR insulin + diet), 13	Fsg < 40 mg/dL: 0 (0.00)	Serum bilirubin > 15 mg/dL: 1 (8.33)	Birth weight > 4000 gm: 2 (10)			Fetal mortality: 0 (0)	NICU admission: 1 (8)	3608 gm (sd: 398)
	G2: glyburide success (glyburide + diet), 56	Fsg < 40 mg/dL: 1 (1.85)	Serum bilirubin > 15 mg/dL: 2 (3.70)	Birth weight > 4000 gm: 15 (18) p > 0.05*			Fetal mortality: 1 (2) p > 0.05*	NICU admission: 4 (7) p > 0.05*	3430 gm (sd: 714) p > 0.05*
Rochon, 2006[49]	G1: Glyburide failure (NPH and regular insulin), 21	Any heel stick ≤ 40 mg/dL: 2 (10)	Requiring NICU admission: 0 (0)	Birth weight > 4000 gm: 2 (11)				NICU admission: 2 (10) OR: ref shoulder dystocia: 2 (11)	3319 gm (sd: 559)
	G2: Glyburide success (glyburide + diet), 80	Any heel stick ≤ 40 mg/dL: 10 (13)	Requiring NICU admission: 2 (3)	Birth weight > 4000 gm: 13 (16) p = 0.445*				NICU admission: 26 (33) p = 0.037 OR: 4.57 (95% CI: 3.04-6.10) shoulder dystocia: 7 (10) p = 0.932	3415 gm (sd: 620) P = 0.518

* Comparing G1 to G2

CI = confidence interval; dL = deciliter; fsg = fingerstick glucose; G = group; gm = gram; ICD-9-CM = International Classification of Diseases – 9th revision – Clinical Modification; LGA = large for gestational age; mg = milligrams; NICU = neonatal intensive care unit; OR = odds ratio; ref = reference group; sd = standard deviation; SGA = small for gestational age

Evidence Table 9. Quality of studies reporting on the effects of oral hypoglycemic agents or insulin on maternal and neonatal outcomes: non-randomized controlled trials and observational studies

Author, year	Are pre-specified hypotheses stated?	Are inclusion and exclusion criteria reported?	Sampling	Were power or sample size calculations used?	Does the article state how the outcome was defined?	Loss to followup / Loss to followup described	Missing data / described how missing data handled
Jacobson, 2005[48]		●	Consecutive		●		
Yogev, 2004[46]		●	Consecutive		●	<10% / NA	<10% / NA
Chmait, 2004[45]	●	●	Consecutive		●	<10% / ●	<10% / ●
Conway, 2004[47]	●	●	Consecutive		●	<10% /	/ ●
Rochon, 2006[49]		●	Consecutive		●	<10% /	

● = Yes; blank space = No/Not reported
NA = not applicable

Evidence Table 10. Characteristics of studies reporting on the effects of labor management on maternal and neonatal outcomes

Author, year Country Study design	Time period	OGTT GA at diagnosis (in weeks)	Mean age (in years), (Age range)	Race, n (%)	Gravida and parity, mean	Intervention/Exposure, N
Kjos, 1993[55] US RCT	Start year: 1987 End year: 1991	100-gm O'Sullivan or NDDG C: 38 weeks, 2 days	C: 31.9 (30.8-33.0)	C: NR	C: Gravidity: 4.1 Parity: 2.4	C: Induced if EFW ≥ 4200 gm or 42 weeks, 100
		I: 38 weeks, 1 day	I: 32.1 (30.9-33.2)	I: NR	I: Gravidity: 4.3 Parity: 2.5	I: Induced at 38 weeks, 100
Conway, 1998[53] US Cohort	Start year: 1990 End year: 1995	100-gm O'Sullivan or NDDG HC: NR	HC: NR	HC: Hisp: (84.7) Cauc: (12.1) AA: (3.2)	HC: NR	HC: Expectant management, 1227
		E: NR	E: NR	E: Hisp: (86.4) Cauc: (9.9) AA: (3.7)	E: NR	E: Ultrasound at 37-38 weeks; CD if EFW > 4250 gm, induced if LGA and EFW < 4250 gm, 1337
Lurie, 1996[58] Israel Cohort	Start year: 1983 End year: 1994	100-gm O'Sullivan or NDDG HC: NR	HC: 33.1	HC: NR	HC: Parity: 2.5	HC: Induced if EFW > 4000 gm CD if EFW > 4500 gm, 164
		E: NR	E: 32.5	E: NR	E: Parity: 1.9	E: Induced at 38 weeks, CD if EFW > 4500 gm, 96
Lurie, 1992[57] Israel Cohort	Start year: 1983 End year: 1988	100-gm O'Sullivan or NDDG NR for any group	NR for any group	NR for any group	NR for any group	GDMA1: > 40 weeks: Induced if EFW > 4000 gm, CD if EFW > 4500 gm, 65 < 40 weeks: Induced if EFW > 4000 gm, CD if EFW > 4500 gm, 65 GDMA2: > 40 weeks: Induced if EFW > 4000 gm, CD if EFW > 4500 gm, 59 < 40 weeks: Induced if EFW > 4000 gm, CD if EFW > 4500 gm, 59

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Evidence Table 10. Characteristics of studies reporting on the effects of labor management on maternal and neonatal outcomes (continued)

Author, year Country Study design	Time period	OGTT GA at diagnosis (in weeks)	Mean age (in years), (Age range)	Race, n (%)	Gravida and parity, mean	Intervention/Exposure, N
Peled, 2004[59] Israel Cohort	Start year: 1980 End year: 1999	100-gm Carpenter and Coustan criteria 100-gm O'Sullivan or NDDG 75-gm ADA NR for any group	NR for any group	NR for any group	NR for any group	Period A: Induced at 42 weeks, CD if EFW > 4500 gm, 878 Period B: Induced at 40 weeks if LGA, CD if EFW > 4000 gm, 347 Period C: Induced at 40 weeks if LGA, CD if EFW > 4000 gm, 317 Period D: Induced at 38 weeks if LGA, CD if EFW > 4000 gm, 518
Rayburn, 2005[56] US Cohort	Start year: 2000 End year: 2004 Planned study period: 49 months	100-gm, 3-hr OGTT, ACOG C: NR	C: 30	C: AA: (1) Cauc: (15) Hisp: (60) Am. Ind: (20) Other: (4)	C: (0, %: 31; 1, %: 20; >=2, %: 49)	C: GDMA1, expectant management, 137
		E: NR	E: 30	E: AA: (0) Cauc: (17) Hisp: (70) Am. Ind: (6) Other: (7)	E: (0, %: 18; 1, %: 33; >=2, %: 49)	E: GDMA2, Induced at 38 weeks, 143
Marchiano, 2004[52] US Cohort	Start year: 1995 End year: 1999	100-gm O'Sullivan or NDDG C: 38.3	C: 31.1	C: AA: (25) Cauc: (57) Asian: (3) Hisp: (11) Other: (4)	C: Gravida: 3.4	C: Trial of labor after CD, 423
		E: 38	E: 32.2	E: AA: (20) C: (64) Asian: (3) Hisp: (9) Other : (5)	E: Gravida: 3.1	E: Repeat elective cesarean, 440
Keller, 1991[54] US Cohort	Start year: 1983 End year: 1989 Planned study period: 70 months	100-gm O'Sullivan or NDDG	NR for any group	NR for any group	NR for any group	C: Trial of labor, 173

AA = African American; ACOG = American College of Obstetrics and Gynecologists; ADA = American Diabetes Association; Asian = Asian or Asian American; C = control group; Cauc = Caucasian; CD = cesarean delivery; E = exposure group; EFW = estimated fetal weight; GA = gestational age; GDMA1 = diet-controlled; GDMA2 = requiring medical therapy; gm = gram; HC = historical control group; Hisp = Hispanic; I = intervention group; LGA = large for gestational age; NDDG = National Diabetes Data Group; NR = not reported; OGTT = oral glucose tolerance test; RCT = randomized controlled trial; US = United States

Evidence Table 11. Effects of labor management on maternal outcomes

Author, year	Level of analysis	Intervention/Exposure, N	GA at delivery (in weeks), mean (SD)	GA determined by	Operative vaginal delivery, n (%)	Cesarean delivery, n (%)
Kjos, 1993[55]	Intervention	C: Induced if EFW ≥ 4200 gm or 42 weeks, 100	40	LMP; 1st trimester ultrasound		31 (31)
		I: Induced at 38 weeks, 100	39	LMP; 1st trimester ultrasound; amniocentesis if indicated		25 (25) p = 0.43
Conway, 1998[53]	Protocol-based	HC: Expectant management, 1227	39.3 (1.5)	NR		266 (21.7)
		E: Ultrasound at 37-38 weeks; CD if EFW > 4250 gm, induced if LGA and EFW < 4250 gm, 1337	39.2 (1.6)	NR		343 (25) p < 0.04
Lurie, 1996[58]	Protocol-based	HC: Induced if EFW > 4000 gm CD if EFW > 4500 gm, 164	39.2	LMP; 1st trimester ultrasound	Vacuum: 9 (6)	31 (19)
		E: Induced at 38 weeks, CD if EFW > 4500 gm, 96	38.4	LMP 1st trimester ultrasound; amniocentesis to confirm fetal lung maturity	Vacuum: 5 (5) p: NS	22 (23) p: NS
Lurie, 1992[57]	Protocol-based	GDMA1: > 40 weeks: Induced if EFW > 4000 gm, CD if EFW > 4500 gm, 65	40.9	LMP; 1st trimester ultrasound	Vacuum: 4 (6)	9 (14)
		< 40 weeks: Induced if EFW > 4000 gm, CD if EFW > 4500 gm, 65	38.2	LMP; 1st trimester ultrasound	Vacuum: 0 (0) p = 0.0997†	7 (11) p = 0.0997†
		> 40 weeks: Induced if EFW > 4000 gm, CD if EFW > 4500 gm, 59	40.5	LMP; 1st trimester ultrasound	Vacuum: 4 (7)	13 (22)
		GDMA2: < 40 weeks: Induced if EFW > 4000 gm, CD if EFW > 4500 gm, 59	37.5	LMP; 1st trimester ultrasound	Vacuum: 1 (2) p = 0.6216†	15 (25) p = 0.6216†

Evidence Table 11. Effects of labor management on maternal outcomes (continued)

Author, year	Level of analysis	Intervention/Exposure, N	GA at delivery (in weeks), mean (SD)	GA determined by	Operative vaginal delivery, n (%)	Cesarean delivery, n (%)
Peled, 2004[59]	Protocol-based	Period A: Induced at 42 weeks, CD if EFW > 4500 gm, 878	39 (2.5)	LMP; +/- 1st trimester ultrasound		184 (21)
		Period B: Induced at 40 weeks if LGA, CD if EFW > 4000 gm, 347	39 (1.5)	LMP; +/- 1st trimester ultrasound		62 (18)
		Period C: Induced at 40 weeks if LGA, CD if EFW > 4000 gm, 317	38 (1.6)	LMP; +/- 1st trimester ultrasound		51 (16)
		Period D: Induced at 38 weeks if LGA, CD if EFW > 4000 gm, 518	38.1 (3.1)	LMP; +/- 1st trimester ultrasound		176 (34)
Additional studies						
Rayburn, 2005[56]	Exposure	C: GDMA1, Expectant management, 137	39 (1)	1st trimester ultrasound; amniocentesis if needed		16 (12)
		E: GDMA2, Induced at 38 weeks, 143	38.1 (0.3)	1st trimester ultrasound; amniocentesis if needed		19 (13) p = 0.8
Marchiano, 2004[52]	exposure	C: Trial of labor after CD, 423	38.3 (2.2)	NR		Failed VBAC: 128 (30)*
		E: Repeat elective cesarean, 440	NR	NR		NA
Keller, 1991[54]	exposure	C: Trial of labor, 173	NR	NR	Forceps: 8	53 (30.6)

* The birth weight was greater than or equal to 4000 gm for 32 (25%) and less than 4000 gm for 96 (75%) of the infants of the 128 women who failed the VBAC attempt.
† Comparing > 40 weeks to < 40 weeks for all modes of delivery

C = control group; CD = cesarean delivery; E = exposure group; EFW = estimated fetal weight; GDMA1 = diet-controlled; GDMA2 = requiring medical therapy; gm = gram; HC = historical control group; I = intervention group; LGA = large for gestational age; LMP = last menstrual period; NR = not reported; NS = not significant; SD = standard deviation; VBAC = vaginal birth after cesarean

Evidence Table 12. Effects of labor management on neonatal outcomes

Author, year	Level of analysis	Intervention/Exposure, N	GA at delivery (in weeks), mean (SD)	GA deter-mined by	Macrosomia or LGA (PW>90%), n (%)	Birth weight (in grams), mean	Shoulder dystocia, n (%)	Birth trauma, n (%)	Mortality, n (%)	Other outcome, n (%)
Kjos, 1993[55]	Intervention	C: Induced if EFW ≥ 4200 gm or 42 weeks, 100	40	LMP; 1st trimester ultrasound	Birth weight > 4000 gm: 27 (27) > 4500 gm: 2 (2) LGA: 23 (23)	3672 (95% CI: 3595 – 3749)	3 (3.00)	Bone fracture, nerve palsy: 0 (0)	Perinatal/ neonatal mortality: 0 (0)	Hypoglycemia: 0 (0) Congenital malformation: 0 (0)
		I: Induced at 38 weeks, 100	39	LMP; 1st trimester ultrasound; amniocen-tesis if indicated	Birth weight > 4000 gm: 15 (15) p = 0.05* > 4500 gm: 0 (0) LGA: 10 (10) p = 0.02*	3446 (95% CI: 3368 – 3522) p < 0.0001*	0 (0)	Bone fracture, nerve palsy: 0 (0)	Perinatal/ neonatal mortality: 0 (0)	Hypoglycemia: 0 (0) Congenital malformation: 0 (0)
Conway, 1998 [53]	Protocol-based	HC: Expectant management, 1227	39.3 (1.5)	NR	Birth weight > 4000 gm: 147 (12) LGA: 233 (19)		(2.8) OR: 1.9 (95% CI: 1 - 3.5)	Bone fracture, nerve palsy: 12 (41)		
		E: Ultrasound at 37-38 weeks; CD if EFW > 4250 gm, induced if LGA and EFW < 4250 gm, 1337	39.2 (1.6)	NR	Birth weight > 4000 gm: 120 (9) p = 0.04† LGA: 227 (17) p: NS†		(1.5)	Bone fracture, nerve palsy: 7 (47)		

Evidence Table 12. Effects of labor management on neonatal outcomes (continued)

Author, year	Level of analysis	Intervention/Exposure, N	GA at delivery (in weeks), mean (SD)	GA determined by	Macrosomia or LGA (PW>90%), n (%)	Birth weight (in grams), mean	Shoulder dystocia, n (%)	Birth trauma, n (%)	Mortality, n (%)	Other outcome, n (%)
Lurie, 1996 [58]	Protocol-based	HC: Induced if EFW > 4000 gm; CD if EFW > 4500 gm, 164	39.2	LMP; 1st trimester ultrasound	Birth weight > 4000 gm: 30 (18)	3430.1 (530.0)	7 (5)	Clavicle fracture, nerve palsy: 3 (1.83)	Perinatal/ neonatal mortality: 0 (0.00)	RDS: 0 (0)
		E: Induced at 38 weeks, CD if EFW > 4500 gm, 96	38.4	LMP; 1st trimester ultrasound; amniocentesis for lung maturity	Birth weight > 4000 gm: 9 (9) p: NS[†]	3406.7 (493.4)	1 (1) p: NS[†]	Clavicle fracture, nerve palsy: 0 (0.00)	Perinatal/ neonatal mortality: 1 (1.04)	RDS: 0 (0)

Evidence Table 12. Effects of labor management on neonatal outcomes (continued)

Author, year	Level of analysis	Intervention/Exposure, N	GA at delivery (in weeks), mean (SD)	GA deter-mined by	Macrosomia or LGA (PW>90%), n (%)	Birth weight (in grams), mean	Shoulder dystocia, n (%)	Birth trauma, n (%)	Mortality, n (%)	Other outcome, n (%)
Lurie, 1992 [57]	Protocol-based; divided into groups based on gestational age at delivery	GDMA1: > 40 weeks: Induced if EFW > 4000 gm, CD if EFW > 4500 gm, 65	40.9	LMP; 1st trimester ultrasound	Birth weight > 4000 gm: 16 (25)	3617.85 (sd: 485.12)	2 (3.57)	Clavicle fracture, nerve palsy: 0 (0)	Perinatal/ neonatal mortality: 0 (0)	Hypoglycemia: 2 (3) RDS: 0 (0) Hyperbilirubine-mia: 2 (3)
		< 40 weeks: Induced if EFW > 4000 gm, CD if EFW > 4500 gm, 65	38.2	LMP; 1st trimester ultrasound	Birth weight > 4000 gm: 10 (15) p = 0.1853‡	3439.00 (sd: 584.21) p = 0.0619‡	0 (0.00) p = 0.5328‡	Clavicle fracture, nerve palsy: 0 (0)	Perinatal/ neonatal mortality: 0 (0)	Hypoglycemia: 2 (3) p: NS‡ RDS: 0 (0) Hyperbilirubine-mia: 1 (2) p: NS‡
		GDMA2: > 40 weeks: Induced if EFW > 4000 gm, CD if EFW > 4500 gm, 59	40.5	LMP; 1st trimester ultrasound	Birth weight > 4000 gm: 12 (20)	3639.15 (sd: 491.84)	1 (2.17),	Clavicle fracture, nerve palsy: 2 (4.35)	Perinatal/ neonatal mortality: 0 (0)	Hypoglycemia: 5 (8) RDS: 0 (0) Hyperbilirubine-mia: 3 (5)
		< 40 weeks: Induced if EFW > 4000 gm, CD if EFW > 4500 gm, 59	37.5	LMP; 1st trimester ultrasound	Birth weight > 4000 gm: 4 (7) p = 0.0567‡	3275.34 (sd: 570.15) p = 0.0003‡	2 (4.55) p = 0.9676‡	Clavicle fracture, nerve palsy: 1 (2.27)	Perinatal/ neonatal mortality: 0 (0)	Hypoglycemia: 6 (10) p: NS‡ RDS: 0 (0) Hyperbilirubine-mia: 3 (5) p: NS‡

Evidence Table 12. Effects of labor management on neonatal outcomes (continued)

Author, year	Level of analysis	Intervention/Exposure, N	GA at delivery (in weeks), mean (SD)	GA deter-mined by	Macrosomia or LGA (PW>90%), n (%)	Birth weight (in grams), mean	Shoulder dystocia, n (%)	Birth trauma, n (%)	Mortality, n (%)	Other outcome, n (%)
Peled, 2004 [59]	protocol period	Period A: Induced at 42 weeks, CD if EFW > 4500 gm, 878	39 (2.5)	LMP; +/- 1st trimester ultrasound	Birth weight > 4000 gm: 167 (19)		18 (2)		Perinatal/ neonatal mortality: 70 (8)	
		Period B: Induced at 40 weeks if LGA, CD if EFW > 4000 gm, 347	39 (1.5)	LMP; +/- 1st trimester ultrasound	Birth weight > 4000 gm: 56 (16)		3 (1)		Perinatal/ neonatal mortality: 10 (3)	
		Period C: Induced at 40 weeks if LGA, CD if EFW > 4000 gm, 317	38 (1.6)	LMP; +/- 1st trimester ultrasound	Birth weight > 4000 gm: 38 (12)		3 (1)		Perinatal/ neonatal mortality: 0 (0)	
		Period D: Induced at 38 weeks if LGA, CD if EFW > 4000 gm, 518	38.1 (3.1)	LMP; +/- 1st trimester ultrasound	Birth weight > 4000 gm: 21 (4)		0 (0)		Perinatal/ neonatal mortality: 5 (1)	
Additional studies										
Rayburn, 2005 [56]	exposure	C: GDMA1, Expectant management, 137	39 (1)	1st trimester ultrasound amniocentesis if needed	Birth weight > 4000 gm: 11 (8)	3311 (sd: 489)	3 (2)	clavicle fracture, nerve palsy: 0 (0.00)	Fetal mortality: 1 (1)	RDS: 0 (0.00)
		E: GDMA2, Induced at 38 weeks, 143	38.1 (0.3)	1st trimester ultrasound amniocentesis if needed	Birth weight > 4000 gm: 6 (4) p = 0.18¶	3306 (sd: 396) p = 0.93¶	6 (4) p = 0.77¶	clavicle fracture, nerve palsy: 0 (0.00)	Fetal mortality: 0 (0)	RDS: 0 (0.00)

Evidence Table 12. Effects of labor management on neonatal outcomes (continued)

Author, year	Level of analysis	Intervention/Exposure, N	GA at delivery (in weeks), mean (SD)	GA deter-mined by	Macrosomia or LGA (PW>90%), n (%)	Birth weight (in grams), mean	Shoulder dystocia, n (%)	Birth trauma, n (%)	Mortality, n (%)	Other outcome, n (%)
March-iano, 2004 [52]	exposure	C: Trial of labor after CD, 423	38.3 (2.2)	NR	Birth weight > 4000 gm: 76 (18)					
		E: Repeat elective cesarean, 440	38 (3.2)	NR	Birth weight > 4000 gm: 145 (33) p < 0.0001¶					

* Comparing C to I.
† Comparing HC to E.
‡ Comparing >40 weeks to <40 weeks.
¶ Comparing C to E.

C = control group; CD = cesarean delivery; CI = confidence interval; E = exposure group; EFW = estimated fetal weight; GA = gestational age; GDMA1 = diet-controlled; GDMA2 = requiring medical therapy; gm = gram; HC = historical control group; I = intervention group; LGA = large for gestational age; LMP = last menstrual period; NR = not reported; NS = not significant; OR = odds ratio; PW = percentile weight; RDS = respiratory distress syndrome; SD = standard deviation

Evidence Table 13. Quality of studies reporting on the effects of labor management on maternal and neonatal outcomes

Author, year	Hypotheses stated	Inclusion criteria reported	Sampling	Power/ Sample size calculations	Outcomes defined	Loss to followup/ reported in analysis	Missing data/ reported in analysis	Analysis adjusted
Conway, 1998[53]	●	●	Consecutive		●	<10%/ NA	<10%/ NA	
Lurie, 1996[58]		●	Consecutive	●	●	<10% / NA	<10% / NA	
Lurie, 1992[57]		●	Consecutive			<10% / NA	<10% / NA	
Peled, 2004[59]			Consecutive		●	<10% / NA	<10% / NA	
Rayburn, 2005[56]		●	Consecutive	●		<10% / NA	<10% / NA	●
Marchiano, 2004[52]	●	●	Consecutive		●	<10% / NA	10-20% / ●	●
Keller, 1991[54]		●	Consecutive		●	<10% / NA	<10% / NA	

Author, year	Randomized	Randomization scheme described	Double blinded	Blinding described	Withdrawals described	Quality score*
Kjos, 1993[55]	●				●	2

● = Yes; blank space = No/Not reported; NA= not applicable
*Total quality score calculated using the Jadad[22] criteria.

Evidence Table 14. Grading of the body of evidence of the effects of labor management on maternal and neonatal outcomes (KQ2)

	Labor management on maternal and neonatal outcomes
Quantity of evidence: Number of studies	8
Total number of patients studied	6648
Quality and consistency of evidence: Were study designs mostly randomized trials (high quality), non-randomized controlled trials (medium quality), observational studies (low quality), or about a 50:50 mix of experimental and observational (medium quality)?	Low
Did the studies have serious (-1) or very serious (-2) limitations in quality? (Enter 0 if none)	-2
Did the studies have important inconsistency? (-1)	-1
Was there some (-1) or major (-2) uncertainty about the directness (i.e. extent to which the people, interventions and outcomes are similar to those of interest)?	0
Were data imprecise or sparse? (-1) (i.e. lack of data or very wide confidence intervals that may change conclusions)	-1
Did the studies have high probability of reporting bias? (-1)	0
Did the studies show strong evidence of association between intervention and outcome? ("strong" if significant relative risk or odds ratio > 2 based on consistent evidence from 2 or more studies with no plausible confounders (+1); "very strong" if significant relative risk or odds ratio > 5 based on direct evidence with no major threats to validity (+2))- use your clinical judgment for absolute differences.	0
Did the studies have evidence of a dose-response gradient? (+1)	0
Did the studies have unmeasured plausible confounders that most likely reduced the magnitude of the observed association? (+1)	+1
Overall grade of evidence (high, moderate, low, very low)	Very low

High = further research is very unlikely to change our confidence in the estimates; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low = any estimate of effect is very uncertain.

Evidence Table 15. List of covariates considered and included in models assessing the association of risk factors with the development of type 2 diabetes following a pregnancy with gestational diabetes

Covariate	Buchanan, 1998[75]	Buchanan, 1999[74]			Cheung, 2006[60]		Cho, 2005[61]	Cho, 2006[62]								Dacus, 1994[65]	Jang, 2003[63]	Kjos, 1995[68]
# abnormal OGTT results																		
# prior GDM pregnancies					○	●												
% pre-pregnancy obesity																		
1-hr plasma glucose diagnostic OGTT		○	●	●														
2-hr glucose																	●	
2-hr OGTT					○	●												
3-hr insulin on diagnostic OGTT																	●	
50-gm GCT																		
75-gm OGTT glucose AUC	○																	
8-year DM risk (%)																		
Additional pregnancy																		
Age	○	○	○	○	○	●	●	●	●	●	●	●	●	●	●	○	●	○
Antepartum 30 min incremental plasma insulin/glucose	●																	
Antepartum OGTT glucose AUC																		●
Antepartum plasma glucose 1-hr at screening		○	○	○														
Area under the glucose curve or pregnancy OGTT																		
AUC at initial postpartum OGTT																		
Basal glucose production rate		●	●	●														
Beta-cell compensation index		○	○	●														
Blood pressure								●	●	●	●	●	●	●	●			
BMI																		
BMI at GTT																		

Evidence Table 15. List of covariates considered and included in models assessing the association of risk factors with the development of type 2 diabetes following a pregnancy with gestational diabetes (continued)

Covariate	Buchanan, 1998[75]	Buchanan, 1999[74]	Cheung, 2006[60]	Cho, 2005[61]	Cho, 2006[62]	Dacus, 1994[65]	Jang, 2003[63]	Kjos, 1995[68]
BMI at index pregnancy			○ ●					
Body fat %					○ ○ ○ ○ ○ ○ ○ ○			
Body fat weight					○ ○ ○ ● ○ ○ ○ ○			
Breastfeeding	○							
Clamp SI		● ● ○						
Class A2								
Completion of 2nd pregnancy								
Contraceptive use								
C-peptide glucose score								
Dose of bedtime intermediate-acting insulin required			● ○					
Duration of followup					● ● ● ● ● ● ● ●			
Duration of OC use								
Fasting blood glucose level			● ○					
Fasting blood sugar								
FHxT2DM			○ ●	●	● ● ○ ● ● ● ● ●		●	
FPG at diagnosis			○ ●	●				
FSIGT acute insulin response		○ ○ ○						
FU months								
GAD and IA-2 antibody status								
GDM class A1							○	
Gestational age at delivery	○	○ ○ ○					○	
Gestational age at GDM diagnosis				●		○	●	●
GTT total								
HDL cholesterol								
Height							●	
Highest antepartum fasting glucose								●
Highest FPG	○							

Evidence Table 15. List of covariates considered and included in models assessing the association of risk factors with the development of type 2 diabetes following a pregnancy with gestational diabetes (continued)

Covariate	Buchanan, 1998[75]	Buchanan, 1999[74]			Cheung, 2006[60]		Cho, 2005[61]	Cho, 2006[62]								Dacus, 1994[65]	Jang, 2003[63]	Kjos, 1995[68]
HLA DR3 or DR4-DQ8																		
Homocysteine level							●											
Hospital					○	●												
Incremental glucose area, diagnostic OGTT		●	○	○														
Insulin																	●	
Interaction term for breastfeeding and OC use																		
Interaction term of OC use and triglyceride level																		
Lipid profile which includes triglyceride, HDL and LDL and cholesterol								●	●	●	●	●	●	●	●			
Mean arterial pressure																		
Mean BMI at 1st antenatal visit																		
Method of glucose control	○				○	●	○									○		
OGTT 30-min incremental insulin: glucose		●	●	○														
OGTT glucose area																		
Parity					○	●	○	●	●	●	●	●	●	●	●		○	○
Postpartum BMI	○	○	○	○				○	○	○	○	●	○	○	○	○		○
Postpartum FPG																		
Postpartum OGTT glucose AUC																		●
Postpartum weight																	●	
Postpartum weight change		○	○	○				○	○	○	○	○	○	●	○			
Pregnancy weight gain	○	○	○	○														

Evidence Table 15. List of covariates considered and included in models assessing the association of risk factors with the development of type 2 diabetes following a pregnancy with gestational diabetes (continued)

Covariate	Buchanan, 1998[75]	Buchanan, 1999[74]		Cheung, 2006[60]	Cho, 2005[61]	Cho, 2006[62]							Dacus, 1994[65]	Jang, 2003[63]	Kjos, 1995[68]
Pre-pregnancy BMI	○	○	○	○	●									●	
Pre-pregnancy weight														●	
Previous macrosomia															
Previous stillbirth															
Prior OC use															
Race	○	○	○	○									○		○
Serum CRP															
Spontaneous abortions															
Subscapular skin fold thickness						○	○	○	○	○	●	○	○		
Suprailiac skin fold thickness						●	○	○	○	○	○	○	○		
Total AUC for diagnostic antepartum 100-gm OGTT glucose	●														
Total cholesterol						○	○	○	○	○	○	○	○		
Triceps skin fold thickness						○	●	○	○	○	○	○	○		
Triglycerides						○	○	○	○	○	○	○	○		
Waist circumference						○	○	○	○	○	○	○	●		
Wait-to-hip ratio						○	○	●	○	○	○	○	○		
Working status						●	●	○	●	●	●	●	●		

Evidence Table 15. List of covariates considered and included in models assessing the association of risk factors with the development of type 2 diabetes following a pregnancy with gestational diabetes (continued)

Covariate	Kjos, 1998[69]	Lobner, 2006[66]	Pallardo, 1999[73]	Peters, 1996[72]	Schaefer-Graf, 2002[70]	Steinhart, 1997[71]	Xiang, 2006[64]			Metzger, 1993[67]	
# abnormal OGTT results			●								
# prior GDM pregnancies			○		●	○					
% pre-pregnancy obesity			○								
1-h plasma glucose diagnostic OGTT											
2-hr glucose										○	●
2-hr OGTT											
3-hr insulin on diagnostic OGTT											
3-hr integrated insulin										●	○
50-gm GCT					●						
75-gm OGTT glucose AUC											
8-year DM risk (%)		○									
Additional pregnancy	○			●							
Age	○	●	○	○	○	○	○	○	○	○	○
Antepartum 30 min incremental plasma insulin/glucose											
Antepartum OGTT glucose AUC											
Antepartum plasma glucose 1-hr at screening											
Area under the glucose curve of pregnancy OGTT					●						
AUC at initial postpartum OGTT	●										

Evidence Table 15. List of covariates considered and included in models assessing the association of risk factors with the development of type 2 diabetes following a pregnancy with gestational diabetes (continued)

Covariate	Kjos, 1998[69]	Lobner, 2006[66]	Pallardo, 1999[73]	Peters, 1996[72]	Schaefer-Graf, 2002[70]	Steinhart, 1997[71]	Xiang, 2006[64]			Metzger, 1993[67]	
Basal glucose production rate										○	○
Basal Insulin										○	●
Beta-cell compensation index											
Blood pressure											
BMI		○									
BMI at GTT						○					
BMI at index pregnancy											
Body fat %											
Body fat weight											
Breastfeeding				●			●	●	○		
Clamp S1											
Class A2					●						
Completion of 2nd pregnancy	●										
Contraceptive use	●			○			●	○	○		
C-peptide glucose score			●								
Diagnostic OGTT											
Dose of bedtime intermediate-acting insulin required											
Duration of followup				○							
Duration of OC use	●										
Fasting blood glucose level											
Fasting blood sugar						○					
FHxT2DM			○				●	●	●	○	○
FPG at diagnosis					●						
FSIGT acute insulin response											

Evidence Table 15. List of covariates considered and included in models assessing the association of risk factors with the development of type 2 diabetes following a pregnancy with gestational diabetes (continued)

Covariate	Kjos, 1998[69]	Lobner, 2006[66]	Pallardo, 1999[73]	Peters, 1996[72]	Schaefer-Graf, 2002[70]	Steinhart, 1997[71]	Xiang, 2006[64]			Metzger, 1993[67]
FU months										
GAD and IA-2 antibody status		●								
GDM class A1										
GDM recurrence			○			○				
Gestational age at delivery				○						
Gestational age at GDM diagnosis					●					
GTT total						○				
HDL cholesterol							●	●	○	
Height										
Highest antepartum fasting glucose										
Highest FPG										
HLA DR3 or DR4-DQ8		○								
Homocysteine level										
Hospital										
Incremental glucose area										
Insulin										
Interaction term for breastfeeding and OC use							○	○	●	
Interaction term of OC use and triglyceride level							○	●	○	
Lipid profile which includes triglyceride, HDL and LDL and cholesterol										
Mean arterial pressure	○									
Mean BMI at 1st antenatal visit										

Evidence Table 15. List of covariates considered and included in models assessing the association of risk factors with the development of type 2 diabetes following a pregnancy with gestational diabetes (continued)

Covariate	Kjos, 1998[69]	Lobner, 2006[66]	Pallardo, 1999[73]	Peters, 1996[72]	Schaefer-Graf, 2002[70]	Steinhart, 1997[71]	Xiang, 2006[64]			Metzger, 1993[67]	
Method of glucose control	●	●				○	○	○	○		
Obesity										●	○
OGTT 30-min incremental insulin: glucose											
OGTT 30-min stimulated insulin secretion										○	●
OGTT glucose area				●							
Parity	○	●	○	○	○	○	○	○	○	●	○
Postpartum BMI	○			●			●	●	●		
Postpartum FPG	○										
Postpartum OGTT glucose AUC											
Postpartum weight											
Postpartum weight change	●			●			●	●	●		
Pregnancy weight gain											
Pre-pregnancy BMI			○								
Pre-pregnancy weight											
Previous GDM					○						
Previous macrosomia					○						
Previous stillbirth					○						
Prior OC use	●										
Race	○		○	○		○	○	○	○	○	○
Serum CRP		○									
Spontaneous abortions						○					
Subscapular skin fold thickness											

Evidence Table 15. List of covariates considered and included in models assessing the association of risk factors with the development of type 2 diabetes following a pregnancy with gestational diabetes (continued)

Covariate	Kjos, 1998[69]	Lobner, 2006[66]	Pallardo, 1999[73]	Peters, 1996[72]	Schaefer-Graf, 2002[70]	Steinhart, 1997[71]	Xiang, 2006[64]			Metzger, 1993[67]
Suprailiac skin fold thickness										
Total AUC for diagnostic antepartum 100-gm OGTT glucose										
Total cholesterol	○									
Triceps skin fold thickness										
Triglycerides							●	○	●	
Waist circumference										
Wait-to-hip ratio										
Working status										

○ = Variable considered in multivariate model; ● = variable included in multivariate model

AUC = area under the curve; BMI = body mass index; CRP= C-reactive protein; DM = diabetes mellitus; FH = family history; FPG = fasting plasma glucose; FSIGT = frequently sampled intravenous glucose tolerance; FU = followup; GAD = glutamic acid decarboxylase; GCT = glucose challenge test; GDM = Gestational diabetes mellitus; gm = gram; GTT = glucose tolerance test; HDL = high density lipoprotein; HLA = human leukocyte antigen; hr = hour; IA-2 = Insulinoma antigen-2; LDL = low density lipoprotein; min = minute; OC = oral contraceptive; OGTT = oral glucose tolerance test; T2DM = Type 2 diabetes mellitus.

Evidence Table 16. Characteristics of studies reporting on the risk associated with the development of type 2 diabetes mellitus following a pregnancy with gestational diabetes

Author, year Country Study design	Age (in years), mean	Race, n (%)	Gravida and parity, mean	N	Diabetes diagnosis	Followup time	Covariates considered
Buchanan, 1998[75] US Cohort	NGT: 30.8 IGT: 29.3 T2DM: 32.3	NGT: Hisp: 49 (100) IGT: Hisp: 61 (100) T2DM: Hisp: 12 (100)	NR	122	Abnormal 75-gm OGTT	0-6 months	Age, race, pregnancy weight gain, pre-pregnancy BMI, postpartum BMI, gestational age at delivery, method of glucose control, 75-gm OGTT glucose AUC, breastfeeding, highest FPG, antepartum 30 minutes incremental plasma insulin/glucose, total AUC for diagnostic antepartum 100-gm OGTT glucose
Buchanan, 1999[74] US Cohort	ND: 30.3 T2DM: 29.6	ND: Hisp: 77 (100) T2DM: Hisp: 14 (100)	NR	91	Abnormal 75-gm OGTT	11-26 months	Age, race, pregnancy weight gain, pre-pregnancy BMI, postpartum BMI, gestational age at delivery, antepartum plasma glucose (1-hr) at screening, incremental glucose area, diagnostic OGTT, postpartum weight change, 1-hr plasma glucose diagnostic OGTT, beta-cell compensation index, basal glucose production rate, OGTT 30-min incremental insulin:glucose, clamp SI, FSIGT acute insulin response
Cheung, 2006[60] Australia Cohort	ND: 32.3 T2DM: 31.9 T: 32.1	NR	ND: parity: 1.6 T2DM: parity: 0.9 T: parity: 1.4	102	Abnormal 75-gm OGTT, self report followed by verification from local doctor or abnormal 75-gm OGTT at retest	0-8 years, mean=4.5 years	Age, parity, FPG at diagnosis, BMI at index pregnancy, 2-hr OGTT, # prior GDM pregnancies, method of glucose control, FHxT2DM, hospital, fasting blood glucose level, dose of bedtime intermediate-acting insulin required
Cho, 2005[61] Korea Cohort	NGT: 30.6 IGT: 32.1 T2DM: 30	NR	NGT: (≥ 3 children (%): 32.1) IGT: (≥ 3 children (%): 55.8) T2DM: (≥ 3 children (%): 33.3)	170	Abnormal 75-gm OGTT	6 weeks and annually thereafter	Age, pre-pregnancy BMI, parity, method of glucose control, gestational age at GDM diagnosis, FHxT2DM, FPG at diagnosis, homocysteine level

Evidence Table 16. Characteristics of studies reporting on the risk associated with the development of type 2 diabetes mellitus following a pregnancy with gestational diabetes (continued)

Author, year Country Study design	Age (in years), mean	Race, n (%)	Gravida and parity, mean	N	Diabetes diagnosis	Followup time	Covariates considered
Cho, 2006[62] Korea Cohort	NGT: 33.2	NR	NGT: (para 1 (%): 39.0; para 2 (%): 51.4; para 3+ (%): 9.5)	909	Abnormal 75-gm OGTT	6 weeks, annually up to 6 years	Age, parity, body fat %, total cholesterol, triglycerides, postpartum BMI, blood pressure, lipid profile,* duration of followup, FHxT2DM, working status, postpartum waist circumference, postpartum weight, postpartum subscapular skin fold thickness, postpartum suprailiac skin fold thickness, postpartum tricep skin fold thickness, postpartum body fat weight, postpartum waist-to-hip ratio
	IGT: 34.2		IGT: (para 1 (%): 37.8; para 2 (%): 56.9; para 3+ (%): 3.4)				
	T2DM: 33		T2DM: (para 1 (%): 39.7; para 2 (%): 56.9; para 3+ (%): 3.4)				
Dacus, 1994[65] US Cohort	ND: ≥30 year (n, %): 40 (47%); <30 year (n, %): 46 (53%)	ND: AA: 60 (70); C: 23 (27); Other: 3 (3)	NR	100	Abnormal 75-gm OGTT	5-10 weeks postpartum	Age, race, gestational age at GDM diagnosis, method of glucose control, postpartum BMI
	T2DM: ≥30 year (n, %): 5 (36%); <30 year (n, %): 9 (64%)	T2DM: AA: 11 (72); C: 2 (21); Other: 1 (7)					
Jang, 2003[63] Korea Cohort	T: 30.9	T: NR	T: parity: 0.5	311	Abnormal 75-gm OGTT	NR	Age, pre-pregnancy weight, pre-pregnancy BMI, parity, gestational age at delivery, GDM class A1, gestational age at GDM diagnosis, 2-hr glucose, 3-hr insulin on diagnostic OGTT, height, FHxT2DM, postpartum weight

Evidence Table 16. Characteristics of studies reporting on the risk associated with the development of type 2 diabetes mellitus following a pregnancy with gestational diabetes (continued)

Author, year Country Study design	Age (in years), mean	Race, n (%)	Gravida and parity, mean	N	Diabetes diagnosis	Followup time	Covariates considered
Kjos, 1995[68] US Cohort	T: 30.3	T: Hisp: 671 (100)	T: parity: 2.8	671	Abnormal 75-gm OGTT	Between 4 to 16 weeks; Additional followup within 7.5 years postpartum	Age, race, postpartum BMI, parity, postpartum OGTT glucose AUC, gestational age at GDM diagnosis, antepartum OGTT glucose AUC, highest antepartum fasting glucose
Kjos, 1998[69] US Cohort	COC: 28.5 Progestin only: 29.4	COC: Hisp: 383 (100) Progestin only: Hisp: 78 (100)	COC: parity: 2.3 Progestin only: parity: 3.1	443	Abnormal 75-gm OGTT	Varied (Cox model)	Age, race, postpartum BMI, parity, method of glucose control, total cholesterol, mean arterial pressure, postpartum FPG, contraceptive use, AUC at the initial postpartum OGTT, prior OC use, additional pregnancy, postpartum weight change, duration of OC use
Lobner, 2006[66] Germany Cohort	Autoantibody (+): 29.9 Autoantibody (-): 31.4 T: NR	NR	NR	302	Abnormal 75-gm OGTT	9 months and 2, 5, 8 and 11 years postpartum	Age, BMI at first pregnancy visit, method of glucose control, HLA DR3 or DR4-DQ8, 8-year DM risk (%), GAD and IA-2 antibody status, parity, serum CRP
Metzger, 1993[67] US Cohort	Model 1 ND: 31.7 IGT: 32.0 T2DM: 33.0 Model 2 ND: 31.4 IGT: 31.7 T2DM: 32.3	NR	Model 1: parity ND: 1.5 IGT: 1.5 T2DM: 1.7 Model 2: parity ND: 1.6 IGT: 1.3 T2DM: 2.1	Model 1 177 Model 2 172	Abnormal 100-gm OGTT	3-6 months (model 1), and year 1,2,3,4,&5 (model 2)	Age, race, FHxT2DM, parity, obesity, basal glucose, basal insulin, 2-hr glucose, 3-hr integrated insulin, OGTT 30-min stimulated insulin secretion

Evidence Table 16. Characteristics of studies reporting on the risk associated with the development of type 2 diabetes mellitus following a pregnancy with gestational diabetes (continued)

Author, year Country Study design	Age (in years), mean	Race, n (%)	Gravida and parity, mean	N	Diabetes diagnosis	Followup time	Covariates considered
Pallardo, 1999[73] Spain Cohort	ND: 33.1	ND: C: 745 (100)	ND: parity: 1.89	788	Abnormal 75-gm OGTT	3-6 months	Age, race, parity, pre-pregnancy BMI, recurrence of GDM, FHxT2DM, # of abnormal OGTT results (including fasting), C-peptide glucose score
	T2DM: 32.6	T2DM: C: 43 (100)	T2DM: parity: 1.94				
Peters, 1996[72] US Cohort	No additional pregnancy: 30.4	No additional pregnancy: Hisp: 578 (100)	No additional pregnancy: parity: 2.8	666	Abnormal 75-gm OGTT	3-89 months	Age, race, parity, gestational age at delivery, duration of followup, oral contraceptive use, additional pregnancy, postpartum weight change, OGTT glucose area, postpartum BMI, breastfeeding
	Additional pregnancy: 29.9	Additional pregnancy: Hisp: 87 (100)	Additional pregnancy: parity: 2.8				
Schaefer-Graf, 2002[70] US Cohort	ND: 31.1	NR	ND: parity: 1.9	1636	Abnormal 75-gm OGTT, taking diabetes medications	1-4 months	Age, parity, previous macrosomia, previous stillbirth, FPG at diagnosis, class A2, area under the glucose curve of pregnancy OGTT, gestational age at GDM diagnosis, previous GDM, 50-gm GCT
	T2DM: 32.2		T2DM: parity: 2.2				
	T: 31.2		T: NR				
Steinhart, 1997[71] US Cohort	ND: 31	ND: American Indian: 41	ND: parity: 2.45	88	Abnormal 75-gm OGTT, type 2 diabetes diagnosed in medical record	9-12 years	Age, race, parity, BMI at GTT, fasting blood sugar, spontaneous abortions, GTT total, recurrent GDM, method of glucose control
	NIDDM: 32.7	NIDDM: American Indian: 47	NIDDM: parity: 3.43				

Evidence Table 16. Characteristics of studies reporting on the risk associated with the development of type 2 diabetes mellitus following a pregnancy with gestational diabetes (continued)

Author, year Country Study design	Age (in years), mean	Race, n (%)	Gravida and parity, mean	N	Diabetes diagnosis	Followup time	Covariates considered
Xiang, 2006[64] US Cohort	DMPA: 30	DMPA: Hisp: 96 (100)	DMPA: parity: 2.6	526	Abnormal 75-gm OGTT	4-6 weeks, 3-6 month intervals thereafter	Age, race, parity, method of glucose control, contraceptive use, postpartum BMI, breastfeeding, FHxT2DM, HDL cholesterol, triglycerides, weight change during followup, interaction term for OC use and triglyceride level, interaction term for breastfeeding and OC use
	COC: 29	COC: Hisp: 430 (100)	COC: parity: 2.3				

* Includes triglyceride, high density lipoprotein, and low density lipoprotein cholesterol

AA = African American; AUC = area under the curve; BMI = body mass index; C = Caucasian; COC = combination oral contraceptive; CRP = C-reactive protein; DMPA = depomedroxyprogesterone acetate; FPG = fasting plasma glucose; FSIGT = frequently sampled intravenous glucose tolerance; GAD = glutamic acid decarboxylase; GCT = glucose challenge test; GDM = gestational diabetes mellitus; gm = gram; GTT = glucose tolerance test; HDL = high density lipoprotein; Hisp = Hispanic; HLA = human leukocyte antigen; hr = hour; IA-2 = insulinoma antigen-2; IGT = impaired glucose tolerance; min = minutes; ND = non-diabetic; NGT = normal glucose tolerance; NIDDM = non-insulin dependent diabetes mellitus; NR = not reported; OC = oral contraceptive; OGTT = oral glucose tolerance test; SI = sensitivity index; T2DM = type 2 diabetes mellitus; T = total; US = United States

Evidence Table 17. Quality of studies reporting on the risk associated with the development of type 2 diabetes following a pregnancy with gestational diabetes

Author, year	Are pre-specified hypotheses stated?	Are inclusion and exclusion criteria reported?	Sampling	Were power or sample size calculations used?	Does the article state how the outcome was defined?	Loss to followup / Report comparisons of those lost to followup vs participants	Percent of missing data / Report how missing data was handled
Buchanan, 1998[75]		●	Consecutive		●	10-20% / ●	
Buchanan, 1999[74]	●	●	Convenience		●	10-20% /	
Cheung, 2006[60]	●	●	Convenience		●	>20% / ●	
Cho, 2005[61]		●	Convenience		●	>20% /	
Cho, 2006[62]		●	Convenience		●	>20% /	
Dacus, 1994[65]	●	●	Convenience		●	>20% /	
Jang, 2003[63]	●	●	Convenience		●	10-20% / ●	
Kjos, 1995[68]	●	●	Convenience		●	>20% /	
Kjos, 1998[69]		●	Consecutive		●		
Lobner, 2006[66]	●	●	Convenience		●	>20% /	
Pallardo, 1999[73]	●	●	Convenience		●	>20% / ●	
Peters, 1996[72]		●	Consecutive		●		
Schaefer-Graf, 2002[70]	●	●	Convenience		●	>20% / ●	10-20% /
Steinhart, 1997[71]		●	Consecutive		●	>20% /	
Xiang, 2006[64]		●	Convenience				

●=yes; blank space=no/not reported

Evidence Table 18. Studies reporting on the association between a family history of type 2 diabetes mellitus and the development of type 2 diabetes mellitus following a pregnancy with gestational diabetes

Author, year	Risk factor	Units	N	Measure of association (95% CI)	Covariates included
Cheung, 2006[60]	FHxT2DM	NR	102	Yes/no	Age, parity, FPG at diagnosis, BMI at index pregnancy, 2-hr OGTT, # prior GDM pregnancies, method of glucose control, hospital
Cho, 2005[61]	FHxT2DM	Yes/no	170	No: ref Yes: RR = 1.706 (0.638 - 4.566)	Age, gestational age at GDM diagnosis, pre-pregnancy BMI, FPG at diagnosis, homocysteine level
Cho, 2006[62]	FHxT2DM	NR	909	NR	Cho reported 8 models, which adjusted for blood pressure, lipid profile*, age, duration of followup, parity, working status, and one of the following measures of adiposity at postpartum: BMI, waist circumference, weight, subscapular skin fold thickness, suprailiac skin fold thickness, tricep skin fold thickness, body fat weight, and waist-to-hip ratio. The relative measure for FHxT2DM was not reported in any of the models.
Jang, 2003[63]	FHxT2DM	Yes/no	311	NR	Pre-pregnancy weight, gestational age at GDM diagnosis, 2-hr glucose, 3-hr insulin on diagnostic OGTT, age, height, pre-pregnancy BMI, postpartum weight
Xiang, 2006[64]	FHxT2DM	Yes/no	526	NR	Contraceptive use, postpartum BMI, breastfeeding, HDL cholesterol, triglycerides, postpartum weight change
Xiang, 2006[64]	FHxT2DM	Yes/no	526	NR	Interaction term for breastfeeding and OC use, postpartum BMI, triglycerides, HDL cholesterol, postpartum weight change
Xiang, 2006[64]	FHxT2DM	Yes/no	526	NR	Interaction term for OC use and triglyceride level, postpartum BMI, breastfeeding, HDL cholesterol, postpartum weight change

* Includes triglyceride, high density lipoprotein, and low density lipoprotein cholesterol

BMI = body mass index; CI = confidence interval; FHxT2DM = family history of type 2 diabetes mellitus; FPG = fasting plasma glucose; GDM = gestational diabetes mellitus; HDL = high density lipoprotein; hr = hour; NR = not reported; OC = oral contraceptive; OGTT = oral glucose tolerance test; ref = reference group; RR = relative risk

Evidence Table 19. Studies reporting on the association between sociodemographics and the development of type 2 diabetes mellitus following a pregnancy with gestational diabetes

Author, year	Risk factor	Units	N	Measure of association (95% CI)	Covariates included
Cho, 2005[61]	Age	Years	170	≤30: ref >30: RR = 2.03 (0.682 - 6.03)	Gestational age at GDM diagnosis, pre-pregnancy BMI, FHxT2DM, FPG at diagnosis, homocysteine level
Dacus, 1994[65]	Age	Years	100	<30: ref ≥30: RR = 0.68 (0.24 - 1.88)	None
Cheung, 2006[60]	Age	NR	102	NR	Parity, FPG at diagnosis, BMI at index pregnancy, 2-hr OGTT, # prior GDM pregnancies, method of glucose control, FHxT2DM, hospital
Cho, 2006[62]	Age	Years	909	NR	Cho reported 8 models, which adjusted for blood pressure, lipid profile*, age, duration of followup, parity, FHxT2DM, working status, and one of the following measures of adiposity at postpartum: BMI, waist circumference, weight, subscapular skin fold thickness, suprailiac skin fold thickness, tricep skin fold thickness, body fat weight, and waist-to-hip ratio. The relative measure for age was not reported in any of the models.
Jang, 2003[63]	Age	Years	311	NR	Pre-pregnancy weight, gestational age at GDM diagnosis, 2-hr glucose, 3-hr insulin on diagnostic OGTT, height, pre-pregnancy BMI, FHxT2DM, postpartum weight
Lobner, 2006[66]	Age	Years	302	NR	GAD and IA-2 antibody status, method of glucose control, BMI at first pregnancy visit, parity, serum CRP
Cheung, 2006[60]	Hospital	NR	102	NR	Age, parity, FPG at diagnosis, BMI at index pregnancy, 2-hr OGTT, # prior GDM pregnancies, method of glucose control, FHxT2DM
Cho, 2006[62]	Working status	Yes/no	909	NR	Cho reported 8 models, which adjusted for blood pressure, lipid profile*, age, duration of followup, parity, FHxT2DM, working status, and one of the following measures of adiposity at postpartum: BMI, waist circumference, weight, subscapular skin fold thickness, suprailiac skin fold thickness, tricep skin fold thickness, body fat weight, and waist-to-hip ratio. The relative measure for working status was not reported in any of the models.
Dacus, 1994[65]	Race	NR	100	Other: ref Black: RR = 1.5 (0.45 - 4.98)	None

* Includes triglyceride, high density lipoprotein, and low density lipoprotein cholesterol

BMI = body mass index; CI = confidence interval; CRP = C-reactive protein; FHxT2DM = family history of type 2 diabetes; FPG = fasting plasma glucose; GAD = glutamic acid decarboxylase; GDM = gestational diabetes mellitus; hr = hour; NR = not reported; OGTT = oral glucose tolerance test; ref = reference group; RR = relative risk

Evidence Table 20. Studies reporting on the association between parity and the development of type 2 diabetes mellitus following a pregnancy with gestational diabetes

Author, year	Risk factor	Units	N	Measure of association (95% CI)	Covariates included
Cheung, 2006[60]	Parity	NR	102	NR	Age, FPG at diagnosis, BMI at index pregnancy, 2-hr OGTT, # prior GDM pregnancies, method of glucose control, FHxT2DM, hospital
Cho, 2006[62]	Parity	NR	909	NR	Cho reported 8 models, which adjusted for blood pressure, lipid profile*, age, duration of followup, parity, FHxT2DM, working status, and one of the following measures of adiposity at postpartum: BMI, waist circumference, weight, subscapular skin fold thickness, suprailiac skin fold thickness, tricep skin fold thickness, body fat weight, and waist-to-hip ratio. The relative measure for parity was not reported in any of the models.
Lobner, 2006[66]	Parity	NR	302	0: ref 1-2: RH = 1.2 (0.8 - 1.7; p = 0.45) >2: RH = 2.5 (1.1 - 5.3; p = 0.02)	GAD and IA-2 antibody status, method of glucose control, BMI at first pregnancy visit, age, serum CRP
Metzger, 1993[67]	Parity	NR	172	OR = 1.21 (p = 0.09)	3-hr integrated insulin, obesity

* Includes triglyceride, high density lipoprotein, and low density lipoprotein cholesterol

BMI = body mass index; CI = confidence interval; CRP = C-reactive protein; FHxT2DM = family history of type 2 diabetes mellitus; FPG = fasting plasma glucose; GAD = glutamic acid decarboxylase; GDM = gestational diabetes mellitus; IA-2 = insulinoma antigen-2; NR = not reported; OGTT = oral glucose tolerance test; OR = odds ratio; ref = reference group; RH = relative hazard

Evidence Table 21. Studies reporting on the association between pregnancy-related factors and the development of type 2 diabetes mellitus following a pregnancy with gestational diabetes

Author, year	Risk factor	Units	N	Measure of association (95% CI)	Covariates included
Kjos, 1995[68]	Gestational age at GDM diagnosis	Weeks	671	Q1: ref Q2: RH = 0.66 (0.39 - 1.12) Q3: RH = 0.73 (0.45 - 1.18) Q4: RH = 0.48 (0.29 - 0.82) p = 0.01	Postpartum OGTT glucose AUC, antepartum OGTT glucose AUC, highest antepartum fasting glucose
Schaefer-Graf, 2002[70]	Gestational age at GDM diagnosis	Weeks	1636	Q1: ref Q2: OR = 1.12 (0.72 - 1.74) Q3: OR = 0.45 (0.27 - 0.76) Q4: OR = 0.35 (0.23 - 0.54)	FPG at diagnosis, class A2, area under the glucose curve of pregnancy OGTT, previous GDM, 50-gm GCT
Cho, 2005[61]	Gestational age at GDM diagnosis	Weeks	170	≥26 weeks: ref <26 weeks: RR = 2.399 (0.875 - 6.577)	Age, pre-pregnancy BMI, FHxT2DM, FPG at diagnosis, homocysteine level
Jang, 2003[63]	Gestational age at GDM diagnosis	Weeks	311	Coefficient = -0.00928 (se = 0.0539)	Pre-pregnancy weight, 2-hr glucose, 3-hr insulin on diagnostic OGTT, age, height, pre-pregnancy BMI, FHxT2DM, postpartum weight
Dacus, 1994[65]	Gestational age at GDM diagnosis	Weeks	100	<24: ref ≥24: RR = 2.49 (0.9 - 6.88)	None
Cheung, 2006[60]	Method of glucose control	Yes/no	102	No insulin: ref Insulin: RR = 3.2 (1.6 - 7)	Age, parity, FPG at diagnosis, BMI at index pregnancy, 2-hr OGTT, # prior GDM pregnancies, FHxT2DM, hospital
Lobner, 2006[66]	Method of glucose control	Yes/no	302	Diet: ref Insulin: RH = 4.7 (3.2 - 7.1; p < 0.0001)	GAD and IA-2 antibody status, BMI at first pregnancy visit, parity, age, serum CRP
Kjos, 1998[69]	Method of glucose control	NR	443	NR	Contraceptive use, AUC at the initial postpartum OGTT, prior OC use, additional pregnancy, postpartum weight loss, duration of OC use
Steinhart, 1997[71]	Method of glucose control	Yes/no	88	No insulin: ref Insulin: OR = 2.83 (0.8 - 11.2)	None
Dacus, 1994[65]	Method of glucose control	Yes/no	100	Diet: ref Insulin: RR = undefined (0 DM treated with diet only)	None
Cheung, 2006[60]	Dose of bedtime intermediate-acting insulin required	Insulin units unspeci-fied	102	RR = 1.09 (1.03 - 1.17)	fasting blood glucose level
Schaefer-Graf, 2002[70]	50-gm GCT	mg/dL	1636	Q1: ref Q2: OR = 2.86 (1.24 - 6.58) Q3: OR = 3.82 (1.72 - 8.48) Q4: OR = 3.46 (1.57 - 7.64)	FPG at diagnosis, class A2, area under the glucose curve of pregnancy OGTT, gestational age at GDM diagnosis, previous GDM

Evidence Table 21. Studies reporting on the association between pregnancy-related factors and the development of type 2 diabetes mellitus following a pregnancy with gestational diabetes (continued)

Author, year	Risk factor	Units	N	Measure of association (95% CI)	Covariates included
Schaefer-Graf, 2002[70]	Class A2 (any FBG ≥ 105)	Yes/no	1636	No: ref Yes: OR = 2.4 (1.22 - 4.72)	FPG at diagnosis, area under the glucose curve of pregnancy OGTT, gestational age at GDM diagnosis, previous GDM, 50-gm GCT
Schaefer-Graf, 2002[70]	Previous GDM	Yes/no	1636	No: ref Yes: OR = 1.63 (1.07 - 2.47)	FPG at diagnosis, class A2, area under the glucose curve of pregnancy OGTT, gestational age at GDM diagnosis, 50-gm GCT
Cheung, 2006[60]	# prior GDM pregnancies	NR	102	NR	Age, parity, FPG at diagnosis, BMI at index pregnancy, 2-hr OGTT, method of glucose control, FHxT2DM, hospital
Steinhart, 1997[71]	Spontaneous abortions	Yes/no	88	No: ref Yes: OR = 1.36 (0.5 - 3.5)	None

AUC = area under the glucose tolerance curve; BMI = body mass index; CI = confidence interval; class A2 = insulin requiring gestational diabetics; CRP = C-reactive protein; DM = diabetes mellitus; FHxT2DM = family history of type 2 diabetes mellitus; FPG = fasting plasma glucose; GAD = glutamic acid decarboxylase; GCT = glucose challenge test; GDM = gestational diabetes mellitus; gm = gram; hr = hour; NR = not reported; OC = oral contraceptive; OGTT = oral glucose tolerance Test; OR = odds ratio; Q = quartile; ref = reference group; RH = relative hazard; RR = relative risk; se = standard error

Evidence Table 22. Studies reporting on the association between postpartum factors and the development of type 2 diabetes mellitus following a pregnancy with gestational diabetes

Author, year	Risk factor	Units	N	Measure of association (95% CI)	Covariates included
Peters, 1996[72]	Additional pregnancy	Yes/no	666	No: ref Yes: RH = 3.34 (1.8 - 6.19)	Postpartum weight change, OGTT glucose area, postpartum BMI, breastfeeding
Kjos, 1998[69]	Additional pregnancy	NR	443	NR	Contraceptive use, AUC at the initial postpartum OGTT, prior OC use, method of glucose control, postpartum weight loss, duration of OC use
Peters, 1996[72]	Breastfeeding	Yes/no	666	NR	Additional pregnancy, postpartum weight change, OGTT glucose area, postpartum BMI
Xiang, 2006[64]	Breastfeeding	Yes/no	526	NR	Contraceptive use, postpartum BMI, FHxT2DM, HDL cholesterol, triglycerides, weight change during followup
Xiang, 2006[64]	Breastfeeding	Yes/no	526	NR	Interaction term for OC use and triglyceride level, postpartum BMI, FHxT2DM, HDL cholesterol, weight change during followup
Cho, 2006[62]	Duration of followup	Yes/no	909	NR	Cho reported 8 models, which adjusted for blood pressure, lipid profile*, age, duration of followup, parity, FHxT2DM, working status, and one of the following measures of adiposity at postpartum: postpartum BMI, waist circumference, weight, subscapular skin fold thickness, suprailiac skin fold thickness, tricep skin fold thickness, body fat weight, and waist-to-hip ratio. The relative measure for duration of followup was not reported in any of the models.
Steinhart, 1997[71]	Recurrent GDM	Yes/no	88	No: ref Yes: OR = 24.8 (3 - 1132.2)	None

* Includes triglyceride, high density lipoprotein, and low density lipoprotein cholesterol

AUC = area under the glucose tolerance curve; BMI = body mass index; CI = confidence interval; FHxT2DM = family history of type 2 diabetes mellitus; GDM = gestational diabetes mellitus; HDL = high density lipoprotein; NR = not reported; OC = oral contraceptive; OGTT = oral glucose tolerance test; OR = odds ratio; ref = reference group; RH = relative hazard

Evidence Table 23. Studies reporting on the association between anthropometric measures and the development of type 2 diabetes mellitus following a pregnancy with gestational diabetes

Author, year	Risk factor	Units	N	Measure of association (95% CI)	Covariates included
Pallardo, 1999[73]	Pre-pregnancy BMI	kg/m2	788	≤27: ref >27: OR = 8.66 (2.27 - 32.94; p < 0.01)	# of abnormal OGTT results (including fasting), C-peptide glucose score
Jang, 2003[63]	Pre-pregnancy BMI	kg/m2	311	NR	Pre-pregnancy weight, gestational age at GDM diagnosis, 2-hr glucose, 3-hr insulin on diagnostic OGTT, age, height, FHxT2DM, postpartum weight
Cho, 2005[61]	Pre-pregnancy BMI	kg/m2	170	≤23: ref >23: RR = 0.779 (0.27 - 2.246)	Age, gestational age at GDM diagnosis, FHxT2DM, FPG at diagnosis, homocysteine level
Jang, 2003[63]	Pre-pregnancy weight	kg	311	Coefficient = 0.3639 (se = 0.1027)	Gestational age at GDM diagnosis, 2-hr glucose, 3-hr insulin on diagnostic OGTT, age, height, pre-pregnancy BMI, FHxT2DM, postpartum weight
Lobner, 2006[66]	BMI at first pregnancy visit	kg/m2	302	≤30: ref >30: RH = 1.5 (1 - 2.2; p = 0.04)	GAD and IA-2 antibody status, method of glucose control, parity, age, serum CRP
Metzger, 1993[67]	Obesity (defined as ≥ 120% of ideal body weight)	%	172	OR = 2.83 (p < 0.001)	3-hr integrated insulin, parity
Cheung, 2006[60]	BMI at index pregnancy	kg/m2	102	RR = 1.1 (1 - 1.2)	Age, parity, FPG at diagnosis, 2-hr OGTT, # prior GDM pregnancies, method of glucose control, FHxT2DM, hospital
Cho, 2006[62]	Postpartum BMI	kg/m2	909	Lowest quartile: ref Highest quartile: OR = 3.34 (1.7 - 6.5)	Blood pressure, lipid profile*, age, duration of followup, parity, FHxT2DM, working status
Cho, 2006[62]	Postpartum weight	kg	909	Lowest quartile: ref Highest quartile: OR = 3.06 (1.6 - 6)	Blood pressure, lipid profile*, age, duration of followup, parity, FHxT2DM, working status
Jang, 2003[63]	Postpartum weight	kg	311	NR	Pre-pregnancy weight, gestational age at GDM diagnosis, 2-hr glucose, 3-hr insulin on diagnostic OGTT, age, height, pre-pregnancy BMI, FHxT2DM
Cho, 2006[62]	Postpartum body fat weight	kg	909	Lowest quartile: ref Highest quartile: OR = 3.76 (1.8 - 7.6)	Blood pressure, lipid profile*, age, duration of followup, parity, FHxT2DM, working status
Cho, 2006[62]	Postpartum subscapular skin fold thickness	mm	909	Lowest quartile: ref Highest quartile: OR = 2.82 (1.4 - 5.6)	Blood pressure, lipid profile*, age, duration of followup, parity, FHxT2DM, working status
Cho, 2006[62]	Postpartum suprailiac skin fold thickness	mm	909	Lowest quartile: ref Highest quartile: OR = 2.1 (1.2 - 3.7)	Blood pressure, lipid profile*, age, duration of followup, parity, FHxT2DM, working status

Evidence Table 23. Studies reporting on the association between anthropometric measures and the development of type 2 diabetes mellitus following a pregnancy with gestational diabetes (continued)

Author, year	Risk factor	Units	N	Measure of association (95% CI)	Covariates included
Cho, 2006[62]	Postpartum tricep skin fold thickness	mm	909	Lowest quartile: ref Highest quartile: OR = 2.02 (1.1 - 3.6)	Blood pressure, lipid profile*, age, duration of followup, parity, FHxT2DM, working status
Cho, 2006[62]	Postpartum waist circumference	cm	909	Lowest quartile: ref Highest quartile: OR = 3.86 (1.8 - 8.2)	Blood pressure, lipid profile*, age, duration of followup, parity, FHxT2DM, working status
Cho, 2006[62]	Postpartum waist-to-hip ratio	no units	909	Lowest quartile: ref Highest quartile: OR = 3.11 (1.7 - 5.6)	Blood pressure, lipid profile*, age, duration of followup, parity, FHxT2DM, working status
Peters, 1996[72]	Postpartum BMI	NR	666	NR	Additional pregnancy, postpartum weight change, OGTT glucose area, breastfeeding
Xiang, 2006[64]	Postpartum BMI	kg/m2	526	NR	Contraceptive use, breastfeeding, FHxT2DM, HDL cholesterol, triglycerides, weight change during followup
Xiang, 2006[64]	Postpartum BMI	kg/m2	526	NR	Interaction term for breastfeeding and OC use, FHxT2DM, triglycerides, HDL cholesterol, weight change during followup
Xiang, 2006[64]	Postpartum BMI	kg/m2	526	NR	Interaction term for OC use and triglyceride level, FHxT2DM, breastfeeding, HDL cholesterol, weight change during followup
Dacus, 1994[65]	Postpartum BMI	kg/m2	100	<27: ref ≥27: RR = 4.11 (0.57 - 29.78)	None
Peters, 1996[72]	Postpartum weight change	Per 10 lbs	666	RH = 1.95 (1.64 - 2.33)	Additional pregnancy, OGTT glucose area, postpartum BMI, breastfeeding
Kjos, 1998[69]	Postpartum weight loss	NR	443	NR	Contraceptive use, AUC at the initial postpartum OGTT, prior OC use, method of glucose control, additional pregnancy, duration of OC use
Xiang, 2006[64]	Weight change during followup	NR	526	NR	Interaction term for breastfeeding and OC use, postpartum BMI, FHxT2DM, triglycerides, HDL cholesterol
Xiang, 2006[64]	Weight change during followup	NR	526	NR	Interaction term for OC use and triglyceride level, postpartum BMI, FHxT2DM, breastfeeding, HDL cholesterol
Xiang, 2006[64]	Weight change during followup	NR	526	NR	Contraceptive use, postpartum BMI, breastfeeding, FHxT2DM, HDL cholesterol, triglycerides
Jang, 2003[63]	Height	NR	311	NR	Pre-pregnancy weight, gestational age at GDM diagnosis, 2-hr glucose, 3-hr insulin on diagnostic OGTT, age, pre-pregnancy BMI, FHxT2DM, postpartum weight

* Includes triglyceride, high density lipoprotein, and low density lipoprotein cholesterol

AUC = area under the glucose tolerance curve; BMI = body mass index; cm = centimeters; CRP = C-reactive protein; FHxT2DM = family history of type 2 diabetes mellitus; FPG = fasting plasma glucose; GAD = glutamic acid decarboxylase; GDM = gestational diabetes mellitus; HDL = high density lipoprotein; hr = hour; IA-2 = insulinoma antigen-2; kg = kilograms; lbs = pounds; m = meters; mm = millimeters; NR = not reported; OC = oral contraceptive; OGTT = oral glucose tolerance test; OR = odds ratio; ref = reference; RH = relative hazard; RR = relative risk; se = standard error

Evidence Table 24. Studies reporting on the association between oral contraceptive use and the development of type 2 diabetes mellitus following a pregnancy with gestational diabetes

Author, year	Risk factor	Units	N	Measure of association (95% CI)	Covariates included
Kjos, 1998[69]	Contraceptive use	Yes/no	443	Combination therapy: ref Progestin only: RH = 2.87 (1.57 - 5.27)	AUC at the initial postpartum OGTT, prior OC use, method of glucose control, additional pregnancy, postpartum weight loss, duration of OC use
Xiang, 2006[64]	Contraceptive use	Yes/no	526	COC use: ref DMPA use: RH = 1.07 (0.61 - 1.89; p = 0.81)	Postpartum BMI, breastfeeding, FHxT2DM, HDL cholesterol, triglycerides, weight change during followup
Kjos, 1998[69]	Duration of OC use	Months	443	≤4: RH = 0.72 (0.09 - 5.89) 4-8: RH = 2.96 (1.35 - 6.52) >8: RH = 4.92 (1.76 - 13.73)	Contraceptive use, AUC at the initial postpartum OGTT, prior OC use, method of glucose control, additional pregnancy, postpartum weight loss
Xiang, 2006[64]	Interaction term for breastfeeding and OC use	NR	526	COC without breastfeeding: ref DMPA w/o breastfeeding: RH = 1.06 (0.58 - 1.95; p = 0.85) DMPA with breastfeeding: RH = 2.21 (0.96 - 5.11; p = 0.06)	Postpartum BMI, FHxT2DM, triglycerides, HDL cholesterol, weight change during followup
Xiang, 2006[64]	Interaction term for OC use and triglyceride level	NR	526	COC & below median triglyceride: ref COC & above median triglyceride: RH = 1.39 (0.88 - 2.19; p = 0.16) DMPA & below median triglyceride: RH = 0.55 (0.22 - 1.31; p = 0.2) DMPA & above median triglyceride: RH = 2.28 (1.08 - 4.81; p = 0.03)	Postpartum BMI, FHxT2DM, breastfeeding, HDL cholesterol, weight change during followup
Kjos, 1998[69]	Prior OC use	NR	443	NR	Contraceptive use, AUC at the initial postpartum OGTT, method of glucose control, additional pregnancy, postpartum weight loss, duration of OC use

AUC = area under the glucose tolerance curve; BMI = body mass index; CI = confidence interval; COC = combination oral contraception; DMPA = depo-medroxyprogesterone acetate; FHxT2DM = family history of type 2 diabetes mellitus; HDL = high density lipoprotein; NR = not reported; OC = oral contraceptive; OGTT = oral glucose tolerance test; ref = reference group; RH = relative hazard

Evidence Table 25. Studies reporting on the association between metabolic risk factors and the development of type 2 diabetes mellitus following a pregnancy with gestational diabetes

Author, year	Risk factor	Units	N	Measure of association (95% CI)	Covariates included
Cheung, 2006[60]	Fasting blood glucose level	mmol/L	102	RR = 1.37 (1.08 - 1.72)	Dose of bedtime intermediate-acting insulin required
Cheung, 2006[60]	FPG at diagnosis	mmol/L	102	RR = 1.5 (1.3 - 1.9)	Age, Parity, BMI at index pregnancy, 2-hr OGTT, # prior GDM pregnancies, method of glucose control, FHxT2DM, hospital
Steinhart, 1997[71]	Fasting blood sugar	mmol/L	88	≤5.83: ref >5.83: OR = 11.05 (2.3 - 103.4)	None
Cho, 2005[61]	FPG at diagnosis	mmol/L	170	≤5.3: ref >5.3: RR = 4.004 (1.405 - 11.409)	Age, gestational age at GDM diagnosis, pre-pregnancy BMI, FHxT2DM, homocysteine level
Schaefer-Graf, 2002[70]	FPG at diagnosis	mg/dL	1636	Q1: ref Q2: OR = 7.82 (1.77 - 34.52) Q3: OR = 11.13 (2.44 - 50.72) Q4: OR = 21.01 (4.58 - 96.29)	FPG at diagnosis, class A2, area under the glucose curve of pregnancy OGTT, gestational age at GDM diagnosis, previous GDM, 50-gm GCT
Kjos, 1995[68]	Highest antepartum fasting glucose	mmol/L	671	Q1: ref Q2: RH= 1.39 (0.7 - 2.75) Q3: RH= 2.09 (1.12 - 3.9) Q4: RH= 2.47 (1.25 - 4.9)	Postpartum OGTT glucose AUC, gestational age at GDM diagnosis, antepartum OGTT glucose AUC
Pallardo, 1999[73]	# of abnormal OGTT results (including fasting)	NR	788	OR = 3.03 (1.43 - 6.37; p = <0.01)	Pre-pregnancy BMI, C-peptide glucose score
Steinhart, 1997[71]	GTT total	mmol/L	88	≤41.63: ref >41.63: OR = 15.5 (2 - 678)	None
Buchanan, 1999[74]	1-hr plasma glucose, diagnostic OGTT	mmol/L	91	Lowest tertile: ref Highest tertile: OR = 15.2 (1.4 - 166.3)	Beta-cell compensation index, basal glucose production rate
Buchanan, 1999[74]	1-hr plasma glucose, diagnostic OGTT	mmol/L	91	Lowest tertile: ref Highest tertile: OR = 22 (1.5 - 328.5)	OGTT 30-min incremental insulin:glucose, basal glucose production rate, clamp SI
Jang, 2003[63]	2-hr glucose	mmol/L	311	Coefficient = 0.0156 (se = 0.0075)	Pre-pregnancy weight, gestational age at GDM diagnosis, 3-hr insulin on diagnostic OGTT, age, height, pre-pregnancy BMI, FHxT2DM, postpartum weight
Metzger, 1993[67]	2-hr glucose	mmol/L	177	OR = 1.03 (p < 0.001)	OGTT 30-min stimulated insulin secretion, basal insulin
Cheung, 2006[60]	2-hr OGTT	mmol/L	102	RR = 1.3 (1.1 - 1.4)	Age, parity, FPG at diagnosis, BMI at index pregnancy, # prior GDM pregnancies, method of glucose control, FHxT2DM, hospital

Evidence Table 25. Studies reporting on the association between metabolic risk factors and the development of type 2 diabetes mellitus following a pregnancy with gestational diabetes (continued)

Author, year	Risk factor	Units	N	Measure of association (95% CI)	Covariates included
Jang, 2003[63]	3-hr insulin on diagnostic OGTT	Pmol/L	311	OR = 0.98 (0.96-0.99)	Pre-pregnancy weight, gestational age at GDM diagnosis, 2-hr glucose, age, height, pre-pregnancy BMI, FHxT2DM, postpartum weight
Metzger, 1993[67]	3-hr integrated insulin	pM.min	172	NR (p < 0.01)	3-hr integrated insulin, parity, obesity
Buchanan, 1998[75]	Antepartum 30 minutes incremental plasma insulin/glucose ratio	NR	122	NR (p = 0.002)	Total AUC for diagnostic antepartum 100-gm OGTT glucose
Buchanan, 1999[74]	OGTT 30-min incremental insulin:glucose	NR	91	lowest tertile: ref highest tertile: OR = 0.1 (0.005 - 2.2)	Incremental glucose area diagnostic OGTT, FSIGT acute insulin response, basal glucose production rate, clamp SI
Buchanan, 1999[74]	OGTT 30-min incremental insulin:glucose	NR	91	lowest tertile: ref highest tertile: OR = 0.08 (0.005 - 1.1)	1-hr plasma glucose diagnostic OGTT, basal glucose production rate, clamp SI
Kjos, 1995[68]	Antepartum OGTT glucose AUC (mmol per min/l)	mmol/l. min. -1	671	Q1: ref Q2: RH = 1.13 (0.58 - 2.22) Q3: RH = 1.42 (0.77 - 2.62) Q4: RH = 2.13 (1.18 - 3.85) p = 0.004	Postpartum OGTT glucose AUC, gestational age at GDM diagnosis, highest antepartum fasting glucose
Schaefer-Graf, 2002[70]	Area under the glucose curve of pregnancy OGTT	g.min/dL	1636	Q1: ref Q2: OR = 0.93 (0.41 - 2.13) Q3: OR = 1.47 (0.73 - 2.99) Q4: OR = 3.64 (1.93 - 6.84)	FPG at diagnosis, class A2, gestational age at GDM diagnosis, previous GDM, 50-gm GCT
Buchanan, 1998[75]	Total AUC for diagnostic antepartum 100-gm OGTT glucose	NR	122	NR (p = 0.003)	Antepartum 30 minutes incremental plasma insulin/glucose
Buchanan, 1999[74]	Incremental glucose area, diagnostic OGTT	min/mol/L	91	lowest tertile: ref highest tertile: OR = 15 (1.1 - 207.9)	FSIGT acute insulin response, OGTT 30-min incremental insulin:glucose, basal glucose production rate, clamp SI
Peters, 1996[72]	OGTT glucose area	NR	666	NR	Additional pregnancy, postpartum weight change, postpartum BMI, breastfeeding

Evidence Table 25. Studies reporting on the association between metabolic risk factors and the development of type 2 diabetes mellitus following a pregnancy with gestational diabetes (continued)

Author, year	Risk factor	Units	N	Measure of association (95% CI)	Covariates included
Kjos, 1998[69]	AUC at the initial postpartum OGTT	NR	443	NR	Contraceptive use, prior OC use, method of glucose control, additional pregnancy, postpartum weight loss, duration of OC use
Kjos, 1995[68]	Postpartum OGTT glucose AUC	mmol/l. min. -1	671	Q1: ref Q2: RH = 2.67 (1 - 7.25) Q3: RH = 5.53 (2.16 - 14.16) Q4: RH = 11.48 (4.52 - 29.14) p < 0.0001	Gestational age at GDM diagnosis, antepartum OGTT glucose AUC, highest antepartum fasting glucose
Buchanan, 1999[74]	Basal glucose production rate	mmol.min .m2	91	Lowest tertile: ref Highest tertile: OR = 7	Incremental glucose area, diagnostic OGTT, FSIGT acute insulin response, OGTT 30-min incremental insulin:glucose, clamp SI
Buchanan, 1999[74]	Basal glucose production rate	mmol.min .m2	91	Lowest tertile: ref Highest tertile: OR = 5.3 (0.63 - 44.4)	1-hr plasma glucose diagnostic OGTT, beta-cell compensation index
Buchanan, 1999[74]	Basal glucose production rate	mmol.min .m2	91	Lowest tertile: ref Highest tertile: OR = 6.8 (0.7 - 65.5)	1-hr plasma glucose diagnostic OGTT, OGTT 30-min incremental insulin:glucose, clamp SI
Buchanan, 1999[74]	Beta-cell compensation index	NR	91	Lowest tertile: ref Highest tertile: OR = 0.09 (0.009 - 0.09)	1-hr plasma glucose diagnostic OGTT, basal glucose production rate
Buchanan, 1999[74]	Clamp SI	mmol.min .m2/microU/ml*1000	91	Lowest tertile: ref Highest tertile: OR = 0.18 (0.03 - 1.2)	1-hr plasma glucose diagnostic OGTT, OGTT 30-min incremental insulin:glucose, basal glucose production rate
Buchanan, 1999[74]	Clamp SI	mmol.min .m2/micro U/ml*1000	91	Lowest tertile: ref Highest tertile: OR = 0.15 (0.02 - 1.2)	Incremental glucose area, diagnostic OGTT, FSIGT acute insulin response, OGTT 30-min incremental insulin:glucose, basal glucose production rate
Buchanan, 1999[74]	FSIGT acute insulin response	mmol/l.min	91	Lowest tertile: ref Highest tertile: OR = 0.08 (0.005 - 1)	Incremental glucose area, diagnostic OGTT, OGTT 30-min incremental insulin:glucose, basal glucose production rate, clamp SI
Pallardo, 1999[73]	C-peptide glucose score	mmol/L	788	OR = 0.46 (0.25 - 0.85; p < 0.05)	Pre-pregnancy BMI, # of abnormal OGTT results (including fasting)
Xiang, 2006[64]	HDL cholesterol	mg/dL	526	NR	Contraceptive use, postpartum BMI, breastfeeding, FHxT2DM, triglycerides, weight change during followup

Evidence Table 25. Studies reporting on the association between metabolic risk factors and the development of type 2 diabetes mellitus following a pregnancy with gestational diabetes (continued)

Author, year	Risk factor	Units	N	Measure of association (95% CI)	Covariates included
Cho, 2006[62]	Blood pressure	NR	909	NR	Cho reported 8 models, which adjusted for blood pressure, lipid profile*, age, duration of followup, parity, FHxT2DM, working status, and one of the following measures of adiposity at postpartum: BMI, waist circumference, weight, subscapular skin fold thickness, suprailiac skin fold thickness, tricep skin fold thickness, body fat weight, and waist-to-hip ratio. The relative measure for blood pressure was not reported in any of the models.
Xiang, 2006[64]	HDL cholesterol	mg/dL	526	NR	Interaction term for breastfeeding and OC use, postpartum BMI, FHxT2DM, triglycerides, weight change during followup
Xiang, 2006[64]	HDL cholesterol	mg/dL	526	NR	Interaction term for OC use and triglyceride level, postpartum BMI, FHxT2DM, breastfeeding, weight change during followup
Xiang, 2006[64]	Triglycerides	mg/dL	526	NR	Contraceptive use, postpartum BMI, breastfeeding, FHxT2DM, HDL cholesterol, weight change during followup
Xiang, 2006[64]	Triglycerides	mg/dL	526	NR	Interaction term for breastfeeding and OC use, postpartum BMI, FHxT2DM, HDL cholesterol, weight change during followup
Cho, 2006[62]	Lipid profile which includes triglycerides, HDL and LDL cholesterol	NR	909	NR	Cho reported 8 models, which adjusted for blood pressure, lipid profile*, age, duration of followup, parity, FHxT2DM, working status, and one of the following measures of adiposity at postpartum: BMI, waist circumference, weight, subscapular skin fold thickness, suprailiac skin fold thickness, tricep skin fold thickness, body fat weight, and waist-to-hip ratio. The relative measure for the lipid profile was not reported in any of the models.
Cho, 2005[61]	Homocysteine level at baseline 6 weeks postpartum	mmol	170	≤6.38: ref >6.38: RR = 3.555 (1.059 - 11.934)	Age, gestational age at GDM diagnosis, pre-pregnancy BMI, FHxT2DM, FPG at diagnosis
Lobner, 2006[66]	GAD and IA-2 antibody status	NR	302	both GAD and IA-2 antibody negative: ref GAD or IA-2 antibody positive: RH = 4.1 (2.6 - 6.7; p < 0.0001)	Method of glucose control, BMI at first pregnancy visit, parity, age, serum CRP
Metzger, 1993[67]	Basal insulin	NR	177	OR = 0.19 (p < 0.0001)	2-hr glucose, OGTT 30-min stimulated insulin secretion
Metzger, 1993[67]	OGTT 30-min stimulated insulin secretion	NR	177	OR = 0.07 (p = 0.07)	2-hr glucose, basal insulin

Evidence Table 25. Studies reporting on the association between metabolic risk factors and the development of type 2 diabetes mellitus following a pregnancy with gestational diabetes (continued)

Author, year	Risk factor	Units	N	Measure of association (95% CI)	Covariates included
Lobner, 2006[66]	Serum CRP	mg/L	302	≤0.8: ref >0.8: RH = 1.2 (0.7 - 2.2; p = 0.47)	GAD and IA-2 antibody status, method of glucose control, BMI at first pregnancy visit, parity, age

AUC = area under the glucose tolerance curve; BMI = body mass index; CI = confidence interval; class A2 = insulin-requiring gestational diabetics; CRP = C = reactive protein; dL = deciliter; FHxT2DM = family history of type 2 diabetes mellitus; FPG = fasting plasma glucose; FSIGT = frequently sampled intravenous glucose tolerance; GAD = glutamic acid decarboxylase; GDM = gestational diabetes mellitus; gm = grams; GTT = glucose tolerance test; HDL = high density lipoprotein; hr = hour; L = liter; m = meters; min = minutes; mg = milligram; mmol = millimole; NR = not reported; OC = oral contraceptive; OGTT = oral glucose tolerance test; OR = odds ratio; ref = reference; Q = quartile; RH = relative hazard; RR = relative risk; se = standard error; SI = sensitivity index

Evidence Table 26. Grading of the body of evidence on the association of risk factors with the development of type 2 diabetes following a pregnancy with gestational diabetes (KQ3)

	Family history type 2 diabetes	Sociodemo-graphics	Maternal lifestyle	Parity	Pregnancy-related factors
Quantity of Evidence: Number of studies	5	6	0	4	9
Total number of patients studied	2018	1894	0	1485	3823
Quality and Consistency of Evidence: Were the study designs mostly high quality (e.g., cohort study or case-control study with multivariate adjustment for most or all major potential confounding factors), medium quality (e.g., cohort study or case-control study with adjustment for only a few major potential confounding factors), or low quality (e.g., no multivariate adjustment for confounding factors)?	low	medium		high	high
Did the studies have other serious (-1) or very serious (-2) limitations in quality? (Enter 0 if none)	0	0		0	0
Did the studies have important inconsistency? (-1)	0	-1		0	0
Was there some (-1) or major (-2) uncertainty about the directness (i.e. extent to which the people, risk factors, and outcomes are similar to those of interest)?	0	0		0	0
Were data imprecise or sparse? (-1) (i.e. lack of data or very wide confidence intervals that may change conclusions)	-1	-1		-1	0
Did the studies have high probability of reporting bias? (-1)	0	0		0	0
Did the studies show strong evidence of association between the risk factors and outcome? ("strong" if significant relative risk or odds ratio > 2 based on consistent evidence from 2 or more studies with no plausible confounders (+1); "very strong" if significant relative risk or odds ratio > 5 based on direct evidence with no major threats to validity (+2))- use your clinical judgment for absolute differences.	-1	-1		0	0
Did the studies have evidence of a dose-response gradient? (+1)	0	0		+1	0
Did the studies have unmeasured plausible confounders that most likely reduced the magnitude of the observed association? (+1)	0	+1		0	0
Overall grade of evidence (high, moderate, low, very low)	very low	low	very low	low	moderate

High = further research is very unlikely to change our confidence in the estimates; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low = any estimate of effect is very uncertain.

Evidence Table 26. Grading of the body of evidence on the association of risk factors with the development of type 2 diabetes following a pregnancy with gestational diabetes (KQ3) (continued)

	Postpartum factors	Measures of anthropometry	Oral contraceptive use	Metabolic risk factors
Quantity of Evidence: Number of studies	5	11	2	15
Total number of patients studied	2632	4489	969	7002
Quality and Consistency of Evidence: Were the study designs mostly high quality (e.g., cohort study or case-control study with multivariate adjustment for most or all major potential confounding factors), medium quality (e.g., cohort study or case-control study with adjustment for only a few major potential confounding factors), or low quality (e.g., no multivariate adjustment for confounding factors)?	medium	medium	Medium	medium
Did the studies have other serious (-1) or very serious (-2) limitations in quality? (Enter 0 if none)	0	0	0	0
Did the studies have important inconsistency? (-1)	-1	0	-1	0
Was there some (-1) or major (-2) uncertainty about the directness (i.e. extent to which the people, risk factors, and outcomes are similar to those of interest)?	0	0	0	0
Were data imprecise or sparse? (-1) (i.e. lack of data or very wide confidence intervals that may change conclusions)	-1	0	0	0
Did the studies have high probability of reporting bias? (-1)	0	0	0	0
Did the studies show strong evidence of association between the risk factors and outcome? ("strong" if significant relative risk or odds ratio > 2 based on consistent evidence from 2 or more studies with no plausible confounders (+1); "very strong" if significant relative risk or odds ratio > 5 based on direct evidence with no major threats to validity (+2))- use your clinical judgment for absolute differences.	0	+1	0	+1
Did the studies have evidence of a dose-response gradient? (+1)	0	0	0	+1
Did the studies have unmeasured plausible confounders that most likely reduced the magnitude of the observed association? (+1)	+1	0	0	+1
Overall grade of evidence (high, moderate, low, very low)	very low	moderate	low	moderate

High = further research is very unlikely to change our confidence in the estimates; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low = any estimate of effect is very uncertain.

Evidence Table 27. Characteristics of studies evaluating the performance characteristics of tests for diagnosing type 2 diabetes following a pregnancy with gestational diabetes

Author, year Country	Study design	Exclusion criteria	Time since delivery	Mean age (in years) (Age range)	Race, n (%)	Weight (in kg) / BMI (in kg/m^2), mean	Reference test*	Comparison test*	Loss to followup
Agarwal, 2004[95] United Arab Emigrates	Retrospective	NR	(range: 4-8 weeks)	32	Arab: (78.8) Indian Nationals: (20.5)	NR	A, B	C	67%
Conway, 1999[97] US	Prospective	NR	Median: 6-weeks (range: 4-13 weeks)	NR	NR	NR	A	B	82%
Costa, 2000[100] Spain	Prospective	NR	(range: 2-12 months)	ND: 33.9 IGT or T2DM: 36	C: 120 (100)	Post-pregnancy BMI: ND: 25.1 IGT or T2DM: 28.5	A	C	NR
Cypryk, 2004[98] Poland	Retrospective	Known T1DM and T2DM (23%) since delivery	Mean: 3.1 years (range 0.5-8 years)	34.3	C: (100)	NR	A	C	66%
Holt, 2003[96] United Kingdom	Retrospective	NR	6 weeks	31.1 (18.7 – 38.9)	C: (86) Asian: (14)	NR	A	C	20%
Kousta, 1999[101] United Kingdom	Prospective	Known T2DM (14%) since delivery	Median: 28 months (range: 1-86 months)	36.6	European: 68 (35) Asian: 56 (29) Afro-Caribbean: 32 (17) Other: 36 (19)	Pre-pregnancy BMI: 28.1	A	B, C	NR
Reichelt, 2002[99] Brazil	Prospective	NR	Mean: 5.7 years (range 4-8 years)	NR	NR	NR	B	C	26%

Evidence Table 27. Characteristics of studies evaluating the performance characteristics of tests for diagnosing type 2 diabetes following a pregnancy with gestational diabetes (continued)

Author, year Country	Study design	Exclusion criteria	Time since delivery	Mean age (in years) (Age range)	Race, n (%)	Weight (in kg) / BMI (in kg/m^2), mean	Reference test*	Comparison test*	Loss to followup
Reinblatt, 2006[94] Canada	Retrospective	NR	(range: 6 weeks-6 months)	32 (15-45)	NR	Pre-pregnancy BMI: 25.6	B	C	79%

* A= FBG > 7.8 mmol/L (140 mg/dL) or 2-hr plasma glucose after 75-gm OGTT > 11.1 mmol/L (200 mg/dL); B = FBG > 7.0 mmol/L (126 mg/dL) or 2-hr plasma glucose after 75-gm OGTT > 11.1 mmol/L (200 mg/dL); C = FBG > 7.0 mmol/L (126 mg/dL)

Asian = Asian or Asian American; BMI = body mass index; C = Caucasian; dL = deciliter; FBG = fasting blood glucose; gm = gram; hr = hour; IGT = impaired glucose tolerance; kg = kilogram; L = liter; m = meter; mg = milligram; mmol = millimole; ND = nondiabetic; NR = not reported; OGTT = oral glucose tolerance test; US = United States; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus

Evidence Table 28. Performance characteristics of tests for diagnosing type 2 diabetes following a pregnancy with gestational diabetes

Author, year	True positive	False positive	False negative	True negative	Total	Sensitivity (%)	95% CI	Specificity (%)	95% CI
Comparison 1: **Reference test: FBG > 7.8 mmol/L (140 mg/dL) or 2-hr plasma glucose after 75-gm OGTT > 11.1 mmol/L (200 mg/dL)** **Comparison test: FBG > 7.0 mmol/L (126 mg/dL) or 2-hr plasma glucose after 75-gm OGTT > 11.1 mmol/L (200 mg/dL)**									
Conway, 1999 [97]	11	3	0	165	179	100*	n/a	98	95, 100
Kousta, 1999[101]	22	3	0	140	165	100*	n/a	98	94, 100
Comparison 2: **Reference test: FBG > 7.0 mmol/L (126 mg/dL) or 2-hr plasma glucose after 75-gm OGTT > 11.1 mmol/L (200 mg/dL)** **Comparison test: FBG > 7.0 mmol/L (126 mg/dL)**									
Reinblatt, 2006[94]	12	0	14	249	275	46	27, 66	100*	n/a
Agarwal, 2004[95]	36	0	14	499	549	72	58, 84	100*	n/a
Reichelt, 2002[99]	8	0	1	108	117	89	52, 100	100*	n/a
Comparison 3: **Reference test: FBG > 7.8 mmol/l (140 mg/dL) or 2-hr plasma glucose after 75-gm OGTT > 11.1 mmol/l (200 mg/dL)** **Comparison test: FBG > 7.0 mmol/l (126 mg/dL)**									
Agarwal, 2004[95]	31	5	14	499	549	69	53, 82	99	98, 100
Cypryk, 2004[98]	1	2	6	139	148	14	0.04, 58	99	95, 100
Holt, 2003[96]	3	7	0	112	122	100	29, 100	94	88, 98
Costa, 2000[100]	2	1	0	117	120	100	16, 100	99	95, 100
Kousta, 1999[101]	16	3	6	140	165	73	50, 89	98	94, 100

* Fixed at 100% by definition of test criteria.

CI = confidence interval; dL = deciliter; FBG = fasting blood glucose; gm = gram; hr = hour; L = liter; mg = milligram; mmol = millimole; n/a = not applicable; OGTT = oral glucose tolerance test

Evidence Table 29. Quality of studies evaluating the performance characteristics of tests for diagnosing type 2 diabetes following a pregnancy with gestational diabetes

Author, year	Data collection	Patient selection	Loss to followup	Disease spectrum	Report of test reproducibility	Calculation of test reproducibility
Agarwal, 2004[95]	Retrospective	Consecutive	67%	Clinical population	Laboratory methods reported	None
Conway, 1999[97]	Retrospective	Consecutive	82%	Clinical population	Laboratory methods reported	None
Costa, 2000[100]	Prospective	NR	NR	Clinical population	Laboratory methods reported	None
Cypryk, 2004[98]	Prospective	Consecutive	33%	Clinical population Excluded T1/2 DM diagnosed after delivery (23%)	NR	None
Holt, 2003[96]	Retrospective	Consecutive	20%	Clinical population	Yes	Yes
Kousta, 1999[101]	Prospective	Consecutive	NR	Clinical population Excluded T2DM diagnosed after delivery (14%)	Laboratory methods reported	Other reference cited
Reichelt, 2002[99]	Prospective	Consecutive	26%	Clinical population	NR	None
Reinblatt, 2006[94]	Retrospective	Consecutive	79%	Clinical population	NR	Other reference cited

NR = not reported; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus

Evidence Table 30. Grading of the body of evidence of the performance characteristics of tests for diagnosing type 2 diabetes following a pregnancy with gestational diabetes (KQ4)

	Comparison 1*	Comparison 2†	Comparison 3‡
Quantity of evidence: Number of studies	2	3	5
Total number of patients studied	344	941	1104
Quality and consistency of evidence: Were the study designs mostly high quality (e.g., prospective, independent comparison of a test to a reference test), medium quality (e.g., retrospective, independent comparison of a test to a reference test), or low quality (e.g., no independent comparison)?	Medium	Medium	Medium
Did the studies have other serious (-1) or very serious (-2) limitations in quality? (Enter 0 if none)	-1	-1	-1
Did the studies have important inconsistency? (-1)	0	-1	-1
Was there some (-1) or major (-2) uncertainty about the directness (i.e. extent to which the people, tests and outcomes are similar to those of interest)?	0	0	0
Were data imprecise or sparse? (-1) (i.e. lack of data or very wide confidence intervals that may change conclusions)	-1	-1	-1
Did the studies have high probability of reporting bias? (-1)	0	0	0
Overall grade of evidence (high, moderate, low, very low)	Very low	Very low	Very low

High = further research is very unlikely to change our confidence in the estimates; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low = any estimate of effect is very uncertain.

*Comparison 1: Reference test: Fasting blood glucose > 7.8 mmol/L (140 mg/dL) or 2-hr plasma glucose after 75 gm OGTT > 11.1 mmol/L (200 mg/dL)
Comparison test: Fasting blood glucose > 7.0 mmol/L (126 mg/dL) or 2-hr plasma glucose after 75 gm OGTT > 11.1 mmol/L (200 mg/dL)

† Comparison 2: Reference test: Fasting blood glucose > 7.0 mmol/L (126 mg/dL) or 2-hr plasma glucose after 75 gm OGTT > 11.1 mmol/L (200 mg/dL)
Comparison test: Fasting blood glucose > 7.0 mmol/L (126 mg/dL)

‡ Comparison 3: Reference test: Fasting blood glucose > 7.8 mmol/l (140 mg/dL) or 2-hr plasma glucose after 75 gm OGTT > 11.1 mmol/l (200 mg/dL)
Comparison test: Fasting blood glucose > 7.0 mmol/l (126 mg/dL)