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Structured Abstract

Background: In a 2003 evidence report, the United States Preventive Services Task Force (USPSTF) concluded that the scientific evidence was insufficient to advise for or against routine screening for gestational diabetes mellitus (GDM) in all pregnant women. The 2003 review did not include evidence pertaining to GDM screening prior to 24 weeks gestation. As the prevalence of women at high risk for type 2 diabetes and GDM has continued to increase dramatically over the intervening years, the issue of early screening has taken on greater importance.

Purpose: This review identifies and evaluates new evidence since the prior review on the risks and benefits of GDM screening at 24 weeks or later; it also newly reviews all of the available evidence pertaining to GDM screening prior to 24 weeks.

Data Sources: We conducted five database searches of MEDLINE®, Cochrane Central Registry of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment, and National Institute for Health and Clinical Excellence from 2000 to September 2006, supplemented by a search for screening prior to 24 weeks gestation from 1966-99. Searches were also supplemented with recommendations from outside experts and reviews of bibliographies of other relevant articles and systematic reviews. We dual-reviewed all citations in the 2003 Evidence Synthesis for inclusion in this review.

Study Selection: In conjunction with USPSTF members and with Agency for Healthcare Research and Quality staff, we developed and refined an analytic framework and five key questions (KQ). For assessing potential benefit of GDM screening and treatment, we included only randomized trials that used the standard, currently accepted one-step and two-step diagnostic criteria to evaluate screening and treatment of GDM. Study design and criteria were less stringent for considering potential harms. Using inclusion/exclusion criteria for each question, two investigators dual-reviewed 1403 abstracts and 277 potentially included articles. Of the potentially included articles, 90 were excluded for study design and 12 for poor quality, and the remainder for other reasons.

Data Extraction: We abstracted, critically appraised, and synthesized 13 total articles meeting criteria for the five KQs. Abstracted elements were arrayed in evidence tables, using criteria specific to each KQ.

Data Synthesis and Results: The best new evidence is a good-quality randomized controlled trial (RCT) that evaluated the maternal and neonatal outcomes for 1,000 pregnancies in which mild GDM was diagnosed between 24-34 weeks gestation and treated, compared to outcomes for pregnancies in which mild GDM was diagnosed but not treated. With treatment, there was a

statistically significant reduction in the composite neonatal outcome of any serious perinatal complication (Adjusted RR 0.33 [95 percent CI 0.14-0.75]). Serious perinatal complications was defined as any of the following: death, shoulder dystocia, bone fracture, and nerve palsy. The absolute rates of these individual perinatal outcomes were also reported in the paper, but could not be compared between groups due to no events for death, bone fracture, or nerve palsy in the treatment group. Overall, there were seven infants with serious perinatal complications in the treatment group (all shoulder dystocia), compared to 23 infants with 25 serious perinatal complications in the non-treated group (five deaths, one fractured humerus, three nerve palsies, and 16 shoulder dystocia). Shoulder dystocia was not a specified health outcome for this evidence review. The remaining components in the composite outcome (neonatal death, fracture, nerve palsy) were health outcomes specified by the Task Force for this review. The causes of the five deaths in the untreated group were: two stillbirths (unexplained intrauterine deaths at term of appropriately grown infants), one stillbirth at 35 weeks gestation associated with pre-eclampsia and intrauterine growth restriction, one infant death from asphyxia during labor without antepartum hemorrhage, and one death from a lethal congenital anomaly.

Treatment of GDM also reduced the risk of maternal pregnancy-induced hypertension (Adjusted RR 0.70 [0.51-0.95]). There was no evidence of harm to mother or infant with treatment in this study. In a sub-set of participants who responded to a post-partum questionnaire, mothers treated for GDM were significantly less depressed and reported a trend towards better quality-of-life at 3 months post-partum; these post-partum data may have some limitations.

Of five treatment comparison trials, two achieved improved glycemic control with intensified management of different types (postprandial monitoring and four times daily insulin) and both found significant reductions in several perinatal complications (a combined outcome for perinatal morbidity in one study, hyperbilirubinemia, and macrosomia). These improved outcomes occurred without evidence of harms from significant maternal hypoglycemia with treatment. The remaining three treatment-comparison trials did not differ in glycemic control achieved and outcomes were similar. Finally, available evidence suggests that diagnosis and treatment of GDM does not worsen quality-of-life except possibly transiently for the first few weeks after diagnosis. As early as 6 weeks after diagnosis, women treated for GDM may have better self-rated quality-of-life.

Limitations: We found no evidence base for trials of screening programs to test screened versus unscreened populations. However, both current clinical practice patterns for GDM and ethical constraints on research in human subjects would now likely preclude such a study in the US. Thus, the available evidence base comprises studies in only screen-detected populations.

Evaluating the potential benefit and harms of screening and treatment of GDM is limited by lack of a consistent standard for screening or diagnosis and the need to consider multiple potential outcomes that are not unique to GDM.

Little information is available on harms of treatment—these are relatively rare outcomes and may not be evident in trials.

While antepartum surveillance was specifically restricted from the scope of this review by the Task Force, it is possible that increased antepartum surveillance of women diagnosed with GDM could result in harms that were not evaluated with this review.

Conclusions: We found limited evidence to evaluate early screening for GDM prior to 24 weeks gestation, the purpose of which would be to detect previously unrecognized diabetes (GDM is defined as onset or first recognition of diabetes during pregnancy). Therefore, more research is needed before this question can be evaluated.

A recent good-quality randomized controlled trial reported that treatment of screen-detected women with mild GDM diagnosed after 24 weeks gestation reduces both maternal and composite neonatal health outcomes, without apparent harm—as reported in this RCT and in several other observational studies.

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I. Introduction

Condition Definition/Burden of Disease

Gestational diabetes mellitus (GDM) is currently defined as any degree of glucose intolerance with onset or first recognition during pregnancy.[1-3] This definition does not exclude glucose intolerance that may have antedated pregnancy. Currently, the prevalence of GDM in the US ranges from 1 to 14 percent, depending on the characteristics of the population screened.[1,4]

A major challenge in evaluating the evidence on GDM screening and treatment is the range of adverse maternal and neonatal outcomes associated with untreated GDM. In 2003, the United States Preventive Services Task Force (USPSTF) reviewed the evidence on health outcomes associated with untreated GDM[5] and found that the pregnancies of women with GDM were associated with a higher percentage of fetal macrosomia, brachial plexus injury, clavicular fracture, and neonatal hypoglycemia. Data were mixed on the association between GDM and increased perinatal mortality. Older data demonstrated an increased risk of perinatal mortality in women with GDM, but more recent studies did not.[5,6] This discrepancy may reflect the rarity of perinatal mortality events and/or that improvements in obstetrical and neonatal practices have concurrently changed during the past 40 years, resulting in reduced adverse maternal and neonatal outcomes. The USPSTF also found the evidence was too limited at that time to determine whether GDM is associated with increased rates of neonatal hypoglycemia, preterm birth, hyperbilirubinemia, hypocalcemia, polycythemia, or long-term implications for the offspring such as an increased risk of impaired glucose tolerance, childhood obesity, and neuropsychological disturbance. Although women with GDM have been demonstrated to have a higher rate of cesarean section and a higher risk of developing type 2 diabetes mellitus, data were limited on other maternal health outcomes, such as a higher rate of pre-eclampsia or third- and fourth-degree perineal lacerations from vaginal delivery.[5] The 2003 USPSTF evidence review suggested that hyperglycemia's impact on adverse maternal and neonatal outcomes is probably continuous. The evidence, however, was insufficient "to determine the magnitude of health benefit for any treatment among the large number of women with GDM at milder degrees of hyperglycemia."[5]

Risk Assessment

While previous reviews were not conclusive as to the benefits of either a universal or risk-based screening program for GDM,[5,6] risk-factor assessment has played a prominent role in GDM screening in the US. Currently, the American Diabetes Association (ADA) states that low-risk women need not be screened and the American College of Obstetrics and Gynecology (ACOG) states that low-risk women may be less likely to benefit from screening.[1,2] ADA and ACOG consider a woman to be at low risk for GDM if she meets all of the following criteria: (1) younger than age 25; (2) not a member of an ethnic group with increased risk for developing

type 2 diabetes; (3) body mass index of 25 or less; (4) no previous history of abnormal glucose tolerance or adverse obstetrics outcomes usually associated with GDM; and (5) no known history of diabetes in a first-degree relative.

Traditionally, women considered to be at higher risk for GDM are those who are obese, have previously delivered a macrosomic infant, have a family or personal history of diabetes, or have had a previous adverse pregnancy outcome.[2,7] As obesity and diabetes mellitus have become more prevalent in US women of child-bearing age,[8] so has gestational diabetes.[9,10] One in five (22 percent) of US women age 20 to 39 are now estimated to be obese (BMI $\geq$30 kg/m2).[11] One US study performed in Colorado found GDM prevalence doubled during the past decade, from 2.1 to 4.1 percent between 1994 - 2002.[9] In 2002, the age-adjusted prevalence of GDM was 3.1 percent in non-Hispanic whites, 5.4 percent in Hispanics, 5.5 percent in African-Americans, and 6.8 percent in Asians. In a second study performed in Northern California, the age- and race/ethnicity-adjusted cumulative incidence rate of GDM increased from 5.1 to 6.9 percent between 1991 and 2000.[10] In 2000, the yearly age-adjusted cumulative incidence of GDM was 5.7 percent in Whites, 6.4 percent in African-Americans, 8.3 percent in Hispanics, and 9.7 percent in Asians. Among Americans Indians in North Dakota and Montana, a review of birth records revealed that the rate of any type of diabetes (pre-gestational or gestational) increased in Montana from 31 to 41 per 1,000 births (p=0.04) from 1989-1991 to 1998-2000 and increased from 38 to 48 per 1,000 births (p=0.06) in North Dakota.[12] Increasing rates of obesity in the general population likely contributes to the increasing prevalence of GDM, it is not clear how this increasing obesity will affect the relative proportion of women with GDM with pre-existing (but unrecognized) type 2 diabetes, versus a transient worsening of glucose intolerance in pregnancy (both classified as GDM), as obesity is a risk factor for these two distinct entities that comprise GDM.

Risk factor based screening for GDM is the current practice in most of Europe and outside of the US, and screening rates with blood glucose testing based on provider surveys ranges from 18 to 37 percent of pregnancies.[13-16] A postal survey in Australia in 360 of 544 hospitals surveyed found that screening for GDM was undertaken by 284 (87 percent) of hospitals and of these, 151 (53 percent) screened all women and 63 (22 percent) selectively screened women.[17] In the US, universal screening is still the most common screening practice. In 2004, Gabbe and colleagues and reported in 569/1,398 ACOG fellows and Junior fellows surveyed (41 percent response rate), and found that 96 percent of obstetricians routinely screen for GDM, nearly all by using a 50-g GCT.[18]

Current Practice

Gestational diabetes is currently diagnosed using either a one- or two-step method. In the one-step method, a 75 g or 100 g oral glucose load is administered in a fasting state without prior plasma or serum screening.[1] Plasma glucose levels are evaluated fasting and 1 and 2 hours after the 75 g load, or fasting and 1, 2, and 3 hours after the 100 g glucose load. The two-step method involves an initial screening test, a 50 g oral glucose challenge test (GCT), followed by either a 75 g or 100 g oral glucose tolerance test (OGTT), if the screening test is abnormal.

Outside the US, the one-step 75 g OGTT is most common.[19] The two-step method (GCT, then OGTT), however, is the currently preferred screening method in the US.[1,2] The GCT screening test comprises a 50 g glucose load, which is administered without regard to fasting state, followed 1 hour later by assessment of the plasma or serum glucose level.[1,2] The two commonly used threshold values for a positive test are >130 mg/dl (7.2 mmol/l) or >140 mg/dl (7.8 mmol/l). The sensitivity of the GCT varies by threshold value and the population's characteristics.[1,20,21]

Various diagnostic criteria exist for the 75 g and 100 g OGTT (Table 1). Currently, the ADA recommends the use of the Carpenter and Coustan diagnostic criteria irrespective of the glucose load.[1] ACOG recommends the 100 g test with use of either the Carpenter and Coustan (C&C) or the National Diabetes Data Group (NDDG) criteria.[2] The World Health Organization (WHO) recommends the one-step 75 g OGTT and has established threshold values that differ from those recommended by Carpenter and Coustan.[19]

Screening for GDM usually occurs between 24-28 weeks gestation[1,2,5] because insulin resistance increases during the second trimester, and glucose levels will rise in women who do not have the ability to produce enough insulin to adapt to this resistance.[22-24] Laboratory studies show that insulin secretion increases in response to an intravenous glucose challenge with advancing gestation (i.e., as women become more insulin resistant, more insulin is needed to metabolize the same stimulus).[22] Early pregnancy is associated with increased insulin sensitivity, however, and in a normal pregnancy fasting glucose values are lower during the first trimester and early second trimester, compared to the non-pregnant state.[22-25] This increased insulin sensitivity is also manifest in women with pre-existing (*pre*-gestational) diabetes who have decreasing insulin requirements early in gestation.[22] While the ideal timing for screening the average-risk woman might be after 24 weeks gestation when insulin resistance is increasing, early screening may benefit high-risk women in order to detect previously unrecognized type 2 diabetes. While it is unclear which screening methodology would be most appropriate in this setting, the current ADA recommendations for the diagnosis of diabetes mellitus include the use of fasting plasma glucose levels.[1] Diabetes mellitus is diagnosed if fasting plasma glucose concentrations are 126 mg/dl or greater on two or more occasions. In a cohort of 4180 pregnancies with gestational (n=3764) or type 2 (n=416) diabetes, fasting glucose levels above 120 mg/dl at entry into prenatal care were associated with an increased prevalence of major congenital abnormalities (7.3 percent) compared with pregnant women with lower fasting glucose levels (2.1 percent); these major congenital abnormalities were in the same organ systems that have been previously described in pregnancies complicated by type 1 diabetes.[26]

Clinical efforts for optimizing maternal glucose control in women with pre-gestational diabetes have been associated with a decreased risk of perinatal death.[22] Uncontrolled pre-gestational diabetes has been associated with an increased risk of congenital malformations, spontaneous abortion, fetal macrosomia, and neonatal hypoglycemia, hypocalcemia, and hyperbilirubinemia.[22] Perinatal mortality rates and congenital malformations among pregnant women with type 2 diabetes may be as high as those observed in women with type 1 diabetes.[27,28] Diagnosis of previously unrecognized type 2 diabetes early in pregnancy, also defined as GDM, could potentially provide an opportunity to impact these outcomes.

The ADA currently recommends screening high-risk pregnant women (marked obesity, personal history of GDM, glycosuria, or a strong family history of diabetes) at the first antenatal

visit.[1] Without making a formal recommendation, ACOG suggests that women with a history of GDM in a previous pregnancy may benefit from early diagnosis in a subsequent pregnancy.[2]

These differing criteria used in clinical practice result in differing prevalences of women diagnosed with GDM and create a conundrum in reviewing the evidence, as there is no single accepted method for screening or diagnosis of GDM. The multiplicity of accepted screening criteria in use is largely a reflection of lack of available evidence demonstrating a benefit of specified health outcomes with any of the national or international standard screening criteria.

Previous USPSTF Recommendation

In 2003, the USPSTF concluded that the scientific evidence was insufficient to advise for or against routine screening of GDM in all pregnant women. They found fair-to-good evidence that screening combined with therapy for GDM can reduce the rate of fetal macrosomia, but were unable to find sufficient evidence that GDM screening reduced adverse health outcomes for mothers or their infants.[5]

With the increasing prevalence of US women at high risk for type 2 diabetes and GDM, the issue of early screening is becoming increasingly important. The previous USPSTF review did not include evidence related to GDM screening prior to 24 weeks gestation. This review considered all evidence from the previous review and identified and evaluated new evidence since the prior review on the risks and benefits of GDM screening at 24 weeks or later. In addition, we newly reviewed all of the available evidence pertaining to GDM screening prior to 24 weeks.

II. Methods Summary

This section briefly details the methods used for conducting this review. These methods were based primarily on published USPSTF methods for systematic reviews.[29] Appendix A includes a more detailed description of our methods.

We developed an analytic framework and five key questions (Figure 1) after consultation and final approval from the USPSTF liaisons. The scope of this report differs from the 2003 USPSTF evidence report in several important ways:

1) We evaluated screening for gestational diabetes at any time during pregnancy so that we could capture evidence of screening before 24 weeks gestation.
2) The Task Force separated final health outcomes from intermediate outcomes for GDM, such as macrosomia and delivery (induction or cesarean). Intermediate outcomes, though of interest, were not systematically reviewed. Although macrosomia is mediated by elevated maternal glucose, which stimulates the baby to produce excess insulin (increasing fetal growth), it is also an intermediate outcome. Therefore, we only reviewed studies addressing specified health outcomes such as perinatal mortality, brachial plexus injury, and clavicular fracture (see analytic framework, Figure 1). We present evidence about macrosomia and other intermediate outcomes for included studies, if reported.
3) We did not systematically review studies of GDM's natural history (only describing outcomes of untreated women).
4) We did not perform a systematic review of antenatal surveillance for women with GDM.
5) We only included studies that used current accepted diagnostic standards for GDM.[1,2,19]

We conducted five database searches of MedLine, Cochrane Central Registry of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, Health Technology Assessment, and National Institute for Health and Clinical Excellence from 2000 to September 2006, supplemented by a search for screening prior to 24 weeks gestation from 1966-99 (Appendix A Table 2). Articles were also obtained from outside experts and through reviewing bibliographies of other relevant articles and systematic reviews. We also considered all articles cited in the 2003 Evidence Synthesis[5] for inclusion. Two investigators reviewed the 2003 USPSTF report's reference list, relevant abstracts, and full articles (168 total), to ensure we were reviewing all prior literature using the updated criteria. Two investigators reviewed 1403 abstracts and 277 articles against inclusion and exclusion criteria for each key question. Discrepancies were resolved by consensus.

We included only randomized trials that used the currently accepted one-step and two-step diagnostic criteria to evaluate GDM screening and treatment for assessing potential benefit of GDM screening and treatment. We considered prospective cohort studies if RCT evidence was not available. Any study design was considered for potential harms, and inclusion criteria were less stringent for study harms. For example, articles that used standard methods, but not

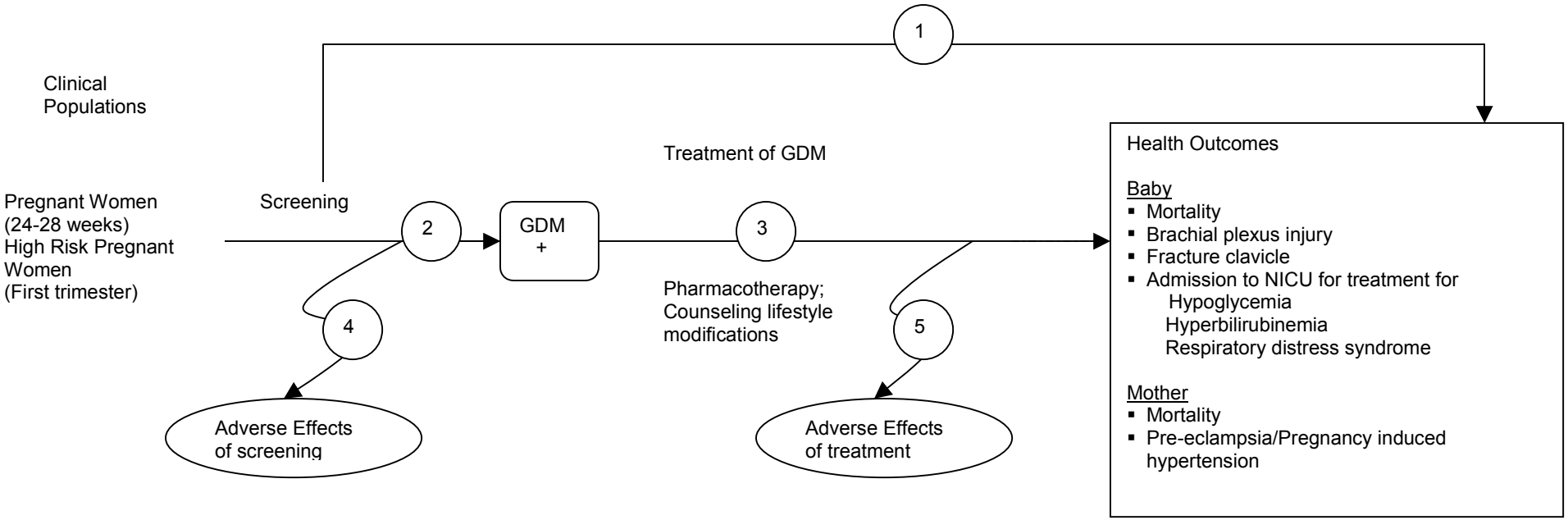
standard cut-off criteria, were accepted. The actual glucose levels used to define GDM were considered less important in assessing the harms of screening than the process used for GDM screening and the receipt of a diagnosis. Details for inclusion and exclusion criteria are provided in Appendix A Table 3. Ninety of the potentially included articles were excluded for study design and 12 for poor quality.

We found no RCTs of screening for KQ1 or studies for KQ2 that reported sensitivity, specificity, and yield rates using one of the three acceptable screening methods (Table 1) for specified health outcomes (Figure 1). We included the following articles that met final inclusion and quality-rating criteria: seven RCTs reported in eight publications that test interventions that alter glycemic control and reported specified health outcomes in women diagnosed at 24 weeks gestation or later for KQ3a; one prospective study addressing treatment of women diagnosed with GDM prior to 24 weeks gestation for KQ3b; three studies reporting harms of screening for GDM were found for KQ4; one additional article, along with six of the eight articles included in KQ3, reported adverse effects of treatment for KQ5. Tables of excluded articles and reason for exclusion are provided in Appendix D. Using the USPSTF's study design-specific criteria (Appendix B), two investigators critically appraised and rated the quality of all included articles as well as those articles excluded for quality reasons only.

USPSTF Involvement

The authors worked with four USPSTF members at key points throughout the review process to develop and refine the analytic framework and key questions and resolve issues involving the scope, treatment modalities, and health outcomes. This research was funded by the Agency for Healthcare Research and Quality (AHRQ) under a contract to support the work of the USPSTF. AHRQ staff provided oversight for the project and reviewed and assisted with the external review of the draft evidence synthesis.

Figure 1. Analytic Framework



Key Questions

1. Does screening for GDM lead to a reduction in perinatal morbidity and mortality for mother and/or infant? A) during the 1st trimester and up to 24 weeks gestation? B) after 24 weeks gestation?
2. What are the sensitivities, specificities, reliabilities and yields of current screening tests for GDM: A) during the 1st trimester and up to 24 weeks gestation? B) after 24 weeks gestation?
3. Does treatment for GDM lead to reduction in perinatal morbidity and mortality for mother and/or infant?
4. What are the adverse effects associated with screening for GDM?
5. What are the adverse effects associated with treatment of GDM?

Table 1. Screening strategies

Three screening tests with generally accepted criteria are frequently used for the diagnosis of GDM with a one- or two-step method. These are typically performed between 24 and 28 weeks' gestation and are defined as follows:

1. 50 g Initial Screening Test: A two-step method using an initial 1-hr 50 g oral glucose challenge test (GCT) and followed by a diagnostic 75 or 100 g oral glucose tolerance test (OGTT) if the GCT is positive. The GCT has two criteria accepted as a positive result, depending on the level of sensitivity desired: [1,2]

- ≥130 mg/dL (identifies 90 percent of women with GDM)[1]
- ≥140 mg/dL (identifies 80 percent of women with GDM)[1]

2. 100 g Diagnostic Test: A one-step or a two-step method using a 3-hour 100 g diagnostic OGTT. This test is defined as positive if two or more of the hourly plasma glucose levels meet or exceed the following values:

Criteria for Abnormal Result on 100 g, Three-Hour Oral Glucose Tolerance Tests in Pregnant Women[1,30]

Blood sample	National Diabetes Data Group Criteria	Carpenter and Coustan Criteria
Fasting	105 mg/dL (5.8 mmol/L)	95 mg/dL (5.3 mmol/L)
1-hour	190 mg/dL (10.5 mmol/L)	180 mg/dL (10.0 mmol/L)
2-hour	165 mg/dL (9.2 mmol/L)	155 mg/dL (8.6 mmol/L)
3-hour	145 mg/dL (8.0 mmol/L)	140 mg/dL (7.8 mmol/L)

3. 75 g Diagnostic Test: A one-step or two-step method using a 75 g diagnostic oral glucose tolerance test (OGTT). This test is defined as positive if two or more of the hourly plasma glucose levels meet or exceed the following values (different criteria apply based upon WHO or ADA recommendations):

Criteria for Abnormal Result on 75-g Oral Glucose Tolerance Test in Pregnant Women[1,2]

Blood Sample	ADA mg/dL	ADA mmol/l	WHO* mmol/l
Fasting	95	5.3	7.0
1-hour	180	10.0	
2-hour	155	8.6	7.8

*Note 7.0 mmol/l=126 mg/dl and 7.8 mmol/L=140 mg/dl)

III. Critical Key Questions & Results

Key Question 1. Does screening for GDM lead to a reduction in perinatal morbidity and mortality for mother and/or infant? A) after 24 weeks gestation? B) during the first trimester and up to 24 weeks gestation?

For this overarching question regarding the benefit of screening and treatment for GDM outcomes, the threshold for evaluating evidence must be higher. Therefore, we required RCT evidence for inclusion for this key question. The ideal study to address the question of whether screening for GDM reduces maternal and/or neonatal morbidity and mortality would be an RCT in which a group of women is not screened and another is screened and, if diagnosed with GDM, treated. No such study for GDM screening was identified. We believe it is unlikely that such a study will ever be conducted in the future in the U.S. given the relatively common current clinical practice of GDM screening and institutionalized ethical constraints for research in human subjects.

Key Question 2. What are the sensitivities, specificities, reliabilities, and yields of current screening tests for GDM: A) after 24 weeks gestation? B) during the first trimester and up to 24 weeks gestation?

Summary. No studies were identified that reported the sensitivity or specificity of GDM screening for the primary maternal and neonatal health outcomes outlined in the analytic framework (Figure 1). Therefore, no articles met inclusion criteria for this key question.

Evaluating screening test performance in GDM is complicated by multiple different accepted standards for screening tests (one-step vs. two-step approach), diagnostic tests (75 g 2 hour OGTT vs. 100 g 3 hour OGTT), and diagnostic criteria (NDDG vs. C&C, see Table 1 for specific cutoff values). Test performance can be evaluated only in the context of how well it accurately identifies people with disease (sensitivity) and excludes those without disease (specificity). With GDM, the "disease" is actually many potential outcomes — and for two different people (mother and baby). Additionally, the primary outcomes against which we were designated to measure test performance (e.g., stillbirth, neonatal death, brachial plexus injury, see Analytic Framework (Figure 1), are rare events, which makes estimates unstable except in a very large study, such as the ongoing Hyperglycemia and Adverse Pregnancy Outcome (HAPO)trial. We found no available evidence that reported sensitivity and specificity for our primary health outcomes — only for the more prevalent macrosomia, which was not a primary outcome. Although we found no studies that met inclusion criteria, we will briefly discuss the limited available data that did not meet inclusion criteria.

Screening at 24 weeks gestation or more.

Sensitivity and specificity of screening tests. There is no universally agreed upon reference test for the diagnosis of GDM. To evaluate the sensitivity and specificity of the 50 g GCT, 75 g OGTT, and 100 g OGTT, we required studies that used perinatal morbidity/mortality measures (primary outcomes) as reference standards and limited our search to current screening and diagnostic tests recommended by the ADA, ACOG, or WHO (Table 1).

Of the studies we considered for inclusion, two cohort studies, one retrospective[31] and one prospective[32] provided data from which sensitivity and specificity of screening for GDM at ≥24 weeks could be calculated for at least one of the primary outcomes, although these results were not reported in the articles themselves. A third study was identified that used macrosomia as the reference standard for assessing the sensitivity and specificity of screening for GDM at ≥24 weeks with the 50 g GCT, 75 g OGTT, and 100 g OGTT.[33] A fourth study conducted in a racially and ethnically diverse population provided only the sensitivity and specificity of the 50 g GCT to detect GDM based on the diagnosis made at 24 or more weeks by 100 g OGTT (C&C criteria). These studies were summarized but ultimately excluded because the authors did not provide the sensitivity and specificity of the screening tests for the primary outcomes and/or because macrosomia, an intermediate outcome, was used as the reference standard.

De Sereday and colleagues used macrosomia, defined as ≥ 4000 g, as the reference standard for evaluating the sensitivity and specificity of the 50 g GCT, 75 g OGTT, and 100 g OGTT.[33] In this study of 99 primarily Caucasian women at high-risk of GDM with a mean BMI was 30.8 (±5.6) kg/m^2, the sensitivity of the 50 g GCT using a cutpoint of 140 mg/dl was 58.3 percent. Using a cutpoint of 137 mg/dl, the sensitivity was marginally higher, 66.7 percent. For the 75 g OGTT, sensitivities were 41.7 percent and 66.7 percent using cutpoints of 140 mg/dl and 119 mg/dl, respectively. The sensitivity for the 100 g OGTT (GDM using NDDG criteria) was 27.3 percent. The specificities of the tests were 67.8 percent (140 mg/dl cutpoint 50 g GCT), 63.2 percent (137 mg/dl cutpoint 50 g GCT), 90.8 percent (140 mg/dl cutpoint 75 g OGTT), 64.4 percent (119 mg/dl cutpoint 75 g OGTT), and 96.5 percent (2 or more abnormal values of 100 g OGTT). The sensitivities of the 75 g or 100 g OGTT diagnostic tests for detecting macrosomia (≥4,000g) were less than the 50 g GCT by current accepted cutoff values (≥130 mg/dl or ≥140 mg/dl), but the sensitivity for the 50 g GCT was still only 58 percent with the 140mg/dl cutoff.[33] In contrast, the specificity was better for either OGTT test (both ≥90 percent specific) than for the 50 g GCT, which had a specificity of 67.8 percent with the 140 mg/dl cutpoint. The OGTT is very specific but not very sensitive, and preceding it by a 50 g GCT increases the sensitivity to a moderate level (but with many more false positive tests after the first test).

Sensitivity calculations for macrosomia (≥ 4000g) based on the prospective study by Deerochanawong and colleagues were 21.4 percent for the 100 g 3 hour OGTT using NDDG criteria compared to 42.9 percent for the 75 g 2-hour OGTT using WHO criteria.[32] Sensitivity for stillbirth, a very rare event, was 0 percent for both tests. For neonatal hypoglycemia, we calculated that the sensitivity of the 100 g OGTT was 40 percent and the sensitivity of the 75 g OGTT was 60 percent. For hyperbilirubinemia, we calculated that the 100 g OGTT had a 3.3 percent sensitivity compared to 15 percent for the 75 g OGTT. Calculated specificities for these outcomes (macrosomia, hypoglycemia, hyperbilirubinemia and still birth) ranged from 84.2 to

99.9 percent with NDDG testing criteria yielding specificities >10 percent higher than WHO for all outcomes.

In a retrospective medical record review of a community-based population, Schwartz compared rates of macrosomia (defined in two ways: ≥ 4000 g and ≥ 4500 g), cesarean delivery and stillbirth for screening threshold of 140 mg/dl for 50 g GCT and NDDG and C&C criteria.[31] Sensitivity was < 30 percent for all outcomes regardless of screening test used. Specificity was > 80 percent for all outcomes and all tests. Women in this study were primarily Caucasian and were screened at approximately 28 weeks gestation. A total of 18.7 percent had 50 g GCT > 140mg/dl.

Reliability of current screening tests. No articles that evaluated the reliability or reproducibility of GDM screening tests met inclusion criteria. Two articles that tested the reproducibility of the 50 g GCT and the 100 g OGTT[34,35] were excluded due to small sample size, samples not representative of the US population, and sparse distribution of outcomes leading to unreliable statistics.

*Yields of current screening tests***.** Using the 75 g oral GTT, de Sereday and colleagues reported a GDM prevalence of 14 percent at a mean gestation of 27.4 (±5.9) weeks.[33] This is comparable to the prevalence of 15.7 percent reported by Deerochanawong for screening between 24 and 28 weeks.[32]

Of those studies that tested for GDM using the 100 g 3 hour OGTT, GDM prevalence ranged from 1.4 to 3.2 percent using the NDDG criteria.[31,32] Whereas, in studies that used the less conservative C&C criteria, the prevalence ranged from 4.9 to 6.3 percent.[20,31,33]

The studies by de Sereday and Deerochanawong compared the yields from both the 50 g GCT followed by the 100 g OGTT using ADA criteria or NDDG criteria to the 75 g OGTT using WHO criteria.[32,33] Yields of GDM diagnoses based on WHO criteria (14 to16 percent) were substantially higher than those based on NDDG (1.4 percent) or ADA (6 percent) criteria. A Brazilian cohort study of 4,977 women diagnosed with GDM between 20-28 weeks gestation by the one-step 75 g OGTT found a prevalence of 2.4 percent GDM (95 percent CI 2.0-2.9) by ADA criteria with the 75 g OGTT and 7.2 percent by WHO criteria (95 percent CI 6.5-7.9).[36]

In a study by Esakoff and colleagues conducted in a diverse population, the prevalence of GDM based on the 50 g GCT and 100 g OGTT (C&C criteria) was 6.3 percent. Stratified by ethnicity, the prevalence of GDM was 4.1 percent in Caucasian, 4.3 percent in African American, 7.0 percent in Latina, and 9.7 percent in Asian.

Screening prior to 24 weeks gestation.

Sensitivity and specificity of screening tests. No articles were identified that reported the sensitivity and specificity of the included GDM screening tests at <24 weeks gestation for our specified health outcomes.

Reliability of current screening tests. No articles were identified that evaluated the reliability or reproducibility of any GDM screening test administered prior to 24 weeks gestation.

Yields of current screening tests. One study that evaluated the ability of the 75 g OGTT measured at ≤16 weeks gestation to predict GDM diagnosis at 24-28 weeks or at 32-34 weeks based on the same test was excluded because it was conducted in a very high-risk Hungarian population that was not representative of primary care practice in the United States.[37] This study

by Bito and colleagues consisted of 155 women who were considered to be at increased risk for GDM and who were referred to the Diabetic Pregnant Outpatient department in Szeged, Hungary.[37] A 2 hour 75 g oral GTT was conducted at ≤16 weeks gestation and again at 24 to 28 weeks and 32 to 34 weeks gestation. Women who tested positive for GDM based on WHO criteria in an early test were not subsequently tested at later gestations. Testing was performed after a 3-day carbohydrate load followed by a 10 to 12 hour fast. The prevalence of GDM was 4.9 percent at ≤16 weeks, 19.6 percent at 24 to 28 weeks, and 29.4 percent at 32 to 34 weeks.

The upcoming results of the HAPO trial may provide new evidence to inform this question.

Key Question 3. Does treatment for GDM lead to reduction in perinatal morbidity and mortality for mother and/or infant? A) after 24 weeks gestation? B) during the first trimester and up to 24 weeks gestation?

Summary. Nine articles were included for this question: eight RCTs[38-44] for treatment after 24 weeks gestation and one prospective cohort[45] of treatment outcomes in women diagnosed at the first prenatal visit compared to 24 weeks gestation or later. A summary of the study population characteristics and primary outcomes of these studies are available in Tables 2 and 3. Further details are available in the Evidence Tables (Appendix C Table 1).

We found two RCTs that tested treatment versus no treatment of GDM in screen-detected populations and met inclusion and quality-rating criteria—one recent (the Australian Carbohydrate Intolerance Study in Pregnant Women [ACHOIS]) and the sentinel O'Sullivan from over 4 decades ago that laid the groundwork for evidence in this field. [39,44] Both of these trials randomized subjects to treatment versus no treatment of GDM on the basis of a universal screening program approach.

The ACHOIS trial reported that dietary management, glucose monitoring, and insulin treatment as needed in 1000 women with mild GDM diagnosed after 24 weeks gestation improved composite, and individual, neonatal and maternal outcomes compared to no treatment.[39] Perinatal mortality, although rare, did not occur in any (0/490) mothers treated, compared to five total stillbirths/neonatal deaths in non-treated (5/510). As glucose control was not part of data collection[46] and was not reported, we cannot estimate the relative impact of glycemic control (vs. weight control) on improving outcomes with treatment ——only that treatment improved outcomes.

The fair-quality RCT by O'Sullivan and colleagues[44] found that treatment in a screened population of women at high risk for GDM (gestational age at screening unspecified) reduced the intermediate outcome of macrosomia, but without differences in perinatal mortality rate with treatment. Treatment was a small daily dose of insulin (10 units) initially, with irregular glucose monitoring of urine and blood (as this was not available 40 years ago). In contrast, the ACHOIS study participants used insulin only if other therapies failed to achieve tight glycemic control based on study glucose targets, and only 17 percent of the treatment group required insulin.

In addition to the ACHOIS results, we found five fair or good quality GDM treatment trials of various therapies including oral hypoglycemic therapy[42,47] and insulin analogues. These

trials were reported in six articles that were either newly located or taken from the previous 2003 USPSTF review. These six included articles were heterogeneous in the treatments used and study populations, so synthesizing results in a meta-analysis was not possible. The trials that showed improved glycemic control also found improvements in some (but not all) neonatal and maternal outcomes.

We identified no RCTs for screening and treatment prior to 24 weeks gestation in high-risk women. Therefore, we searched for articles of the next best level of evidence, prospective cohort studies. One fair-quality prospective cohort study of early screening and treatment for GDM was identified in a consecutive population of 3,986 women in Spain screened at the first prenatal visit, and then again at 24 to 28 weeks gestation in those women normal at the initial screen. Its results suggest that an early diagnosis of GDM may represent pre-gestational diabetes as women diagnosed early were more likely to require insulin and had a higher proportion of hypertension, perinatal deaths, and neonatal hypoglycemia than those diagnosed late.

Study Details.

Diagnosis and Treatment at 24 weeks gestation or more.

RCTs of Treatment versus No Treatment of GDM in Screen-Detected Populations. We found one good-quality study from the recent ACHOIS results reported by Crowther and colleagues, a multi-center blinded randomized controlled trial, conducted at 14 sites in Australia, and four sites in the United Kingdom (UK), that compared treatment versus no treatment of mild GDM.[39] ACHOIS was designed to determine whether the treatment of mild gestational diabetes would reduce perinatal complications and to assess the effects of treatment on maternal outcomes, mood, and quality–of-life. Women with chronic disease (except essential hypertension) were not eligible to participate. Inclusion criteria were a singleton or twin pregnancy at 16-30 weeks gestation and positive screening for GDM, which was done in two steps. Step 1: Positive risk factors for GDM or a positive 50 g GCT (≥ 7.8 mmol/l [140 mg/dl] 1 hour post-challenge; 93 percent of women had a positive GCT). Step 2: a 75 g OGTT was given after an overnight fast, with inclusion criteria (a) fasting plasma glucose of < 7.8mmol/l (140 mg/dl) and (b) 2 hour post-OGTT glucose 7.8-11.0 mmol/liter (140-198 mg/dl). At the time of the study, the WHO classified these glucose criteria as glucose intolerance of pregnancy (i.e., intermediate between normal and GDM), and thus it was ethical to randomize and evaluate treatment compared to a blinded untreated group. Subsequently, the WHO changed the classification of GDM so that a 2 hour value 7.8-11.0mmol/l is now defined as GDM, and so the results of the ACHOIS trial can provide direct evidence for treatment of this mild GDM by current practice standards.

The 1000 women who met inclusion criteria were randomized by computer-generated numbers, 490 to treatment (who were informed in writing that they had GDM and an intervention plan), and 510 to no treatment (who received a slip indicating they did NOT have GDM, and no follow-up treatment was provided by the study [only as clinically indicated by their provider]). The full numerical results of the OGTT were not released to the women or their providers until after birth.

Women in the intervention group received both individualized dietary advice and instructions to self-monitor glucose four times daily until it was within the specified range for two weeks, and insulin was initiated and titrated as needed. Glucose goals were as follows: fasting of at least ≤3.5 mmol/l (63 mg/dl) and no more than 5.5 mmol/l (99 mg/dl), pre-prandial

levels <5.5 mmol/l, and 2 hour postprandial <7.0 mmol/l (126 mg/dl). The care of the women in the intervention group replicated clinical care in which universal screening and treatment for GDM are available. In contrast, the routine-care (non-treated) group replicated clinical care in which screening for GDM is not available.

After randomization, the treated and non-treated groups were similar in age, BMI, race/ethnicity, gestational age at screening (mean 29 weeks), primiparity, history of GDM, and by screening test results on both the 50 g GCT and the 75 g OGTT (Appendix C Table 1). One population characteristic of note is that the women in this study were, on average, slightly overweight (mean BMI approximately 26 kg/m^2). However, recent weight estimates for US women of child-bearing age are similar to ACHOIS (current mean BMI 26.8 kg/m^2 and 27.9 kg/m^2 for US women age 20-29 years and 30-39 years, respectively).[11] In the ACHOIS trial about 75 percent of the women were Caucasians (also similar to the US),[48] with Asians comprising the next largest race/ethnicity group.

In ACHOIS, the treated group gained significantly less weight (8.1kg) during pregnancy (measured as difference between first and last prenatal visit weight) compared to the non-treated group (9.8 kg, multivariate adjusted p =0.01). No information is available on glucose values during pregnancy in the treated or not-treated group, as this was not part of the study's data collection.[46] However, 100 women (17 percent of the intervention group) required insulin therapy; there were 17 (3 percent) in the non-treated group whose physicians began insulin for clinical indications. Results are presented by intention-to-treat in the article tables (including all women randomized).

The treatment group had one-third the overall risk of the composite outcome of any serious perinatal complication, and this remained significant after adjustment for maternal age, race, and parity (RR 0.33 [95 percent CI 0.14-0.75]). Serious perinatal complications were defined as any of the following: death, shoulder dystocia, bone fracture, and nerve palsy. The absolute rates of these individual perinatal outcomes were also reported in the paper, but could not be compared between groups due to no events for death, bone fracture, or nerve palsy in the treatment group. Overall, there were seven infants with serious perinatal complications in the treatment group (all shoulder dystocia), compared to 23 infants with perinatal serious complications in the non-treated group (five deaths, one fractured humerus, three nerve palsies, and 16 shoulder dystocia [25 total events, but calculated as 23 infants in the analysis as one had both a fractured humerus and a radial-nerve palsy and another infant had both shoulder dystocia and Erb's palsy in the non-treated group]). Shoulder dystocia was not a specified health outcome for this evidence review. The remaining components in the composite outcome (neonatal death, fracture, nerve palsy) were final health outcomes specified by the Task Force for this review. The causes of the five deaths in the untreated group were: two stillbirths (unexplained intrauterine deaths at term of appropriately grown infants), one stillbirth at 35 weeks gestation associated with pre-eclampsia and intrauterine growth restriction, one infant died from asphyxia during labor without antepartum hemorrhage, and one had a lethal congenital anomaly.

The majority of infants in both groups were admitted to the neonatal nursery and differed by treatment group: 357/506 (71 percent) in the treated group, and 321/524 (61 percent) in the non-treated group (adjusted RR 1.13 (1.03-1.23). The length of stay in the neonatal nursery among the infants admitted did not differ significantly between groups (median of 1 day for both groups; interquartile range, 1 to 2 days in the intervention group and 1to 3 days in the routine-care group; adjusted p=0.81).

The rate of admission to the neonatal ICU was not specifically reported, but treatment for the relevant specified health outcomes for this evidence report (hypoglycemia, hyperbilirubinemia, respiratory distress syndrome) were reported individually. There was no significant difference in infants requiring intravenous therapy for hypoglycemia after birth based on mother's treatment group: 35/506 (7 percent) in the treated group, and 27/524 (5 percent) in the routine-care group (adjusted RR 1.42 [95 percent CI 0.87-2.32]). There was no significant difference in risk of needing phototherapy for jaundice among infants whose mothers were treated or not treated for GDM: 44/506 (9 percent) in the treated group, and 48/524 (9 percent) in the routine-care group (Adjusted RR 0.93 [95 percent CI 0.63-1.37]). Similarly, risk of respiratory distress syndrome in the neonate (needing supplemental oxygen > 4 hours after birth) was not significantly different based on mother's GDM treatment 27/506 (5 percent) in the treated group, and 19/524 (4 percent) in the routine-care group (Adjusted RR 1.52 [95 percent CI 0.86-2.71]).

In addition to having significantly less weight gain during pregnancy, women in the treatment group had a 30 percent lower risk of pre-eclampsia (defined as blood pressure > 140/90 mm Hg more on two occasions more than four hours apart) compared to women who were not treated for GDM: (58/490 [12 percent] in the treated group and 93/510 [18 percent] in the untreated group; Adjusted RR 0.70 [95 percent CI 0.51-0.95]).

Other outcomes assessed with ACHOIS that were not part of our key question are summarized here. Infants of the treated mothers had a modest reduction of a mean 145g in birth weight (3335 g vs. 3482 g, $p< 0.001$) compared to those whose mothers were not treated. The proportion of large babies was also significantly reduced based on mothers' treatment for GDM when measured either as LGA (defined as $>90^{th}$ percentile) or macrosomia ($\geq$ 4000 g). The infants of mothers treated for GDM had about half the rate of macrosomia compared to those whose mothers were not treated (Adjusted RR 0.47 [95 percent CI 0.34-0.64]). Shoulder dystocia (as reported by the primary caregiver) occurred in seven babies whose mothers were treated, compared to 16 babies whose mothers were not treated (Adjusted RR 0.46 [95 percent CI 0.19-1.10]). There were no significant differences in other infant outcomes based on mother's treatment group for GDM (i.e., small for gestational age, 5-minute Apgar score < 7, neonatal convulsions).

Women treated for GDM were more likely to be induced for labor (189/506 [39 percent]) compared to women not treated (150/524 [29 percent]), Adjusted RR 1.36 [95 percent CI 1.15-1.62]. Women treated for GDM also had a slightly earlier gestational age at birth, which was statistically significant (mean 39.0 vs. 39.3 weeks, $p=0.01$). Overall rates of cesarean, however, did not differ in the treated group (152/506 [31 percent]) compared to the untreated group (164/524 [32 percent]); Adjusted RR 0.97 (0.81-1.16). The lack of difference by treatment group remained when c-sections were stratified by indication (emergency or elective). There were also no differences in other maternal outcomes by treatment group (i.e., any perineal trauma, puerperal pyrexia ($\geq$ 38 degrees Celsius), length of postnatal stay, or proportion breast-feeding at discharge).

The fair-quality rated RCT of screening for GDM in women at high risk for diabetes mellitus was reported in 1966 by O'Sullivan and colleagues.[44] The authors screened 943 women with a 1 hour 50 g GCT, followed by a 3-hour 100 g OGTT. If the women had a GCT value of $\geq$ 130mg/dl or one or more risk factors for GDM, they underwent a 3 hour 100 g OGTT. Women were ineligible for the study if they had previously been diagnosed with diabetes, had blood

sugars exceeding 300 mg/dl, had classic diabetic symptoms, or registered for prenatal care at ≥37 weeks gestation: 615 women tested positive for GDM, and were randomly allocated to treatment (n=307) and no treatment (termed 'positive controls'; n=308) A third group of women (termed 'negative controls', n=238) was selected randomly at regular intervals and had to have completely normal glucose tolerance. We will discuss only the results of the women with GDM randomized to treatment versus no treatment in the text as this normal group was not randomized and reported results for all three groups were unadjusted (see Appendix C Table 1 for further details). The gestational age at screening was not specifically reported, but early screening or screening upon entry was implied as the authors stated: "women who had normal glucose tolerance in one trimester received repeat tests in subsequent trimesters."[44]

Women who were treated for GDM received an individualized diet (40 percent carbohydrates, 30 calories/kg ideal body weight, and 1.5-2 g protein/kg ideal body weight) and 10 units of NPH insulin once each morning. The insulin dose increased if glycosuria was noted by tests performed daily at home or during a clinic visit. At the time of this study, home capillary blood glucose monitoring was not yet available. The untreated GDM group received routine prenatal care. The treated GDM patients did not differ from untreated GDM in mean postprandial blood sugars, except for between 1 and 2 hours post-prandial (88.8 vs. 92.6 mg/dl, $p<0.01$), but they did have significantly lower fasting blood sugars (69.1 vs.74.3 mg/dl, $p<0.05$).

The perinatal loss rate was 4.3 percent for treated GDM patients and 4.9 percent for untreated GDM patients (p=non-significant). The number of infants weighing nine pounds or more at birth (macrosomia) was three times higher in the untreated group (13/305 [4.3 percent] viable deliveries in treated versus 40/306 [13.1 percent] in the untreated group, p=not reported). There were no significant differences between treated and untreated GDM in the number of infants diagnosed with congenital anomalies (13.6 percent vs. 16.0 percent) or delivered preterm (8.5 percent vs. 7.8 percent). When stratifying by weight (either normal or underweight vs. 10 percent overweight) and comparing treated and untreated GDM patients, the authors found those who were treated were less likely to have large babies and that the relative reduction was greatest in lean women (2.3 percent vs. 10.0 percent among normal or underweight women and 7.6 percent vs. 16.4 percent for overweight women, p=not reported). For both treated and untreated GDM, women who were overweight were more likely to have large babies.

This fair-quality RCT must be considered in the historical context of clinical care 4 decades ago.[44] At that time, home blood glucose meters (and thus regular monitoring of glycemic control) were not available, so it was not possible to tightly control glucose levels—only to look for hyperglycemia severe enough to cause "overflow" of glucose into the urine that can then be detected by a urine test strip. Also, significant (life-threatening) maternal hypoglycemia was a greater risk in an era when subjects were not able to accurately monitor blood glucose levels regularly or accurately. The treatment options with shorter-acting insulins that clinicians have today were also not available in the 1960s.

The rate of macrosomia observed by O'Sullivan in the GDM group treated with once daily insulin was significantly lower in treated versus untreated GDM patients (4.3 percent vs. 13.1 percent). In contrast, there was no significant difference observed in rate of fetal or neonatal death. There are several possibilities for this discordance in treatment effect including power, since rare events require a very large sample to detect a difference. One possibility is that treatment does not have an effect on mortality risk. Another is that the physiologic changes of normalizing fasting glucose reduces macrosomia, but normalization of post-prandial levels is

also required to affect mortality risk. One limitation to note is that mean glucose values were calculated from 2701 measured blood sugars (an average of six blood draws per woman during pregnancy). These were likely not as representative of mean glucose values that can currently be assessed by home glucose monitoring.

Although it is implied from O'Sullivan that early screening occurred (as testing was repeated in each trimester if negative on the initial screening), we found no RCTs that directly compared screening at <24 weeks with screening at ≥24 weeks gestation. One fair-quality prospective cohort study was identified that reported results for women who were serially screened for GDM, and is detailed below under early screening.[45]

RCT of Treatment Comparisons for GDM. The six included articles from five randomized controlled trials for KQ3 (one good-quality, five fair-quality) compared different treatment strategies for GDM. Given the treatments involved, it was not feasible to blind the subjects to type of treatment (e.g., insulin before or after a meal). It was also not possible to synthesize the results as treatments were heterogeneous.

The best comparative evidence came from one good-quality RCT reported by Langer and colleagues that compared perinatal outcomes with treatment of GDM with the oral hypoglycemic agent glyburide versus the standard treatment of insulin (note: Glyburide is not currently approved by the Food & Drug Administration (FDA) for use in GDM).[47] Women with GDM and singleton pregnancies who attended maternal health clinics in San Antonio, Texas (83 percent Hispanic, 12 percent White, 5 percent Black), and required medical treatment for their GDM were randomized (n=404) to treatment with either glyburide or insulin. Outcomes evaluated were glycemic control and maternal and neonatal complications.

Gestational diabetes was diagnosed by the two-step method among women with singleton pregnancies at 11-33 weeks gestation. Step 1: A 50 g GCT was performed, and those with a 1-hour plasma glucose > 130 mg/dl had a 100 g OGTT. Step 2: Two or more abnormal values on the 3-hour OGTT by C&C criteria were diagnostic of GDM. Women with fasting plasma glucose (FPG) < 95 mg/dl were initially treated with diet alone, but were later eligible for randomization to medical treatment if their FPG became > 95mg/dl or they had postprandial plasma glucose levels ≥120 mg/dl. The majority of women were defined as obese (BMI>27.3 kg/m2), 70 percent and 65 percent in the glyburide and insulin-treated groups, respectively. The two randomized groups were also similar in age, nulliparity, gestational age at screening (mean 24 and 25 weeks for glyburide and insulin-treated), history of prior GDM, and screening test results.

Both randomized groups received nutritional instructions for three meals and four snacks a day and instructions in glucose monitoring, with glycemic goals for titration of medication. The glyburide group was initiated on a 2.5 mg dose of glyburide in the morning, and increased as needed by 2.5 mg up to a 20 mg daily dose. The average dose of glyburide a day was 9 mg (± 6 mg). Eight women (4 percent) on glyburide did not achieve good glycemic control and were switched to insulin. The insulin group received an average daily dose of 85 units/day (± 48 units). The mean glycosylated hemoglobin was 5.7 for the glyburide group, and 5.6 for the insulin-treated group (p=0.42). Glucose control during pregnancy also did not differ between the two groups with glucose monitoring (measured as fasting, pre-prandial, postprandial, or mean glucose). However, women in the glyburide group were significantly less likely to have hypoglycemia (<40 mg/dl) during pregnancy. Specifically, only four women in the glyburide

group (versus 41 women in the insulin group) experienced hypoglycemia (p=0.03). None of the women in either group reported severe symptoms with hypoglycemia. Weight gain during pregnancy (week prior to delivery minus pre-pregnancy weight) also did not differ with glyburide versus insulin treatment (mean 21 kg for both groups).

There were no differences in any of the neonatal outcomes based on maternal treatment with glyburide or insulin. Specifically, perinatal mortality rates (stillbirth or neonatal death), metabolic outcomes (NICU admission, need for IV therapy for hypoglycemia, hyperbilirubinemia, polycythemia, hypocalcemia, lung complications, need for respiratory support, congenital anomalies), and anthromorphometric features (birth weight, proportion with macrosomia or LGA) did not differ by treatment group.

A secondary analysis by Langer and colleagues of the above RCT was recently published and was rated as fair quality. Their analysis compared outcomes (both for glyburide and insulin-treated groups) stratified by whether the fasting glucose on the diagnostic OGTT was ≤ 95 mg/dl vs. > 95 mg/dl.[47] Consistent with the results of O'Sullivan in 1966,[44] a normal fasting glucose was associated with a significant reduction in LGA babies in both glyburide and insulin treatment groups (18 percent LGA if diagnostic OGTT fasting glucose was > 95 mg/dl in both treatment groups, and 7-8 percent LGA if OGTT fasting glucose was ≤ 95 mg/dl), but level of maternal fasting glucose did not show any difference for either treatment group in neonatal complications including metabolic complications or a composite neonatal outcome. The composite neonatal outcome was defined as any of the following: metabolic complications (neonatal hypoglycemia, hyperbilirubinemia, polycythemia); LGA/macrosomia; neonatal intensive care unit admission >24 hours; the need for respiratory support). Appendix C, Table 1 provides a more detailed explanation.

Bancroft and colleagues reported a fair-quality small randomized controlled pilot study in the UK to evaluate neonatal outcomes in 68 women with mild GDM treated with diet and home glucose monitoring up to four times daily compared to diet without home glucose monitoring .[38] Both groups received dietary counseling and monthly glycosylated hemoglobin testing (though glycosylated hemoglobin results were not made available for the standard care group during the study). The glucose monitored group had significantly lower 2 hour OGTT levels at study entry , and achieved significantly lower glycosylated hemoglobin levels only at the 32 weeks measurement point, compared to standard treatment (glycosylated hemoglobin was generally lower but not significantly different at 28 weeks, 36, 38 weeks, or at term). The rates of admission to the special care baby unit (the primary outcome) were 2/32 [6 percent] in the glucose monitored group, and 6/36 [17 percent] in the standard care group, and did not reach statistical significance. One shoulder dystocia in the unmonitored group resulted in admission to a special baby care unit but no long-term consequences. The frequency of hypoglycemia was 2/32 [6 percent] in the glucose monitored group, and 6/36 [17 percent] in the standard care group, which did not reach statistical significance. There were no stillbirths or neonatal deaths in either group. Other neonatal outcomes were not notably or significantly different (gestational age at delivery, birthweight, LGA [> 90th percentile]). The authors acknowledged the lack of power to assess the significant differences in outcomes between the two treatments with the small sample size, and concluded that they had demonstrated the feasibility of a larger study, which was then commencing with ACHOIS.

Jovanovic and colleagues randomized 42 women with GDM (95 percent Hispanic) who required medical treatment into two groups comparing treatment with NPH+lispro insulin versus

NPH+regular women.[41] While the trial was small and designed to assess differences in insulin antibodies, and primarily provides information regarding lack of harm with treatment (KQ5), there were none of the following complications in either of the treatment groups: neonatal hypoglycemia or hypocalcemia, fetal abnormality, or macrosomia (> 90th percentile). There were no statistically significant differences in rate of cesarean delivery, gestational age at delivery, or newborn 1- and 5-minute Apgar scores.

Nachum and colleagues randomized 274 women in Israel with gestational diabetes who required insulin treatment, diagnosed at a mean 26 weeks gestation, to insulin four times daily (regular insulin before three meals and an intermediate duration insulin before bedtime) versus insulin twice daily (mixed dose of intermediate and regular insulin morning and evening).[43] Baseline characteristics, including BMI (mean 28 kg/m^2), were similar in both treatment groups after randomization. With intensified treatment, the four-times-daily insulin treatment group had significantly better glycemic control (mean daily glucose, HbA1c, and fructosamine) than the twice-daily insulin treated group. The HbA1c values were 5.5 percent and 5.8 percent in the four-times-daily and twice-daily insulin treatment groups, respectively. Moreover, 91 percent of the four-times-daily insulin group reached target mean glucose values (< 5.8 mmol/l) versus only 74 percent of the twice-daily insulin group. Of note, this excellent glycemic control did not increase severe maternal hypoglycemia (requiring help from another person); 1/138 and 1/136 women in the four-times-daily and twice-daily insulin groups experienced severe hypoglycemia. Neonatal hypoglycemia and hyperbilirubinemia were both significantly reduced in the intensified four-times-daily insulin versus twice-daily insulin maternal GDM treatment groups (RR 0.12[95 percent CI 0.02-0.97] and RR 0.51[95 percent CI 0.29-0.91], respectively, for hypoglycemia and hyperbilirubinemia). Neonatal hypoglycemia was defined as plasma glucose <1.9 mmol/l in term infants or <1.4 mmol/l in preterm infants ≥ 2 occasions in first 48 hours of life. Hyperbilirubinemia was defined as >205 mmol/l at >=34 weeks gestation or >137 mmol/l at <34 weeks gestation. There was only one perinatal death, and it occurred with a mother who was in the twice-daily insulin (less intensive) treatment group. Overall neonatal morbidity rates were reduced by half in the four-times-daily versus twice-daily insulin treatment groups (RR 0.51[0.29-0.91]). The authors did not specify which elements were combined in this composite overall morbidity.

Finally, the last fair-quality RCT was a small trial of 66 women who required insulin treatment for GDM, randomized to postprandial versus preprandial glucose monitoring to guide insulin dose titration.[40] Baseline characteristics were similar after randomization, including BMI, gestatational age at diagnosis and treatment, 1 hour 50 g GCT and fasting plasma glucose on the 3 hour diagnostic 100 g OGTT. Weight gain during pregnancy and percent achieving glycemic control goals were the same in both treatment groups. In this context, while there were no differences in glycosylated hemoglobin at baseline (8.9 percent vs. 8.6 percent, p=0.55), the final glycosylated hemoglobin was both significantly improved and different in the group with postprandial monitoring compared to preprandial monitoring (6.5 percent vs. 8.1 percent, p=0.006). The postprandial group also received more daily insulin than the preprandial group (1.1u/kg vs. 0.9 u/kg, p=0.0001). The rate of neonatal hypoglycemia (defined as <= 30 mg/dl [1/7 mmol/l]) was 1/33 [3 percent] vs. 7/33 [21 percent] in the post versus preprandial treatment groups (p=0.05). Macrosomia (>4 ,000 g) was also dramatically reduced in post versus preprandial groups (9 percent vs. 26 percent of babies in each treatment group, p=0.01). There was only one stillbirth, which occurred in the group with less intensive glycemic control (in this case the preprandial group). Cesarean for cephalopelvic disproportion was reduced in the

postprandial versus the preprandial treatment groups (12 percent vs. 36 percent of women, p=0.04). There were no differences in rates of pre-eclampsia in the two groups. In summary, while this was a small RCT, it found significant improvements in glycemic control and reduction in neonatal hypoglycemia and macrosomia, and there was no apparent increased harm associated with this improved glycemic control. Given that the initial HbA1c values were high in both groups (more severe GDM), and that the postprandial group had both greater improvement in hyperglycemia and higher doses of insulin used for treatment, it is not clear if it was improvement in glycemic control or timing of the treatment (post vs. preprandial) that resulted in improved health outcomes.

Diagnosis and Treatment prior to 24 weeks gestation.

Prospective cohort study early vs. late screening. Bartha and colleagues administered a 50 g GCT (cutoff 140 mg/dl) to 3986 consecutive pregnant Spanish women at their first antenatal visit (early-onset).[45] Abnormal results were followed by administration of the 100 g 3-hour OGTT (NDDG criteria). Women with negative testing at the first visit were retested again at 24-28 weeks (late-onset). Women diagnosed with GDM were hospitalized and capillary glucose values were assessed, and those with pre-prandial glucose levels of <105mg/dl and 2-hour postprandial glucose concentrations of <120mg/dl were given only dietary recommendations. Insulin therapy was initiated for women who did not meet these criteria. The mean gestational age at hospitalization was 18.1 ± 6.5 weeks for those diagnosed early and 33.1 ± 3.9 weeks for those diagnosed late ($p<0.000001$). Of 3986 women, 65 (1.6 percent) were diagnosed early with GDM and 170 (4.3 percent) were diagnosed later with GDM.

Women with early-onset gestational diabetes were more likely to have hypertension (18.5 percent vs. 5.9 percent, p=0.006), largely due to a high rate of pre-existing chronic hypertension (10.8 percent vs. 2.4 percent, p=0.01). With all cases of pre-eclampsia analyzed together (pre-eclampsia plus superimposed pre-eclampsia), the rate was significantly higher in the early-onset group (6.2 percent vs. 0.6 percent, p=0.02). The authors did not specify the definitions used for hypertension, pre-existing hypertension, pre-eclampsia, or superimposed pre-eclampsia.

There were no significant differences in most pregnancy outcomes (cesarean delivery, preterm birth, 5-minute Apgar < 7, mean neonatal weight, fetal weight > 4000g or < 2500g, meconium passage, and admission to special care baby unit) between those diagnosed early and late. The neonates of women diagnosed early were more likely to have hypoglycemia (8 percent vs. 0 percent, p=0.005) and perinatal death (6 percent vs. 0 percent, p=0.02). The definition of neonatal hypoglycemia used was also not specified.

Women with early-onset GDM differed significantly ($p<0.05$) from those with late-onset GDM in all but one measure of glycemic control (glycosylated hemoglobin). Women with early-onset? GDM had higher mean fasting glucose levels, higher mean 2 hour postprandial glucose levels (after breakfast, lunch, and dinner), and higher mean pre-dinner glucose levels. In addition, 33.9 percent of women who were diagnosed early required insulin compared to 7.1 percent of those diagnosed late ($p<0.00001$).

This single study of early screening suggests an early diagnosis of GDM may represent pre-gestational diabetes as women diagnosed early were more likely to require insulin and had a higher proportion of perinatal deaths and neonatal hypoglycemia than those diagnosed at 24 weeks gestation or later.

Key Question 4. What are the adverse effects associated with screening for GDM?

Summary. The primary adverse effects associated with screening would be the psychological impact of screening to the mother with GDM – and potentially to the mother who does not have GDM but has the added time, cost, and psychological burden of screening. A review of the literature revealed that available evidence is mixed in terms of the initial psychological impact of GDM screening. In the first few weeks after screening, women who screen positive for GDM may report higher anxiety, more psychological distress, and poorer perceptions of their general health than women who screen negative. Available evidence, however, suggests that these differences, even if present shortly after diagnosis, do not persist into the late third trimester or postpartum period.[49-51]

Study Details. Three fair quality articles, two prospective cohort studies, and one cross-sectional study met inclusion criteria (Appendix C Table 4).[49-51]

Rumbold and Crowther serially assessed 209 Australian women (two-step method: 50 g GCT, 75 g GTT, WHO criteria) at 24-28 weeks and again toward the end of the third trimester at about 36 weeks: 150 women who screened negative on the OGCT, 37 who had a positive GCT screen but normal OGTT, and 25 women diagnosed with GDM (2-hour glucose>11.1 mmol/l after a 75 g OGTT).[49] The validated measures used in the questionnaire were the Spielberger State-Trait Anxiety Inventory (STAI), the Edinburgh Postnatal Depression Scale (EPDS), and the Short Form 36 Item Health Survey (SF-36).[49,52-54]

No differences were found for the mean STAI scores after screening, between women screening negative or positive. Similarly, none of the groups differed from those that screened negative in the late third trimester.

No differences in rates of depression (EPDS>12) were found in women after screening or in the late third trimester among the screen negative, false positive GCT, or GDM groups.

For the SF-36 measures, in the first post-screening assessment, women who had negative GCTs had better health perceptions, lower vitality, and were more likely to rate their health as much better than one year before compared to women who screened positive with GCTs. They did not differ in any of the other six SF-36 health status domains. In the late third trimester, women who had a negative GCT reported less vitality than women who had a positive GTT, and greater social functioning than women who had a false positive GCT; these groups did not differ in any other domain or in health rating compared to one year before. After screening, women with negative GCTs were more likely than those with positive GCTs to rate their experience of screening as positive (77 percent vs. 57 percent, $p<0.01$), but did not differ in the likelihood of requesting screening during a future pregnancy. Later in pregnancy (towards the end of the third trimester), there were no differences in the experience of screening between women with false positive GCTs and women with positive GTTs (GDM).

Daniells and colleagues conducted a prospective cohort study of 50 women with GDM diagnosed at the beginning of the third trimester and 50 women with normal glucose tolerance.[51] During the 30th week of gestation, women diagnosed with GDM had higher mean scores on the

Mental Health Inventory 5 (13.9 ± 4.8 vs. 11.4 ± 3.8, p<0.004) and higher mean anxiety scores on the Spielberger State-Trait anxiety inventory (40.6 ±13.3 vs. 34.2 ± 9.9, p<0.007) than women with normal glucose tolerance, indicating greater psychological distress and anxiety. There were no statistically significant differences at 36 weeks of gestation or at 6 weeks postpartum. The GDM and control groups did not differ in their attitudes toward testing for GDM at any assessment period.

Spirito and colleagues used the Profile of Mood States-Bipolar From to assess the psychological status of 68 women with GDM, diagnosed at approximately 28 weeks gestation, and 50 non-diabetic pregnant controls at about 35 weeks of gestational age.[50] Women with GDM did not differ from controls on any of the Profile of Mood States-Bipolar form subscales, indicating no differences in emotional status. In addition, the 33 women with GDM who were prescribed insulin did not differ in emotional status from the 33 who were not. None of the Profile of Mood States-Bipolar Form subscales was predictive of glycemic control.

Key Question 5. What are the adverse effects associated with treatment of GDM?

Summary. We identified two potential domains of adverse treatment effect in GDM: physical and psychological. For the mother, hypoglycemia is the potentially most serious (that is, life-threatening or requires assistance to treat). In the psychologic domain, maternal adverse effects could potentially arise from diagnosis and treatment. The potential teratogenicity of certain newer treatments for GDM (oral hypoglycemic agents or insulin analogues) is a potential physical harm to the fetus that clearly could relate to GDM treatment, but this would be treatment–specific, for relative benefits and harms of differing treatment modalities compared to insulin and thus is a sub-question. That is, the primary purpose of this Task Force update is to review the evidence regarding potential benefits and harms of screening and treatment for GDM, not to determine which treatment regimen is preferred. Several of the studies of newer agents assess placental crossing of the treatment modality which we will report, but one must put this in the context that most treatments for GDM began in the second trimester (after the period of major organogenesis),[55] and thus data is very limited to assess potential teratogenicity of newer agents for treatment.

Several studies included for treatment benefit also provided evidence for potential harm, with the best evidence again arising from the ACHOIS results. Overall for KQ5, we found two good-quality trials[39,42] and five fair-quality studies[38,40,41,43,56], including six trials from KQ3. The additional study [56] was a fair-quality prospective cohort study evaluating the emotional adjustment to diagnosis and treatment of GDM. (Appendix C Table 3; Table 2).

Not all studies monitored or reported maternal hypoglycemia, but the rates are rare with treatment and no worse with alternate therapies in those that did. For the psychological domain, the evidence suggests no harm from treatment. The best evidence comes from the ACHOIS trial, which found in a subgroup that responded to the questionnaire that treatment was potentially associated with overall improved self-reported health status and reduced post-partum depression at three months post-partum compared to no treatment. Crowther and colleagues reported that the full numerical results of the OGTT for the ACHOIS were not released to the women or their providers in the treatment group until after birth, but the exact timing is not specified.

Alternative explanations for the reduced post-partum depression and improved quality-of-life responses in the treated group could include unblinding prior to the three months post-partum before the questionnaire was completed or what is sometimes termed the Hawthorne effect (in which additional attention given to the treatment group rather than the treatment itself could improve perceptions).[57] Finally, a prospective study found that mood did not differ with in women treated for GDM compared to controls.[56]

In summary, we found no evidence for significant harms associated with treatment with GDM, and it is possible that treatment may impart an additional benefit to maternal quality-of-life.

Study Details.

Treatment versus No Treatment of GDM: The one good-quality article (detailed in study design in KQ1) reported on the ACHOIS clinical trial of treatment for mild GDM. Maternal hypoglycemia rates were not reported for the treatment group, so we cannot assess this outcome in this trial. However, detailed analyses of psychological well-being were done six weeks after diagnosis and three months post-partum, among a subset that responded. At six weeks after diagnosis, 332/490 treated women and 350/510 non-treated women completed a questionnaire about quality-of-life (QOL). Multiple QOL components were measured by the SF-36, a well-validated QOL questionnaire that ranges from zero (worst) to 100 (best) on multiple components.[58-60] The treated and non-treated groups differed significantly on six components—and all of these differences favored a better QOL (higher score) with treatment. Anxiety was also assessed by the Spielberger State-Trait Anxiety Inventory (with scores below 15 considered normal), and no differences in anxiety were detected at six weeks after diagnosis (mean score 11, or normal, for both groups).

At three months post-partum, 278/490 treated and 295/510 non-treated women completed the QOL questionnaire. Three components on the SF-36 bordered on significant difference (physical functioning, general health, and overall physical component), with these differences favoring better self-ratings with treatment. Mean anxiety levels were normal for both groups (again assessed by the Spielberger State-Trait Anxiety Inventory) and did not differ (mean = 11 for both). Post-partum depression was also assessed at three months with the Edinburgh Postnatal Depression Scale (EDPS; a score above 12 is considered abnormal). In the treatment group, 23 women (8 percent) had an EDPS>12, compared to 50 women (17 percent) in the non-treated group. Thus, the risk of post-partum depression was reduced by half in treated women, i.e., the relative risk of post-partum depression was 0.46 (95 percent CI 0.29-0.73) with treatment of GDM. These results should be interpreted with caution in that, unlike the other ACHOIS results, only a subgroup responded to the QOL questionnaire. The data, however, suggest lack of harm and raise the question of potential benefit of decreased post-partum depression and improved QOL in the mother treated for GDM.

Studies of Treatment Comparisons for GDM. Another good-quality RCT reported by Langer and colleagues evaluated potential harms of glyburide versus insulin, and was also detailed in the treatment (KQ3) section (note: Glyburide is not currently approved by the Food & Drug Administration (FDA) for use in GDM).[42] Although glycemic control did not differ between the two treatments (fasting, post-prandial or glycosylated hemoglobin percent), women in the glyburide group were significantly less likely to have hypoglycemia (<40 mg/dl) during pregnancy. Specifically, only four women in the glyburide group, versus 41 women in the

insulin group, experienced hypoglycemia (p=0.03). None of the women in either group reported severe symptoms with hypoglycemia.

Evaluation of the glyburide group for safety revealed no detectable glyburide in the cord serum of any infant (mean sampling of the cord blood was 8 ± 4 hours after the last dose of maternal glyburide). In 12 women randomly selected from the glyburide group, glyburide was measured simultaneously in the maternal and cord serum. Maternal serum concentrations were easily detectable (range 50-150 mg/ml), but were undetectable in cord serum. Finally, the authors stratified outcomes in this trial based on whether the women entered the study prior to or after 20 weeks (prior to 20 weeks would be during the period of organogenesis where risk of congenital anomalies is greater). They found no differences in any outcomes based on treatment groups (glyburide vs. insulin).

A fair-quality small study of 42 mostly Hispanic women randomized to NPH+lispro versus NPH+regular insulin, reported by Jovanovic and colleagues, also assessed treatment with lispro, an insulin analogue (which has a theoretical concern of teratogenicity because of the modified amino acid structure that might be metabolized differently than the natural hormone).[41] Maternal hypoglycemia (glucose <55 mg/dl) was rare in both groups, and tended to be lower with lispro, but this was only statistically significant with the fasting pre-breakfast measurements (percent of all fasting blood glucoses in the hypoglycemic range was 0.93 percent for regular insulin vs. 0.65 percent for insulin lispro, p=0.025). The primary outcome was antibody response to insulin (because placental transfer of insulin occurs when complexed to immunoglobulin). Neither the lispro-insulin nor regular-insulin treated groups showed a statistically significant change in antibody response with treatment compared to the baseline antibody response for individual patients. In a subset of patients who received a continuous infusion of insulin lispro during delivery, there were measurable maternal concentrations of insulin lispro, but no insulin lispro could be detected in the cord blood, suggesting that insulin lispro does not cross the placenta.

Bancroft compared treatment with diet+glucose monitoring versus diet without glucose monitoring.[38] Only six monitored women required insulin; rates of maternal hypoglycemia were not reported. Nachum and colleagues randomized 274 women in Israel with GDM who required insulin treatment four times daily versus twice daily.[43] With intensified treatment, the four–times-daily group had significantly better glycemic control (mean daily glucose, HbA1c, and fructosamine) than the twice-daily groups as detailed in KQ3. However, this excellent glycemic control did not increase the rate of severe maternal hypoglycemia (requiring help from another person); 1/138 and 1/136 women in the four-times-daily and twice-daily insulin groups, respectively, experienced severe hypoglycemia.

A fair-quality randomized trial reported by deVeciana and colleagues comparing pre-prandial versus post-prandial glucose monitoring to guide insulin treatment in GDM did not report specific rates of maternal hypoglycemia.[40] However, in the text where they report no differences in hospitalization to optimize glycemic control during pregnancy between the treatment groups and similar rates of pre-eclampsia in the groups, the authors note that were no other maternal complications.

The one fair-quality paper that was specifically included for this question (but not for KQ1 or KQ3) was the prospective cohort study by Langer and Langer that evaluated emotional adjustment to GDM diagnosis and intensified treatment.[56] Diagnosis was based on an OGTT at a

mean gestational age of 28 weeks in 69 diet-controlled and 137 insulin-treated women. These 206 women with newly diagnosed GDM and 95 pregnant women with normal OGTT (controls) were administered the Profile of Mood States Bipolar Test. The women with GDM (both diet controlled and insulin treated) had a mean age of 29 years, and those without GDM had a mean age of 24 years. Obesity rates (definition not specified) were 20 percent in diet controlled, 50 percent in insulin treated, and 26 percent in controls. On each of the six poles of the mood scale (composed-anxious, agreeable-hostile, elated-depressed, confident-unsure, energetic-tired, clearheaded-confused), the overall mean values did not differ between the diet-treated or insulin-treated groups compared to the controls. When the two GDM treatment groups were stratified by good versus poor glycemic control, those with better glycemic control had significantly better moods ($p<0.05$) on four of the six axes tested. These results suggest that treatment does not harm psychological well-being, and that improving glycemic control might be associated with improved well-being.

Table 2. Summary characteristics of treatment trials (Key Question 3)

Author/Yr	N	Treatment	Setting	Population	BMI	Gestational age at screening, wks	Screening test used	Quality Rating
Treated vs. Untreated								
Crowther 2005[39]	1000	Treatment of mild GDM vs. No treatment	Australia, UK	White 75 % Asian 16 % Other 8 %	IG: 26.8 (23.3-31.2) † CG: 26.0 (22.9-30.9) †	IG: 29.1 (28.2-30.0) † CG: 29.2 (28.2-30.0) †	Step 1: RF or 50 g GCT (≥7.8 mmol/L) 1-hr cut-off (93% were positive with 50-g) Step 2: 75 g OGTT (1) Fasting <7.8 mmol/L and (2) 2-hour value 7.8 to 11.0 mmol/L	Good
O'Sullivan 1966[44]	943	Positive screen treated vs. Positive screen control vs. Negative screen control	Boston, MA	NR	≥ 20 % over ideal body weight IG: 27.7% CG: 30.5%	NR	Step 1: 50 g GCT whole blood > 130 mg/dL Step 2: 100 g OGTT with ≥ 2 abnormal glucose values	Fair
Treatment Comparisons								
Langer 2000, 2005[42,47]	404	Glyburide vs. Insulin treatment	San Antonio, TX	83 % Hispanic 12 % White 5 % Black	BMI ≥ 27.3 prior to pregnancy N (%) IG_{INS}: 141 (70) IG_{GLY}: 132 (65)	Mean±SD IG_{INS}: 24±7 CG_{GLY}: 25±7	Step 1: 50 g GCT > 130 mg/dL Step 2: 100 g OGTT with ≥ 2 abnormal glucose values by C&C criteria	Good
Bancroft 2000[38]	68	Diet+Intensive glucose monitoring vs. Diet+Standard clinic glucose monitoring	UK	Asian: 31% Caucasian: 69 %	Mean (SD) $IG_{DietgluM}$: 32.2(6.7) IG_{Diet}: 27.5(6.1)	Median (range) $IG_{DietgluM}$: 31(24-38) IG_{Diet}: 32(15-37) wks	Step 1: <7.0 mmol/L Step 2: 75 g OGTT 2-hour value 7.8 to 11.0 mmol/L GTT done at the discretion of individual clinicians.	Fair
Jovanovic 1999[41]	42	NPH+Lispro insulin vs. NPH+Regular insulin treatment	California	Hispanic IG_{ana}: 89% IG_{reg}: 100%	Mean±SEM IG_{ana}: 31.5±1.1 IG_{reg}: 33.3±1.2 NS	At enrollment, Mean±SEM IG_{ana}: 27.3±1.4 IG_{reg}: 25.6±1.3 NS	NDDG Criteria (2-step 50 g GCT, then 100 g OGTT)	Fair

Author/Yr	N	Treatment	Setting	Population	BMI	Gestational age at screening, wks	Screening test used	Quality Rating
Nachum 1999[43]	274	4x daily insulin vs. 2x daily insulin treatment	Israel	Jewish IG_{4X}: 57% CG_{2X}: 55%	IG_{4X}: 27.9±2.6 CG_{2X}: 27.8±2.7	At diagnosis IG_{4X}: 25.9±2.6 CG_{2X}: 26.3±7.2 Initiated treatment IG_{4X}: 27.4±6.8 CG_{2X}: 28.0±6.9	100 g OGTT with ≥2 serum glucose concentrations ≥5.9, 10.6, 9.2, 8.1 mmol/L at 0, 1, 2, and 3 hrs respectively.	Fair
De Veciana 1995[40]	66	Pre-prandial vs. Post-prandial monitoring of glucose to inform treatment decisions	California	Hispanic: 85% White: 11% Black/Asian: 5%	IG_{pre}: 29.0±3.2 IG_{post}: 28.4±3.8 NS	At diagnosis IG_{pre}: 22.9±7.5 IG_{post}: 21.8±6.5 NS Initiated treatment IG_{pre}: 24.3±5.2 IG_{post}: 25.1±5.1 NS	Step 1: One-hour 50 g GCT > 140 mg/dL, but <190 mg/dL; those >190 mg/dL started insulin immediately. Step 2: 3-hour 100 g OGTT with ≥ 2 abnormal glucose values (fasting > 105 mg/dL, 1 hr > 190 mg/dL, 2 hrs > 165 mg/dL, 3 hrs > 145 mg/dL).	Fair

†Median (interquartile range)

IG-intervention group; CG-control group; NS-not significant; OGTT-oral glucose tolerance test; GCT-glucose challenge test.

Table 3. Health outcomes of treatment trials (Key Question 3)

	Neonatal Outcomes							*Maternal Outcomes*	
Author/Yr	Mortality	Clavicular fracture	Brachial plexus injury	NICU admissions	Hypoglycemia	Hyper-bilirubinemia	Respiratory distress	Death	Pregnancy-induced hypertension or Pre-eclampsia
Treated vs. Untreated									
Crowther 2005[39]	N (%) IG: 0 CG: 5(1)	N (%) IG: 0 CG: 1(<1)	N (%) IG: 0(0) CG: 3(1)	NICU-NR Neonatal nursery N (%) IG: 357(71) CG: 321(61) Adj RR 1.13 (1.03-1.23)	N (%) IG: 35(7) CG: 27(5) Adj RR 1.42 (0.87-2.32)	N (%) IG: 44(9) CG: 48(9) Adj RR 0.93 (0.63-1.37)	N(%) IG: 27(5) CG: 19(4) Adj RR 1.52 (0.86-2.71)	NR	N (%) IG: 58 (12) CG: 93 (18) Adj RR 0.70 (0.51-0.95)
O'Sullivan 1966[44]	N (%) IG: 13 (4.3) CG: 15 (4.9)	NR	NR	NR	NR	NR	NR	NR	NR
Treatment Comparisons									
Langer 2000[42]	N (%) IG_{GLY}: 2(1.0) IG_{INS}: 2(1.0)	NR	NR	N (%) IG_{GLY}: 12(6) IG_{INS}: 14(7)	N (%) IG_{GLY}: 18(9) IG_{INS}: 12(6)	N (%) IG_{GLY}: 12(6) IG_{INS}: 8(4)	N (%) IG_{GLY}: 4(2) IG_{INS}: 6(3)	NR	IG_{GLY}: 6% IG_{INS}: 6%
Bancroft 2000[38]	None	NR	N $IG_{DietgluM}$: 0 IG_{Diet}: 1	N(%) $IG_{DietgluM}$: 2(6) IG_{Diet}: 6(17)	N(%) $IG_{DietgluM}$: 2(6) IG_{Diet}: 6(17)	NR	NR	None	NR
Jovanovic 1999[41]	NR	NR	NR	NR	None	NR	NR	NR	NR
Nachum 1999[43]	N (%) IG_{INS4X}: 0 IG_{INS2X}: 1(0.7)	NR	NR	NR	N(%) IG_{INS4X}: 1(0.7) IG_{INS2X}: 8(5.9) RR: 0.12(0.02 to 0.97)	N(%) IG_{INS4X}: 15(11) IG_{INS2X}: 29(21) RR: 0.51(0.29 to 0.91)	NR	NR	IG_{INS4X}: 11(8) IG_{INS2X}: 12(9) Diff (95%CI): -1 (-11 to 9)
deVeciana 1995[40]	N (%) IG_{pre}: 1(3) IG_{post}: 0	NR	NR	NR	N(%) IG_{pre}: 7(21) IG_{post}: 1(3) RR: 7.0(0.9 to 53.8)	N (%) IG_{pre}: 4(12) IG_{post}: 3(9)	Transient tachypnea N (%) IG_{pre}: 2(6) IG_{post}: 2(6)	NR	N (%) IG_{pre}: 2(6) IG_{post}: 2(6)

IG-intervention group; CG- control group; NR-not reported; NICU-neonatal intensive care unit; adj-adjusted; RR-relative risk; PIH-pregnancy-induced hypertension; INS-insulin; GLY-glyburide; pre-preprandial; post-postprandial.

IV. Discussion

Summary of Review Findings

The details of each included study are available in the Evidence Tables, and results are synthesized in Table 4. The best new evidence comes from a good quality RCT, ACHOIS,[39] which is the first RCT to compare treatment of mild GDM to no treatment. ACHOIS found that treatment improved outcomes in mild GDM (severe levels of hyperglycemia in the pre-existing diabetes range were excluded), with a statistically significant reduction in both serious neonatal (as a composite outcome) and maternal outcomes. There was no evidence of harm to mother or infant with treatment. In a sub-set of participants who responded to a post-partum questionnaire, mothers treated for GDM were significantly less depressed and, on a few measures that differed by treatment group, had better quality-of-life three months post-partum; these post-partum data have some limitations.

In a review by the American College of Physicians' Journal Club, the major criticism in was that the ACHOIS investigators' use of a composite outcome given the rare individual neonatal events. While this composite outcome was significantly improved, the Journal Club review commented that it was not reasonable to combine mortality with the range of morbidities, particularly since the more-prevalent shoulder dystocia was driving the overall results.[61] While it is true that these outcomes differ in severity, all of the serious rare outcomes (death, bone fracture, nerve palsy) occurred in zero cases of the treated group and ranged from one to five events for each outcome in the non-treated group. In particular, although perinatal and neonatal mortality are rare, there were zero deaths with treatment, compared to five deaths without treatment (three stillbirths, two neonatal deaths). The causes of the five deaths in the untreated group with mild GDM were: two stillbirths (unexplained intrauterine deaths at term of appropriately grown infants), one stillbirth at 35 weeks gestation associated with pre-eclampsia and intrauterine growth restriction, one death from asphyxia during labor without antepartum hemorrhage, and one lethal congenital anomaly. It would be ideal to know how glycemic control differed between the two groups in order to discern any relative contribution of improved glycemic control compared to the diminished weight gain in pregnancy that resulted from treatment. Nevertheless, regardless of mechanism, treatment of mild GDM improved neonatal and maternal outcomes.

This new evidence adds to the evidence that began with O'Sullivan's RCT findings of a reduction in macrosomia with GDM treatment compared to no treatment.[44] With the results of the ACHOIS trial, there is additional evidence that benefits may be extended beyond macrosomia to other maternal outcomes and a composite neonatal outcome. Several of the treatment comparison trials that achieved differences in glycemic control also suggest that improved glycemic control with intensified management (whether postprandial monitoring or four times daily) reduces perinatal complications. Overall, the evidence suggests that the improved outcomes observed with GDM treatment occur without apparent harm, including no evidence of worsened significant maternal hypoglycemia with treatment. Finally, available

evidence suggests that diagnosis and treatment of GDM does not worsen maternal quality-of-life–except possibly transiently for the first few weeks after diagnosis. As early as six weeks after diagnosis continuing to at least three months post-partum women treated for GDM may have improved self-rated quality-of-life, including half the risk of post-partum depression compared to women not treated for GDM. Although this evidence has limitations in establishing a benefit to maternal quality-of-life with treatment, there is no evidence of harm in this domain with treatment of GDM.

Contextual Issues

Background of Increasing Obesity in US population

When O'Sullivan conducted the first RCT of GDM screening and treatment,[44] obesity was rare in the US and type 2 diabetes was virtually unseen in young women of child-bearing age. Less than 30 percent of women diagnosed with GDM in O'Sullivan's study were more than 120 percent of their ideal body weight.[44] In a separate cohort study by O'Sullivan of 752 GDM women in the 1960s, only 2 percent of women who tested positive for GDM had persistent diabetes immediately after pregnancy, but the remainder had a 16-year cumulative risk of developing type 2 diabetes of over 60 percent.[62,63] Currently, two-thirds of all US adults are estimated to be overweight or obese,[64] and there has been a parallel epidemic of type 2 diabetes in US adults, with young adults, especially females, representing the fastest growing group for obesity and type 2 diabetes.[65-67] For every two adults diagnosed with diabetes in the US, one remains undiagnosed.[68] Thus, against a background of increasing obesity and type 2 diabetes, increasing rates of previously unrecognized diabetes during pregnancy are an increasingly important issue in current clinical practice. The recent US obesity epidemic also makes it increasingly important to distinguish the effect of obesity and previously unrecognized diabetes in pregnancy (also classified as GDM) from diabetes with transient onset during pregnancy when evaluating the evidence for GDM screening and treatment. In the ACHOIS results reported by Crowther and colleagues, the median BMIs of the treated and untreated groups were similar after randomization (26.8 and 26.0 kg/m2, respectively). By designing the study to include only mild GDM (fasting plasma glucose of < 7.8 mmol/l and 2 hour post OGTT 7.8-11.0 mmol/l), tested at a median of 29 weeks gestation, the ACHOIS investigators excluded severe pre-existing but unrecognized diabetes.

Different International Diagnostic Standards for Gestational Diabetes

In the United States, a two-step approach to screening and diagnosis of GDM (1-hour 50 g GCT, followed by a 100 g diagnostic OGTT) has been the most common method of GDM diagnosis for over 4 decades, based on early work by O'Sullivan in which he demonstrated the relation between the 100 g, 3 hour OGTT in 752 pregnant women and their subsequent long-term risk of developing type 2 diabetes.[62] His original work was based on testing of whole blood. Serum and plasma glucose values—which became the new technique of measuring glucose—are approximately 14 percent higher than whole blood values.[69] To account for this change between whole blood and plasma glucose measures, both the National Diabetes Data Group (NDDG) in 1979 and Carpenter and Coustan (C&C) in 1982 developed slightly different criteria based on

mathematical conversions of the original O'Sullivan data.[69-71] The most recently published Fourth International Workshop Conference on Gestational Diabetes Mellitus recommended using the C&C criteria—which yield a higher prevalence of GDM—based on data presented at the meeting that the women who met the lower C&C threshold "were at similar risk for perinatal morbidity, including macrosomia."[3] These C&C criteria for the 100 g OGTT are currently diagnostic for the ADA,[1] and ACOG uses both NDDG and C&C.[2] The initial screening 50 g GCT, also evaluated by O'Sullivan, had an initial non-fasting 1-hour cutoff of 130 mg/dl using whole blood glucose values;[62,63] this was also later revised to a 140 mg/dl 1-hour cutoff to compensate for the higher values in plasma or serum compared to whole blood.[69] Both a 140 mg/dl and 130 mg/dl plasma or serum 1 hour cutoff value are recommended with the 2 step approach in current US clinical recommendations.[1,2]

In the US, while the 2 hour 75 g OGTT is also now recognized as an acceptable method of diagnosing GDM,[1-3] it is most commonly used for diagnosis of diabetes outside of pregnancy. In contrast, the WHO diagnostic criterion for GDM is the 2 hour 75 g OGTT, which is used for GDM diagnosis by most countries outside the US. When the ACHOIS was initiated, WHO distinguished mild GDM (2 hour plasma glucose after the 75 g OGTT > 7.8 mmol/l [140 mg/dl] but less than 11.0 mmol/l [200 mg/dl]) as "glucose intolerance of pregnancy."[72] In 1998, WHO revised the criteria to consider any glucose value > 7.8 mmol/l 2 hours after the 75 g OGTT during pregnancy as diagnostic of GDM.[19] Thus, the recently published ACHOIS results provide a unique opportunity to evaluate the evidence for outcomes with mild GDM treatment versus non-treatment. The ACHOIS design likely could not be replicated today, as most Institutional Review Boards that govern research in human subjects would consider it unethical not to treat gestational diabetes with current practice standards. ACHOIS findings also provide the first good RCT evidence of improved perinatal and maternal outcomes with treatment versus non-treatment of mild GDM. These results in GDM diagnosed by a 75 g OGTT will likely intensify the conundrum of the best clinical criteria for diagnosis of GDM. The ACHOIS screening method represents a mix of several current approaches, as the first step was the 50 g GCT or risk factors (93 percent were positive on the GCT). The second step was the diagnostic 75 g OGTT. However, it is the charge of the USPSTF to evaluate and present the evidence, and despite the added controversy on the best screening method, the ACHOIS findings provide us with important good-quality new evidence on maternal and perinatal outcomes with treatment versus no treatment of GDM.

Timing of Gestational Screening

During a normal pregnancy, glucose values will decrease during the first trimester, before they begin to rise higher than in non-pregnancy during the second trimester due to physiologic insulin resistance that results from pregnancy-related hormones.[25,23,73] This insulin resistance stabilizes glucose levels for the rapidly growing fetus between its mother's meals. That is, pregnancy is the only condition in which developing a diabetogenic state is normal physiology.[23]

The purpose of GDM screening is to identify women who have an excessive (pathologic) increase in glucose while they became transiently insulin resistant in the second trimester (and reduce related complications). This is the basis for the original recommendations to time GDM screening between the 24th and 28th week of gestation.[74] O'Sullivan found only 2 percent of his sample had persistent diabetes after pregnancy, although the 16-year cumulative incidence of developing diabetes again after pregnancy was 60 percent.[63] A study in 1990 found that 9 percent

of women with GDM had persistent type 2 diabetes after pregnancy, and an additional 10 percent had impaired glucose tolerance.[75] With the markedly increased US rates of obesity and type 2 diabetes in the last decade, previously unrecognized diabetes – also classified as GDM – that persists after pregnancy is likely now even higher. Thus, identifying women at high risk for unrecognized type 2 diabetes early in pregnancy (also classified as GDM) is increasing against the background of increasing prevalence of type 2 diabetes among women of child-bearing age in the US.

Clinical practice has changed based on clinical practice recommendations to also consider screening for previously unrecognized diabetes (defined as GDM if first recognized during pregnancy) in very high-risk women at the first prenatal visit.[1] In addition to the 1-step and 2-step OGTT diagnostic test, a fasting plasma glucose > 126 mg/dl or a random plasma glucose > 200 mg/dl on two occasions is also part of practice guidelines for diagnosing previously unrecognized diabetes in the first trimester.[1]

The timing of diagnosis in pregnancy must be considered when evaluating the evidence, as those who can be diagnosed in the first trimester (previously unrecognized diabetes) represent a different group than those women who meet criteria beginning in the second trimester (onset of diabetes in pregnancy). Although we searched extensively, we found no good-quality evidence that evaluated screening or treatment of gestational diabetes early in pregnancy. The one fair-quality included RCT for screening by O'Sullivan did not specify the mean age of diagnosis, but over 97 percent of women with GDM had normal glucose tolerance within six months of delivery,[44] the population is certainly one with onset of diabetes during pregnancy. All but one of the studies that met inclusion criteria for evidence of treatment were also in women diagnosed ≥ 24 weeks gestation (Table 2). Thus, current evidence about screening for GDM is limited to screening at 24 weeks or more gestation.

Additional Considerations

Are there other positive outcomes of screening for mother and/or infant?

We did not systematically review the evidence for potential long-term benefits to a mother or her future child that could arise from screening for GDM during pregnancy. Likewise, none of the included studies in this review evaluated these long-term outcomes. However, we will briefly summarize these potential long-term benefits. It is well recognized that women who develop GDM during pregnancy have an increased risk of future type 2 diabetes after pregnancy.[76] O'Sullivan's original evaluation of a cohort of GDM women, on which current diagnostic criteria for the OGTT are based, used the sensitivity and specificity of the OGTT as it related to future type 2 diabetes in the mother, not to macrosomia or other neonatal outcomes.[62,63,69] In the 1960s, type 2 diabetes was primarily a future risk. As the prevalence of type 2 diabetes in young adults (and women) rises, screening for GDM has the increasing additional benefit of identifying women with previously unrecognized type 2 diabetes – in addition to those at future risk of developing it.

A plethora of recent work has studied the possibility that a hyperglycemic intrauterine environment may adversely program, or imprint, the metabolic system of the fetus for increased

risk of future obesity and type 2 diabetes. While a parental history of diabetes increases a person's risk of type 2 diabetes, the "metabolic imprinting" of a diabetes pregnancy increases the child's risk of obesity and type 2 diabetes more than would be predicted from genetics alone.[77-83] Diabetes in pregnancy has been associated with an increased rate of childhood obesity, impaired glucose tolerance, the Metabolic Syndrome, and type 2 diabetes in the offspring;[84-89] Pettit et al found that obesity in Pima offspring of women with diabetes (ODM) was independently associated with maternal diabetes in pregnancy after controlling for maternal obesity.[84] Pettit and colleagues subsequently showed that by age 20-24, 45 percent of ODM had developed type 2 diabetes in the Pima population, compared to 8.6 percent of offspring of women who did not have diabetes during pregnancy but developed type 2 diabetes after pregnancy, and only 1.4 percent of offspring had developed type 2 diabetes by age 20-24 if their mother had not had GDM or later type 2 diabetes.[85,90] These data suggest that the metabolic milieu in women with diabetes in pregnancy alters the metabolic make-up of the offspring beyond that expected by genetics alone. Pre-existing (diagnosed) diabetes was not distinguished from GDM in most of these studies of diabetes in pregnancy, so it is difficult to evaluate the independent effect that GDM would have on childhood obesity or type 2 diabetes risk. One cohort study evaluating obesity in offspring associated with mild, diet-treated GDM found no difference in obesity risk at age 5-10 years in 58 children of mothers with mild GDM compared to 257 children whose mothers did not have GDM.[91] In summary, the data on long-term risk to the offspring of GDM women remain limited at this time.

Does treatment for GDM affect intermediate outcomes (cesarean section/operative delivery, induction of labor, perineal lacerations, macrosomia)?

Although these intermediate outcomes were not systematically reviewed, if they were reported in the studies included for other key questions (and primary outcomes), they were also abstracted and summarized under the key questions (Appendix C).

If screening for GDM is found to be effective, what are the cost implications?

We did not systematically review the evidence for cost implications. Similarly, cost-effective analyses were beyond the scope of this update.

Limitations

We found no evidence base for trials of screening programs to test screened versus unscreened populations. However, both current clinical practice patterns for GDM and ethical constraints on research in human subjects would now likely preclude such a study in the US. Thus, the available evidence base comprises studies in screen-detected populations diagnosed with GDM and randomized to treatment versus no treatment.

Evaluating the potential benefit and harms of screening and treatment of GDM is limited by lack of a consistent standard for screening or diagnosis, multiple potential outcomes for two individuals (mother and baby) that are not unique outcomes to GDM. To have consistency in

interpreting potential benefits and harms, the Task Force limited this review to current national and international standard criteria for diagnosis of GDM. Use of this consistent definition of GDM resulted in eliminating some studies considered in other reviews.

Available evidence, including the ACHOIS RCT of screen-detected treated versus non-treated women with GDM did not reveal evidence of harm. However, there is little information available on harms of treatment as these are relatively rare outcomes and may not be evident in trials.

Antepartum surveillance (e.g., ultrasound and non-stress test evaluations of the pregnancy to determine if delivery should be induced) was specifically restricted from the scope of this review by the Task Force. However, it is possible that increased antepartum surveillance of women diagnosed with GDM could result in harms that were not evaluated with this review.

Emerging Issues/Next Steps

There is increasing need to evaluate screening and treatment of GDM for very high-risk women in the first trimester (previously unrecognized type 2 diabetes), but currently no high quality evidence is available to guide us. Both conditions that GDM encompasses (previously unrecognized type 2 diabetes and the transient abnormality of glucose tolerance during pregnancy) are important to evaluate—but separately—for their impact on maternal and neonatal outcomes. Larger observational studies and clinical trials in medical care settings are needed to assess this emerging issue.

Despite the recent good-quality evidence from ACHOIS that treating GDM can reduce a composite perinatal morbidity and mortality outcome, the trial does not address the issues of how glycemic level may relate to outcomes, and what an ideal diagnostic threshold may be. Also, ACHOIS does not provide evidence to validate the current 2-step diagnostic method most commonly used in the US; two large studies are now under way that address these issues. The HAPOprospective cohort study of 25,000 pregnant women in 10 countries is nearing completion and preliminary results may be available next year.[92] Women in HAPO are screened at 24-32 weeks gestation with a 75 g OGTT, and enrolled to be observed untreated with mild GDM, with results blinded to the women and their caregivers if they do not have glucose values that are outside predefined levels (FPG >105 mg/dl and/or 2-hr OGTT glucose >200mg/dl, random plasma glucose at 34-37 weeks > 160 mg/dl, or a value any time < 45 mg/dl). The aim is to determine how differing levels of glucose relate to outcomes, and if this relationship is continuous or has an ideal cut-point. The primary outcomes assessed in the trial are cesarean rates (with blinded providers), fetal size (macrosomia/LGA/obesity), neonatal hypoglycemia, and fetal hyperinsulinism.[93] The blinding of this study is an important design in this cohort study, as many prior studies that have compared outcomes in general populations to the consequences of GDM, or to outcomes of pregnancies that are complicated by GDM, did not address the likely provider bias that diagnosis and treatment of the GDM potentially has in making obstetrical decisions. Thus they are not able to separate the impact on hyperglycemia per se on these outcomes. Also, a multi-center RCT, conducted by the academic centers participating in the Maternal-Fetal Medicine Unit network (MFMU), and sponsored by NICHD—is still recruiting, so results are more than several years from being available. This multi-center US trial is designed to test outcomes with treatment versus no treatment of mild GDM detected by a 2-step

approach (with 1-hour 50 g GCT values of 135 mg to 200 mg/dl, and for the 3-hour 100 g OGTT a normal fasting level of < 95 mg/dl and two of the three remaining post-challenge measurements abnormal.[94,95] There is also a RCT comparing treatment of metformin to insulin which is under way in Australia, the Metformin in Pregnancy (MiG) trial, that will provide the first evidence of metformin treatment in GDM.[96]

Future Research

Several important gaps in current evidence need further research. Prospective studies evaluating the prevalence, sensitivity, and specificity of current diagnostic tests as they relate to primary outcomes of GDM would help with the conundrum about the best way to screen and diagnose GDM. Research is also strongly needed evaluating early screening of GDM in the first trimester—both to determine the best screening method for this high-risk group, but also to determine the additional value of early screening compared to current screening practices at 24-28 weeks gestation.

Conclusions

When considering the final evidence to guide GDM screening recommendations, it is important to weigh the evidence in light of the unique screening circumstances that screening and treatment one individual has the potential to benefit or harm two individuals (mother and baby).

Our systematic review found very limited evidence for screening and treatment of GDM diagnosed less than 24 weeks gestation—one fair-quality prospective cohort study, which suggests that an early diagnosis of GDM may represent pre-gestational diabetes as women diagnosed early were more likely to require insulin and had a higher proportion of perinatal deaths and neonatal hypoglycemia than those diagnosed late. More research is needed to evaluate screening for GDM prior to 24 weeks gestation.

Our systematic review also found new good-quality evidence for treatment improving outcomes in mild GDM in both the mother and baby in women diagnosed with GDM at 24 weeks gestation or later, compared to no treatment among a population similar to the US in ethnicity and obesity. Other randomized trials comparing different treatments of GDM suggest that improving glycemic control improves outcomes. We found limited evidence for a possible short-term worsened anxiety and psychological distress in the mother for the first several weeks after screening, and the same limited evidence suggested this does not persist throughout the pregnancy or post-partum. We found no evidence to suggest other serious harms to the mother or infant with treatment of GDM including to maternal quality-of-life. In contrast, findings from one randomized trial (in a subgroup analysis) that women treated for GDM may have less depression and improved general health perceptions up to three months post-partum compared to women not treated for GDM.

Table 4. Summary of evidence.

No. of studies	Design	Limitations	Consistency	Applicability	Overall Quality	Summary of Findings	Comment
KQ1. Does screening for GDM lead to a reduction in perinatal morbidity and mortality for mother and/or infant?							
A. During the 1st trimester up to 24 weeks gestation?							
No evidence							
B. After 24 weeks gestation?							
No evidence							
KQ2. What are the reliabilities and yields of current screening tests for GDM?							
A. During the 1st trimester and up to 24 weeks gestation?							
No evidence							
B. After 24 weeks gestation?							
No evidence							
KQ3. Does treatment for GDM lead to a reduction in perinatal morbidity and/or mortality for mother and/or infant?							
Treated vs. Untreated							
2[39,44]	RCT	No serious limitations. 1 of 2 RCT occurred 40 years ago when ability to achieve tight glucose control was limited	No inconsistencies	Studies conducted in Inner-city Boston (race/ethnicity NR) and Australia (75 percent Caucasian).	Good	Maternal: Only reported in 1 study; gestational hypertension reduced with treatment compared to no treatment (Adj RR 0.70 [0.51-0.95]) Neonatal: Composite outcome (stillbirth, neonatal death, shoulder dystocia, bone fracture, and nerve palsy) reduced with treatment of mild GDM compared to no treatment (Adj RR 0.33 [0.14-0.75]); 0 vs. 5 stillbirths/neonatal deaths with treatment vs. no treatment. Older study did not find a significant difference in perinatal mortality (only macrosomia improved with treatment).	Both used 50 g GCT; Recent study used 75g diagnostic OGTT and only included women with mild GDM (2 hr OGTT < 200 mg/dL).
Trials of treatment comparisons							
6[38,40-43,47]	RCT	3 of the 6 studies evaluated <75 women	Studies varied in treatment tested but none had serious inconsistencies with other trials regarding outcomes	4 of 6 trials included predominantly Hispanic women and limited numbers of other ethnic groups	Fair	Maternal: None reported maternal death or found significant differences in gestational hypertension with treatment. Neonatal: Outcomes either did not differ with treatment or improved if treatment improved glycemic control (e.g., neonatal hyperbilirubinemia and hypoglycemia).	No evidence available for metformin. The MiG trial (Metformin in Gestational Diabetes) is in progress.

No. of studies	Design	Limitations	Consistency	Applicability	Overall Quality	Summary of Findings	Comment
Diagnosis and Treatment prior to 24 weeks gestation							
1[45]	Prospective cohort	Definition of hypertension categories not provided	Not applicable	Conducted in Spain	Fair	Maternal: Women with early-onset GDM (1st antenatal visit) were significantly more likely to have pre-existing chronic hypertension, hypertension, combined pre-eclampsia (pre-eclampsia and superimposed pre-eclampsia) then those diagnosed >24 weeks Neonatal: Neonates of women with early-onset were more likely to have perinatal death and hypoglycemia.	
KQ4. What are the adverse effects of screening for GDM?							
3[49-51]	2 prospective cohort; 1 cross-sectional	No serious limitations. Studies do not attempt to isolate the psychological impact of antenatal surveillance, such as the modified biophysical profile. Antenatal surveillance is presumed to be more common among women with GDM and thus represented by the diagnosis itself.	No serious inconsistencies	2 Australian and 1 US study, all included primarily Caucasian women	Fair	Maternal: Limited data are mixed on whether anxiety/QOL is worsened in the first several weeks after screening. The RCT found no differences between women who screened positive vs. negative in measures of anxiety, depression, or concern for baby's health immediately after screening or later in pregnancy. The prospective cohort found health perceptions (in a minority of self-reported health domains) were worse at 30 weeks gestation among screen positive women, but did not differ at 36 weeks gestation or 6 weeks postpartum. The cross-sectional study found no differences in anxiety or depression at 35 weeks. Neonatal: No adverse effects identified in the literature.	
KQ5. What are the adverse effects of treatment of GDM?							
7[38-43,56]	RCT, 1 Prospective Cohort	Limited data available and only 2 of the studies included >100 women with GDM.	No serious inconsistencies	1 RCT is Australian, but reasonably representative of US primary care practice, with 75 percent Caucasian. The remaining studies included primarily Hispanic women.	Fair	Maternal: No maternal deaths were reported. Significant maternal hypoglycemia was rarely reported, irrespective of treatment modality. There was no evidence supporting psychological harm with treatment. On the contrary, one RCT found a significant reduction in postpartum depression (based on the Edinburgh Postnatal Depression Scale questionnaire) among women treated for GDM compared to no treatment (Adj RR 0.46 [0.29-0.73]). Neonatal: Limited data in small studies found no harm to the fetus nor placental transfer of glyburide or lispro insulin; We found no quality data on other potential harms to the offspring associated with maternal treatment of GDM.	No data is available for metformin.

N/A-not applicable; GDM-gestational diabetes mellitus; RCT-randomized controlled trials; NR-not reported; Adj RR-adjusted relative risk; GCT-glucose challenge test; OGTT-oral glucose tolerance test; QOL-quality of life

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Appendix A: Methods

Terminology

Terms used in this report are defined in Appendix A, Table 1.

Key Questions and Analytic Framework

Using the USPSTF's[1] methods we developed an analytic framework (Figure 1) and five key questions (KQs) to guide our literature search. KQ1 examined direct evidence addressing whether screening for GDM, during the first trimester or after 24 weeks, reduced perinatal morbidity and mortality for mother and/or infant. KQ2 looks at the sensitivities, specificities, reliabilities and yields of current screening tests for GDM. KQ 3 examined evidence dealing with the effectiveness of treatment during the first trimester or after 24 weeks. KQ 4 and 5 assess the harms of screening and the adverse effects of treatment respectively.

Literature Search Strategy

We conducted six database searches (Appendix A, Table 2) of Medline, Cochrane Central Registry of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, Health Technology Assessment, and the National Institute for Health and Clinical Excellence from 2000 to September 2006. The search regarding early screening searched 1966 to 2006 as this was not systematically reviewed for the 2003 report. Searches were extensively supplemented with the previous 2003 USPSTF[2] review, outside source material from experts in the field, and from examining the bibliographies of other relevant systematic reviews.

Inclusion and Exclusion

While we conducted five searches to cover the separate focus of each KQ, we dual-reviewed all abstracts for potential inclusion for any of the KQs, utilizing the inclusion/exclusion criteria described in Appendix A, Table 3. For KQ1 and 3, we limited study design to randomized controlled trials (RCT) and controlled clinical trials (CCT) and accepted prospective studies if no RCTs or CCTs were available. For KQ 2, 4, and 5 we accepted RCTs, CCTs, and good quality observational studies.

Article Review and Data Abstraction

We reviewed a total of 1403 abstracts and 277 complete articles for all KQs. No RCTs comparing screening with no screening were located for KQ1. We found no articles for KQ2 that reported sensitivity, specificity, and yield rates in a US population using one of the three acceptable screening methods compared to an acceptable reference standard of the specified health outcomes. Seven studies reported in eight publications are included for KQ3a of which two are treatment versus no treatment. The remaining five studies are treatment comparisons. One prospective study evaluating early screening versus late screening and neonatal and maternal outcomes is included for KQ3b. Three trials reporting on the harms of screening were included for KQ4. Seven articles were found to address the harms of treatment (KQ5). Six of these seven also reported treatment outcomes in KQ3 and one is a unique reference.

Two investigators applied the inclusion/exclusion criteria to each article and marked articles for exclusion as soon as any one exclusion criteria was met. They then rated the quality of all articles meeting inclusion criteria, using the USPSTF's study-design specific criteria (Appendix B), which resulted in additional excluded articles for quality reasons. Listings of excluded articles along with the reason for exclusion are in Appendix D Table 1.

There are 13 studies included in this review: seven from the 2003 USPSTF review and six were located from searches or outside sources. One primary reviewer abstracted relevant information such as study setting, population, screening method, and outcomes into standardized evidence tables for each included article (Appendix C). A second reviewer checked the abstraction process for accuracy.

Literature Synthesis

We were unable to conduct quantitative synthesis for any key question due to the heterogeneity of the screening methods and interventions. Instead, we qualitatively summarized our findings in the results text and summary tables. For KQ3, we stratified the evidence by those trials comparing treatment versus no treatment and trials comparing treatments.

External Review Process

The USPSTF appointed four liaisons to guide the scope and reporting of this review. In addition, five outside experts provided feedback on a draft version of this evidence synthesis.

Reference List

(1) Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med* 2001; 20(3 Suppl):21-35.

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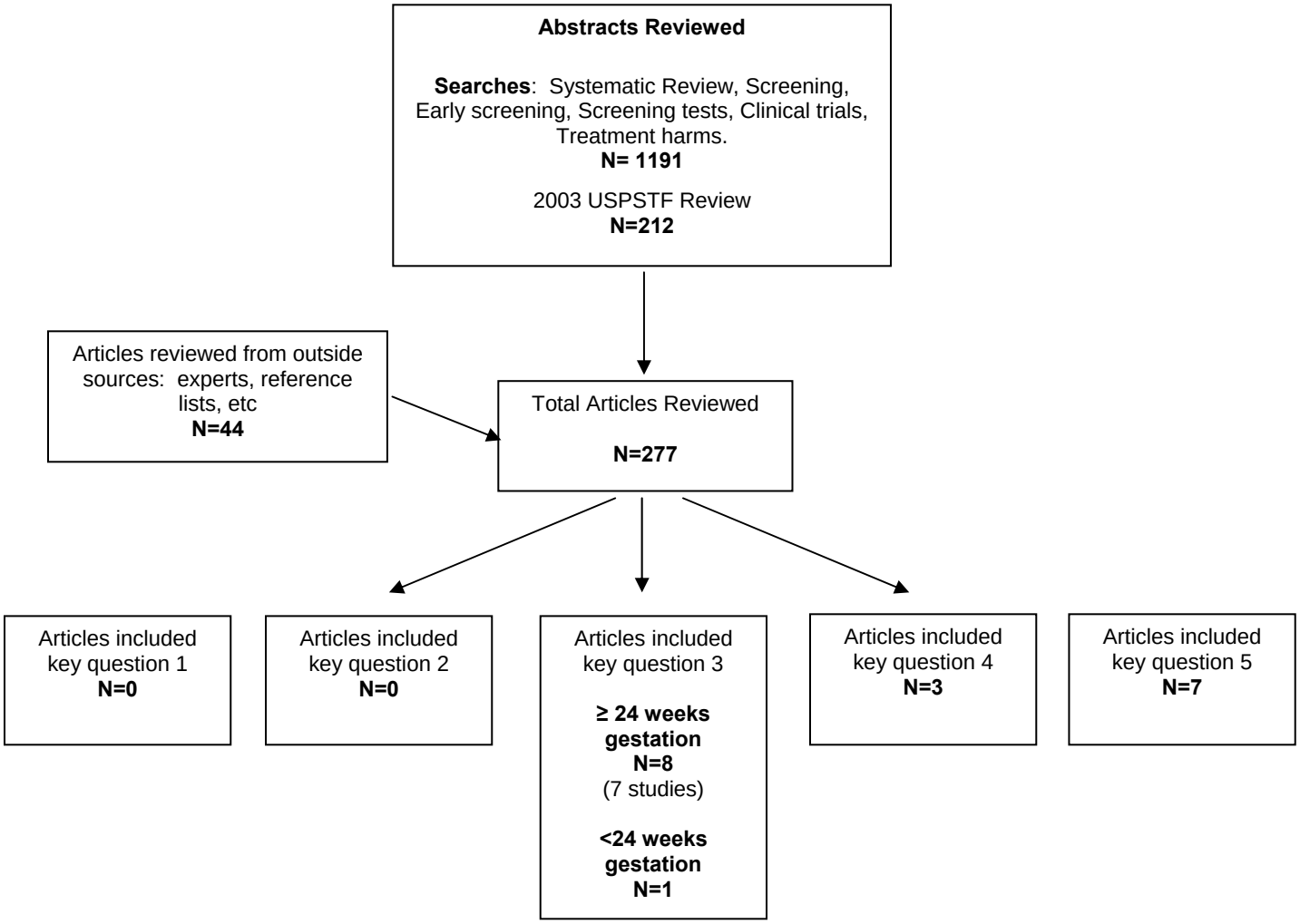
Appendix A: Figure 1. Search Results and Article Flow by Key Question



Appendix A: Table 1. Glossary of Terms

ACHOIS: Australian Carbohydrate Intolerance Study in Pregnant Women

ADA: The American Diabetes Association

APGAR: The APGAR score is a quick test performed at 1 and 5 minutes after birth to determine the physical condition of the newborn. The rating is based on a scale of 1 to 10. Ten suggests the healthiest infant, and scores below 5 indicate that the infant needs immediate assistance in adjusting to his or her new environment (http://www.nlm.nih.gov/medlineplus/ency/article/003402.htm) Date Accessed 10-23-06

BMI: Body Mass Index (BMI). Your BMI estimates whether you are at a healthy weight for your height and is calculated as kg/m^2. (http://www.nlm.nih.gov/medlineplus/ency/article/007196.htm) Date Accessed 10-23-06

DM2: Type 2 diabetes is a life-long disease marked by high levels of sugar in the blood. It occurs when the body does not respond correctly to insulin, a hormone released by the pancreas. Type 2 diabetes is the most common form of diabetes (http://www.nlm.nih.gov/medlineplus/ency/article/000313.htm) Date Accessed 10-23-06

FPG: Fasting Glucose Tolerance test. The fasting glucose tolerance test is the simplest and fastest way to measure blood glucose and diagnose diabetes. Fasting means that you have had nothing to eat or drink (except water) for 8 to 12 hours before the test

GCT: Oral Glucose Challenge Test. This is a screening test for GDM that is the first step in a two-step screening program. A 50-gram glucose drink is typically given irrespective of fasting state and blood glucose is measured one after the test. If the blood sugar exceeds a certain threshold (e.g. 140 mg/dl or 130 mg/dl) at 1 hour, then the second step of a diagnostic OGTT is performed.

LGA: The term "large for gestational age", or LGA, means a fetus or infant is larger or more developed than normal for the baby's gestational age. Gestational age is a measure of the growth and development of the fetus in the uterus and the infant after birth. A fetus or infant larger than expected for the age and gender, or with a birth weight above the 90th percentile, is referred to as LGA. (http://www.nlm.nih.gov/medlineplus/ency/article/002248.htm) Date Accessed 10-23-06

NDDG: The National Diabetes Data Group (NDDG) serves as the major Federal focus for the collection, analysis, and dissemination of data on diabetes and its complications. Drawing on the expertise of the research, medical, and lay communities, the NDDG initiates efforts to 1) define the data needed to address the scientific and public health issues in diabetes; 2) foster and coordinate the collection of these data from multiple sources; 3) identify important data sources on diabetes, and analyze and promulgate the results of these analyses to the scientific and lay public; 4) promote the timely availability of reliable data to scientific, medical, and public organizations and individuals; 5) modify data reporting systems to identify and categorize more appropriately the medical and socioeconomic impact of diabetes; 6) promote the standardization of data collection and terminology in clinical and epidemiologic research; and 7) stimulate development of new investigator-initiated research programs in diabetes epidemiology. The NDDG developed diagnostic criteria for GDM with a OGTT test.

NICHD: National Institute of Child Health & Human Development. The NICHD, established by Congress in 1962, conducts and supports research on topics related to the health of children, adults, families, and populations. (http://www.nichd.nih.gov/about/) Date Accessed 10-23-06

NPH: NPH is a type of human insulin with intermediate onset of action. Insulin is a naturally-occurring hormone secreted by the pancreas. Insulin is required by the cells of the body in order for them to remove and use glucose from the blood. From glucose the cells produce the energy that they need to carry out their functions. Regular (rapid onset of action, short duration of action) and NPH (slower onset of action, longer duration of action) human insulin are the most commonly-used preparations. Regular insulin has an onset of action (begins to reduce blood sugar) within 30 minutes of injection, reaches a peak effect at 2-3 hours, and has effects that last up to about 6 hours. NPH insulin is an insulin with an intermediate duration of action. It has an onset of action starting about 2 hours following injection. It has a peak effect 4-12 hours after injection, and an effective duration of action about 12-18 hours. (http://www.diabetes.org/type-1-diabetes/basics.jsp) Date Accessed 10-23-06

OGTT: Oral Glucose Tolerance Test. This is a test to diagnose GDM that may be performed either following an abnormal GCT (in a two-step screening program) or as the initial screening and diagnostic test (one-step). Women have a fasting blood test (after fasting overnight), and then are given a glucose drink (either 75 gram or 100gram) and have hourly blood samples taken to measure glucose up to 3 hours after the drink. There are differing criteria internationally used for what glucose threshold defines GDM with the OGTT.

WHO: World Health Organization

Appendix A: Table 2. Search Strategies

Systematic Review
Database: MedLine, DARE, CDSR, HTA
2000 to September 2006
1 "Diabetes, Gestational"[MeSH:NoExp]
2 "Fetal Macrosomia"[MeSH]
3 "gestational diabetes"[ti]
4 gdm[ti]
5 macrosomia[ti]
6 antepartum[tiab] AND surveillance[tiab]
7 1 OR 2 OR 3 OR 4 OR 5 OR 6
8 "gestational diabetes"[tiab]
9 "gestational diabetic*"[tiab]
10 gdm[tiab]
11 macrosomia[tiab]
12 8 OR 9 OR 10 OR 11
13 12 AND (in process[sb] OR publisher[sb])
14 7 OR 13
15 14 AND systematic[sb]
16 14 AND systematic[sb] Field: All Fields, Limits: Publication Date from 2000 to 2006, English

Screening
Database: MedLine
2000 to September 2006
1 Diabetes, Gestational/
2 gestational diabet$.ti,ab.
3 1 or 2
4 Mass Screening/
5 screen$.ti,ab.
6 4 or 5
7 3 and 6
8 Diabetes, Gestational/di [Diagnosis]
9 7 or 8
10 limit 9 to english language
11 limit 10 to humans
12 limit 10 to animals
13 12 not 11
14 10 not 13
15 limit 14 to yr="2000 - 2006"

Early screening
Database: MedLine
1966 to 1999
1 Diabetes, Gestational/
2 gestational diabet$.ti,ab.
3 Pregnancy in Diabetics/
4 1 or 2 or 3
5 Mass Screening/
6 screen$.ti,ab.
7 5 or 6
8 4 and 7
9 Diabetes, Gestational/di [Diagnosis]
10 Pregnancy in Diabetics/di [Diagnosis]
11 8 or 9 or 10
12 Pregnancy Trimester, First/
13 first trimester.ti,ab.
14 first pregnancy trimester.ti,ab.
15 Pregnancy Trimester, Second/
16 second trimester.ti,ab.
17 second pregnancy trimester.ti,ab.
18 early.ti,ab.

19 earlier.ti,ab.
20 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21 11 and 20
22 limit 21 to english language
23 limit 22 to humans
24 limit 22 to animals
25 24 not 23
26 22 not 25
27 limit 26 to yr="1966 - 1999"

Screening Tests
Database: MedLine
2000 to September 2006
1 Glucose Tolerance Test/
2 oral glucose tolerance.ti,ab.
3 ogtt.ti,ab.
4 glucose challenge test$.ti,ab.
5 Glucose Intolerance/
6 Blood Glucose/
7 Diabetes, Gestational/
8 gestational diabet$.ti,ab.
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10 Pregnancy/
11 pregnan$.ti,ab,hw.
12 10 or 11
13 9 and 12
14 "Sensitivity and Specificity"/
15 "Predictive Value of Tests"/
16 ROC Curve/
17 specificit$.ti,ab.
18 sensitiv$.ti,ab.
19 predictive value.ti,ab.
20 accurac$.ti,ab.
21 False Negative Reactions/
22 False Positive Reactions/
23 Diagnostic Errors/
24 exp "Reproducibility of Results"/
25 Reference Values/
26 Reference Standards/
27 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28 13 and 27
29 1 or 2 or 3 or 4
30 12 and 29
31 limit 30 to (clinical trial or controlled clinical trial or randomized controlled trial)
32 clinical trials/ or controlled clinical trials/ or randomized controlled trials/
33 double-blind method/ or random allocation/ or single-blind method/
34 random$.ti,ab.
35 32 or 33 or 34
36 30 and 35
37 Glucose Tolerance Test/st [Standards]
38 28 or 31 or 36 or 37
39 limit 38 to english language
40 limit 39 to humans
41 limit 39 to animals
42 41 not 40
43 39 not 42
44 limit 43 to yr="2000 - 2006"

Clinical Trials
Database: MedLine, Cochrane Central Registry of Controlled Trials
2000 to September 2006

1 Diabetes, Gestational/
2 gestational diabet$.ti,ab.
3 1 or 2
4 limit 3 to (clinical trial or controlled clinical trial or randomized controlled trial)
5 clinical trials/ or controlled clinical trials/ or randomized controlled trials/
6 double-blind method/ or random allocation/ or single-blind method/
7 random$.ti,ab.
8 5 or 6 or 7
9 3 and 8
10 4 or 9
11 limit 10 to english language
12 limit 11 to humans
13 limit 11 to animals
14 13 not 12
15 11 not 14
16 limit 15 to yr="2000 - 2006"

Treatment Harms

Database: MedLine
2000 to September 2006

1 Diabetes, Gestational/dh, dt, pc, th [Diet Therapy, Drug Therapy, Prevention & Control, Therapy]
2 Insulin/
3 Glyburide/
4 Metformin/
5 Sulfonylurea Compounds/
6 Hypoglycemic Agents/
7 (administration dosage or "therapeutic use").fs.
8 treat$.ti,ab,hw.
9 therapy.ti,ab,hw.
10 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11 Diabetes, Gestational/
12 gestational diabet$.ti,ab.
13 11 or 12
14 10 and 13
15 1 or 14
16 (adverse effects or mortality or poisoning or toxicity).fs.
17 adverse effect$.ti,ab.
18 harm$.ti,ab.
19 Prenatal Exposure Delayed Effects/
20 Abnormalities, Drug-Induced/
21 anxiety.ti,ab,hw.
22 depression.ti,ab,hw.
23 Depressive Disorder/
24 labeling.ti,ab.
25 labelling.ti,ab.
26 labeled.ti,ab.
27 labelled.ti,ab.
28 Hypoglycemia/
29 Hypoglycemi$.ti,ab.
30 Hypoglycaemi$.ti,ab.
31 Acidosis/
32 Acidosis, Lactic/
33 acidosis.ti,ab.
34 Teratogens/
35 teratogen$.ti,ab.
36 pain.ti,ab,hw.
37 unnecessary.ti,ab,hw.
38 Pre-Eclampsia/
39 Pre-Eclamp$.ti,ab.
40 preeclamp$.ti,ab.
41 Hypertension, Pregnancy-Induced/

42 pregnancy induced hypertension.ti,ab.
43 gestational hypertension.ti,ab.
44 Hypertension/ and Pregnancy Complications, Cardiovascular/
45 Infant Mortality/
46 infant mortality.ti,ab.
47 neonatal mortality.ti,ab.
48 perinatal mortality.ti,ab.
49 hyperbilirubinemia, neonatal/ or jaundice, neonatal/
50 hyperbilirubin$.ti,ab.
51 Phototherapy/
52 phototherapy.ti,ab.
53 Polycythemia/
54 Polycythemi$.ti,ab.
55 Polycythaemi$.ti,ab.
56 Respiratory Distress Syndrome, Newborn/
57 Respiratory Distress.ti,ab.
58 Intensive Care, Neonatal/
59 neonatal intensive care.ti,ab.
60 nicu.ti,ab.
61 Infant, Small for Gestational Age/
62 Small for Gestational Age.ti,ab.
63 Fetal Growth Retardation/
64 Intrauterine Growth Retardation.ti,ab.
65 Intrauterine Growth Restriction.ti,ab.
66 IUGR.ti,ab.
67 Fetal Growth Retardation.ti,ab.
68 Fetal Growth Restriction.ti,ab.
69 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68
70 15 and 69
71 limit 70 to english language
72 limit 71 to humans
73 limit 71 to animals
74 73 not 72
75 71 not 74
76 limit 75 to yr="2000 - 2006"

Appendix A: Table 3. Inclusion and Exclusion Criteria for Key Questions

Inclusion Criteria:

Key Question 1

1. Study evaluates screening for gestational diabetes < 24 weeks or ≥ 24 weeks in a population relevant to primary care
2. Acceptable screening methods: one-step (75 g or 100 g); two step (50 g/100 g; 50 g/75 g); fasting glucose for <24 weeks
3. Positive screen includes:
    a. 50 g: ≥130 mg/dL or ≥140 mg/dL
    b. 75 g: Carpenter & Coustan; ADA; or WHO criteria
    c. 100 g: Carpenter & Coustan; or NDDG criteria
4. Primary outcomes systematically identified
    a. Maternal: mortality; pre-eclampsia/pregnancy induced hypertension
    b. Perinatal outcomes: mortality; brachial plexus injury; fractured clavicle; admission to NICU for treatment of hypoglycemia, hyperbilirubinemia, or respiratory distress syndrome
    c. Secondary or intermediate outcomes (not systematically included): macrosomia; cesarean section; induction of labor; pre-term birth; maternal 3rd or 4th degree perineal lacerations
5. Study Design: RCT, CCT or prospective cohort if no RCT available

Key Question 2

1. Study evaluates screening test sensitivity, specificity, reliability and yield
2. Acceptable screening methods: one-step (75 g or 100 g); two step (50 g/100 g; 50 g/75 g); fasting glucose for < 24 weeks
3. Positive screen includes:
    a. 50 g: ≥130 mg/dL or ≥140 mg/dL
    b. 75 g: Carpenter & Coustan; ADA; or WHO criteria
    c. 100 g: Carpenter & Coustan; or NDDG criteria
4. Outcomes: sensitivity, specificity, yields, reliability
5. Study Design: RCT, CCT, Observational
6. Uses sensitivity and specificity criterion to assess primary health outcomes specified in the analytic framework

Key Question 3

1. Study evaluates treatment of gestational diabetes including glyburide, any sulfonylurea, metformin, insulin, diet and/or exercise therapy
2. Acceptable screening methods: one-step (75 g or 100 g); two step (50 g/100 g; 50 g/75 g); fasting glucose < 24 weeks
3. Positive screen includes:
    a. 50 g: ≥130 mg/dL or ≥140 mg/dL
    b. 75 g: Carpenter & Coustan; ADA; or WHO criteria
    c. 100 g: Carpenter & Coustan; or NDDG criteria
4. Primary outcomes systematically identified
    a. Maternal: mortality; pre-eclampsia/pregnancy induced hypertension
    b. Perinatal outcomes: mortality; brachial plexus injury; fractured clavicle; admission to NICU for treatment of hypoglycemia, hyperbilirubinemia, or respiratory distress syndrome
    c. Secondary or intermediate outcomes (not systematically identified): macrosomia; cesarean section; pre-term birth; maternal 3rd or 4th degree perineal lacerations
5. Study Design: RCT, CCT, or prospective cohort if no RCT available

Key Question 4

1. Study presents harms of screening tests accepted in KQ1 or KQ3
2. Acceptable screening methods: one-step (75 g or 100 g); two step (50 g/100 g; 50 g/75 g); fasting glucose < 24 weeks
3. Positive screen includes:
    a. 50 g: ≥130 mg/dL or ≥140 mg/dL
    b. 75 g: Carpenter & Coustan; ADA; or WHO criteria
    c. 100 g: Carpenter & Coustan; or NDDG criteria
    d. Exception allowed if used an accepted screening method and nonstandard cutoff criteria
4. Study design: RCT, CCT, or prospective cohort if no RCT available

Key Question 5

1. Study presents harms of treatment accepted in KQ3
2. Acceptable screening methods: one-step (75 g or 100 g); two step (50 g/100 g; 50 g/75 g); fasting glucose < 24 weeks
3. Positive screen includes:
    a. 50 g: ≥130 mg/dL or ≥140 mg/dL
    b. 75 g: Carpenter & Coustan; ADA; or WHO criteria
    c. 100 g: Carpenter & Coustan; or NDDG criteria
    d. Exception allowed if used an accepted screening method and nonstandard cutoff criteria
4. Study design: RCT, CCT, or prospective cohort if no RCT available

Exclusion Criteria:

1. Not an acceptable study design, including methodology of accepted study types or mixing GDM/IGT/Normal groups
2. Not generalizable to US population
3. Does not address morbidity and/or mortality
4. Not one of established screening criteria used (hgbA1c), or 50 gram OGTT used as a diagnostic test (non-standard) or 75/100 gram 100 gram OGTT diagnostic tests using different diagnostic criteria than the current standards as outlined in our workplan (e.g., cutoffs +SD to a different population mean)
5. No info on yield (prevalence), sens/spec or reliability
6. Not one of established screening criteria used (e.g. HgbA1c)
7. Not one of the included treatments for GDM; (e.g., thiazolidinediones)
8. Editorials, comments, and letters
9. Non-systematic reviews
10. Does not address one of the key questions
11. Systematic Review, but search strategy too old to be relevant for our interval update of the USPSTF 2003 GDM review
12. SER used as source document
13. Prevalence outside U.S
14. Prevalence only articles
15. Natural history only articles
16. Does not report sensitivity and specificity criterion to assess specified health outcomes in the Analytic Framework
17. Poor quality

Appendix B: Table 1. USPSTF Hierarchy of Research Design and Quality Rating Criteria.[1]

Hierarchy of Research Design

I	Properly conducted randomized controlled trial (RCT)
II-1:	Well-designed controlled trial without randomization
II-2:	Well-designed cohort or case-control analytic study
II-3:	Multiple time series with or without the intervention; dramatic results from uncontrolled experiments
III:	Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees

Design-Specific Criteria

Systematic Reviews

Criteria:

- Comprehensiveness of sources considered/search strategy used
- Standard appraisal of included studies
- Validity of conclusions
- Recency and relevance are especially important for systematic reviews

Case-Control Studies

Criteria:

- Accurate ascertainment of cases
- Nonbiased selection of cases/controls with exclusion criteria applied equally to both
- Response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variables

Randomized Controlled Trials and Cohort Studies

Criteria:

- Initial assembly of comparable groups
    - -for RCTs: adequate randomization, including first concealment and whether potential confounders were distributed equally among groups.
    - -for cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of the interventions
- All important outcomes considered

Diagnostic Accuracy Studies

Criteria:

- Screening test relevant, available for primary care, adequately described
- Study uses a credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Handles indeterminate result in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Administration of reliable screening test

1. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med* 2001; 20(3 Suppl):21-35.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Type of trial	Length of trial	Study Setting	Primary Study Objectives/ Outcomes	Inclusion/ Exclusion Criteria	N, Subjects	BMI	Race/ Ethnicity	Gravidity/ Parity	Age
Treated vs. Untreated										
Crowther 2005[39] ACHOIS	RCT	Screened 16-30 weeks f/u 3 mos. Post-partum	18 centers: 14 Australia; 4 UK Initiated prior to change in WHO criteria Recruitment 9/93-6/03	To assess whether treatment of GDM reduces perinatal complications; or has an effect on maternal outcomes; mood; or quality-of-life	**Inclusion**: Singleton or twin pregnancy 16-30 weeks gestation; RF for GDM or 50-g GCT (≥7.8 mmol/l) AND 75-g OGTT (24-34 weeks gestation) 2-hr plasma glucose 7.8-11.0 mmol/l with fasting plasma glucose <7.8 mmol/l **Exclusion**: Previously treated GDM; active chronic disease (except essential hypertension)	N=1,000 **IG:** 490 **CG:** 510	Median (Interquartile range) **IG:** 26.8 (23.3-31.2) **CG:** 26.0 (22.9-30.9)	**IG:** 73% White 19% Asian 9% Other **CG**: 78% White 14% Asian 8% Other	Primiparous N (%) **IG:** 212 (43%) **CG:** 251 (49%)	Mean (SD) **IG:** 30.9 (5.4) **CG:** 30.1(5.5)

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Screening Test/ Mode of Diagnosis	Test preparation	Screening test results	Gestational age at screening	Previous GDM or macrosomic infant	Intervention	Control	Follow-up Measures Surveillance	Insulin required
Treated vs. Untreated									
Crowther 2005[39] ACHOIS	Two steps Step 1: RF or 50-g GCT (≥7.8 mmol/l) 1-hr cut-off (93% were positive with 50-g) Step 2: 75 g OGTT	50-g GCT NR 75 g OGTT 48 hr normal diet; 8 hr overnight fast	Median (Interquartile range) **GCT, mmol/l** **IG:** 8.8 (8.2-9.7) **CG:** C: 8.8 (8.3-9.7) **75-g OGTT, mmol/l** **IG:** 8.6 (8.1-9.3) **CG:** 8.5 (8.1-9.1)	Median (Interquartile range) **IG:** 29.1 weeks (28.2-30.0) **CG:** 29.2 weeks (28.2-30.0)	Previous pregnancy ending in perinatal death **IG:** 12/278 (4%) **CG:** 7/259 (3%)	**IG:** Replicated clinical care in which universal screening and treatment for GDM are available Received a slip indicating a diagnosis of glucose intolerance and the plan for intervention Intervention was individualized dietary advice from dietician; instructions to self-monitor glucose QID until within specified range for 2 weeks; insulin initiated if not in range and titrated to glucose range	**CG:** Replicated clinical care in which screening for GDM was not available Received a slip indicating they did not have gestational diabetes A proportion (not fewer than one in 5) had normal OGTT results assigned to routine care to help maintain blinding Glucose monitoring and insulin initiated at the discretion of the attending clinician	Visit with a dietician 453 (92%) IG vs. 51 (10%) CG. Visit with a diabetes educator 460 (94%) IG vs. 56 (11%) CG. Number of antetal visits (median) 5.0 IG vs. 5.2 CG. Number of MD visits after enrollment (median) 3 IG vs. 0 CG.	**IG:** 100 (20%) **CG:** 17 (3%)

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Maternal hypoglycemia	Glycemic control/ separation	Perineal injury	Maternal Wt change/ separation	Induction/ Delivery Mode	Preeclampsia/ PIH	Death	Depression/Anxiety	QOL (ante & postpartum)
Treated vs. Untreated									
Crowther 2005[39] ACHOIS	NR	NR	Any perineal trauma, N (%) **IG:** 255 (52%) **CG:** 254 (50%) Adj RR: 1.05 (0.93 to 1.19) p=0.42	Weight gain from first to last prenatal visit (kg; mean, sd) **IG:** 8.1 (0.3) **CG:** 9.8 (0.4) Adj p =0.01	Adj RR Induction of Labor: 1.36 (1.15-1.62) p,0.001 C-section overall 0.97 (0.81-1.16) p=0.73 Also non-significant for elective and emergency c-section	Adj RR 0.70 (0.51-0.95) p=0.02 PIH def: BP ≥ 140/90 mmHg on 2 occasions more than 4 hours apart	NR	Depression Adj RR 0.46 (0.29-0.73) p=0.001 Defined as: Likely depressed (EPDS score >12) at 3 months post-partum Anxiety score Adj mean diff -0.3 (-0.9-0.4; p=0.41)	Antepartum: **IG:** SF-36 increased emotional role, overall physical component, health state utility 3 mos. Post-partum No sig diff

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Stillbirth	Neonatal death	Shoulder dystocia/ BPI	Clavicle FX	Respiratory distress	Hyperbilirubinemia/ jaundice	Hypoglycemia/ Hypocalcemia	NICU admission for treatment	Birth weight
Crowther 2005[39] ACHOIS	**IG:** 0 **CG:** 3 p=0.26 RR not calculated as zero in IG	**IG:** 0 **CG:** 2 p=0.50 RR not calculated as zero in IG	**Shoulder Dys:** Adj RR 0.460.19-1.10) p=0.08 **Nerve palsy** **IG**:0 **CG**: 3 p=0.11 RR not calculated as zero in IG	Bone Fracture* **IG:** 0 **CG:** 1 p=0.38 *RR not calculated as zero in IG	Adj RR 1.52 (0.86-2.71) p=0.15 RDS def: Needed oxygen >4 hrs. after birth	Adj RR 0.93 (0.63-1.37) p=0.72 Defined as: Requiring phototherapy	Adj RR 1.42 (0.87-2.32) p=0.16 Required IV therapy Adj mean diff 0.52 (0.05-5.69) p=1.0 Neonatal convulsions	NICU-NR "neonatal nursery" N(%) IG: 357(71) CG: 321(61) Adj RR 1.13 (1.03-1.23) p=0.01	Adj mean diff -145 g; (-219 to -70; p<0.001)

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	%LGA/ macrosomia	Other Outcomes	MV Analysis	Adverse Effects	Comments	Quality rating
Crowther 2005[39] ACHOIS	LGA Adj RR 0.62 (0.47-0.81; p<0.001) LGA def: >90%ile Macrosomia Adj RR 0.47 (0.34-0.64; p<0.001) Macrosomia def: ≥ 4kg	Combined outcome for any serious perinatal complication (death, shoulder dystocia, bone fracture, nerve palsy) Adj RR 0.33 (0.14-0.75)	NR	Marginal QOL antepartum and postpartum improved for IG	Glucose values during pregnancy NR	Good

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Type of trial	Length of trial	Study Setting	Primary Study Objectives/ Outcomes	Inclusion/ Exclusion Criteria	N, Subjects	BMI	Race/ Ethnicity	Gravidity/ Parity	Age
O'Sullivan 1966[44]	RCT	1954-1960	Patients attending the Prenatal Metabolic Clinic at Boston City Hospital	Study relationship of maternal blood glucose to pregnancy (fetal) outcomes and assess effect of diet + insulin therapy	**Inclusion:** All pregnant women attending the clinic were screened with 50g GCT; Randomized to treatment versus no treatment if 3 hr. OGTT 100g with ≥2 values: Fasting ≥ 110 mg/dl; 1 hr ≥ 170 mg/dl; 2 hr ≥ 120 mg/dl; 3 hr ≥ 110 mg/dl *(NOTE: This is whole blood and formed later basis of current criteria)* **Exclusion:** Previous diabetes; blood sugar > 300 mg/dl; classic diabetes symptoms; clinic visit ≥ 37th week gestation	**IG:** 307 **+CG:** 308 **-CG:** 328 **IG:** defined as +OGTT, treated **+CG:** defined as +OGTT but not treated **-CG:** def as normal glucose tolerance	**% Ideal Weight: N(%)** **≥ 20%** **IG:** 85 (27.7%) **+CG:** 94 (30.5%) **-CG:** 38 (11.6%) **10-19%** IG: 49 (16%) +CG: 50 (16.2%) -CG: 48 (14.6%) **-09% to +09%** **IG:** 122 (39.7%) **+CG**: 121 (39.3%) **-CG:** 162 (49.4%) **≤ -10%** **IG:** 51 (16.6%) **+CG:** 43 (14%) **-CG:** 80 (24.4%)	NR	**Mean Parity:** **IG:** 3.6 **+CG:** 3.7 **-CG:** 2.2	**Mean yrs:** **IG:** 30.3 **+CG**: 31.2 **-CG:** 25.1

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Screening Test/ Mode of Diagnosis	Test preparation	Screening test results	Gestational age at screening	Previous GDM or macrosomic infant	Intervention	Control	Follow-up Measures Surveillance	Insulin required
O'Sullivan 1966[44]	**Two Steps: Screen:** venous whole blood ≥130 mg/dl with 50 g GCT or +RF **Diagnosis:** 100 g OGTT (3 hr).	250 g carbohydrate daily diet x 3 days prior to OGTT; Fasting prior to test (length of time NR)	NR other than in the same range for randomization to treatment	NR; except "women who had normal glucose tolerance in one trimester received repeat tests in subsequent trimesters" and excluded if ≥ 37 weeks	RF to have OGTT included prior fetal death, neonatal death, congenital anomaly, baby weighing ≥ 9lb., prematurity (<5 lb 6 oz), or toxemia (excessive weight gain, HTN, or proteinuria) in 2 or more pregnancies; however frequency in this sample NR	**IG:** Individualized diet (40%CHO, 30cal/kg ideal body weight, 1.5-2g protein/kg ideal body weight) + AM NPH Insulin titrated to glucosuria (daily home testing or in clinic), starting dose 10 units	+**CG; -CG:** Routine OB and diet instructions	2,701 post-prandial blood sugars in 432 patients, average of 6 blood draws per person , abnl values set arbitrarily at >100mg/dl fasting and 150 mg/dl 2hr pp)*NOTE: Capillary home glucose monitroing was not feasible at the time of this study.)*	**IG:** All given insulin +**CG:** NR **-CG:** NR

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Maternal hypoglycemia	Glycemic control/ separation	Perineal injury	Maternal Wt change/ separation	Induction/ Delivery Mode	Preeclampsia/ PIH	Death	Depression/Anxiety	QOL (ante & postpartum)
O'Sullivan 1966[44]	NR	Overall # abnormal values: IG and +CG "had significantly more abnormal blood sugars" than -CG but "were not significantly different from each other" p=NR Differences in mean glucose values: -CG "had significantly lower mean blood sugar levels for each pp time period" (p=NR) IG vs. +CG did not differ at 1/2-1, 2-3, 3-4 hrs pp (p=NR). mean (SD) Glucose at 1-2 hrs pp* **IG**: 88.8 (23.1) **+CG**: 92.6 (23.2) p<0.01 Glucose at >4 hr pp or fasting* **IG**: 69.1 (16.9) **+CG**: 74.3 (15.4) p<0.05	NR	NR	NR	NR	NR	NR	NR

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Stillbirth	Neonatal death	Shoulder dystocia/ BPI	Clavicle FX	Respiratory distress	Hyperbilirubinemia/ jaundice	Hypoglycemia/ Hypocalcemia	NICU admission for treatment	Birth weight
O'Sullivan 1966[44]	**IG:** 8 (2.6%) **+CG:** 8 (2.6%) **-CG:** 4 (1.2%) Defined: Death of viable fetus > 28 weeks	**IG:** 5 (1.6%) **+CG:** 7 (2.3%) **-CG**: 2 (0.6%) Total viable losses: **IG**: 13 (4.3%)*† **+CG**: 15 (4.9%)* **-CG**: 6 (1.9%)*† *p<0.01 for IG and +CG vs -CG †p<0.05 for IG vs -CG	NR	NR	NR	NR	NR	NR	NR

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	%LGA/ macrosomia	Other Outcomes	MV Analysis	Adverse Effects	Comments	Quality rating
O'Sullivan 1966[44]	**IG:** 13 (4.3%) **+CG:** 40 (13.1%)) **-CG:** 12 (3.7%) Note: overall p-value NR, but IG "showed a sig diff (from +CG) for all but weight >4.5-5.0 lb." Def: ≥ 9lbs. -CG and IG "are not significantly different from each other" p=NR % with large babies by Maternal wt status ≤9%: **IG**: 2.3% **+CG**: 10.% **-CG**: 2.5% Maternal wt status ≥10%: **IG**: 7.6% **+CG**: 16.4% **-CG**: 7.0%	**Congenital Abnormality:** **IG:** 40 (13.1%) **+CG**: 49 (16%) **-CG:** 44 (13.6%) NS, p=NR **Born Premature:** **IG:** 26 (8.5%) **+CG:** 24 (7.8%) **-CG:** 25 (7.7%) NS, p=NR	NR	NR	Across all study groups, overweight women had higher % of large babies. In discussion section authors stated that 97% of IG and +CG had normal f/u OGTT postpartum, so true GDM .	Fair

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Type of trial	Length of trial	Study Setting	Primary Study Objectives/ Outcomes	Inclusion/ Exclusion Criteria	N, Subjects	BMI	Race/ Ethnicity	Gravidity/ Parity	Age
Treatment Comparison										
Langer 2000[42] Langer 2005[47]	RCT	Screened 11-33 weeks F/U to postpartum	Inner-city maternal health clinics in San Antonio, TX	To assess whether glyburide is an effective alternative to insulin for control of hyperglycemia during pregnancy; glycemic control; maternal and neonatal complications.	**Inclusion**: Singleton pregnancy 11-33 weeks; 50-g GCT > 130 mg/dL at 1 hr. AND 100-g OGTT with ≥ 2 abnormal glucose values by C&C criteria. Those with fasting plasma glucose <95 mg/dL were initially treated with diet and enrolled if levels increased to ≥95 mg/dL or postprandial levels were ≥ 120 mg/dL. **Exclusion**: NR	N=404 **IG_{GLY}:** 201 **IG_{INS}:** 203	BMI ≥ 27.3 prior to pregnancy N (%) **IG_{GLY}:** 141 (70) **IG_{INS}:** 132 (65) Pre-pregnancy weight, kg **IG_{GLY}**: 74±19 **IG_{INS}**: 76±18	83% Hispanic 12% White 5% Black	Nulliparity N (%) **IG_{GLY}:** 56 (28) **IG_{INS}:** 59 (29)	yrs, Mean±SD **IG_{GLY}:**29±7 **IG_{INS}:** 30±6

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Screening Test/ Mode of Diagnosis	Test preparation	Screening test results	Gestational age at screening	Previous GDM or macrosomic infant	Intervention	Control	Follow-up Measures Surveillance	Insulin required
Treatment Comparison									
Langer 2000[42] Langer 2005[47]	Step 1: 50-g GCT > 130 mg/dL Step 2: 100-g OGTT with ≥ 2 abnormal glucose values by C&C criteria.	Fasting for OGTT	Screening plasma glucose mg/dL,mean±SD **IG_{GLY}:** 169±28 **IG_{INS}:** 169±31 OGTT mg/dL,mean±SD <u>Fasting</u> **IG_{GLY}:** 97±14 **IG_{INS}:** 98±16 <u>1 hr</u> **IG_{GLY}:** 197±31 **IG_{INS}:** 201±30 <u>2 hr</u> **IG_{GLY}:** 174±31 **IG_{INS}:** 174±29 <u>3 hr</u> **IG_{GLY}:** 140±37 **IG_{INS}:** 134±37	wks, mean±SD **IG_{GLY}:**24±7 **IG_{INS}:** 25±7	Previous GDM N(%) **IG_{GLY}:** 24(12) **IG_{INS}:** 22(11) Previous macrosomic infant N(%) **IG_{GLY}:** 36(18) **IG_{INS}:** 45(22)	**IG_{GLY}:** Initial oral dose of 2.5 mg of glyburide in the morning, when indicated the dose increased the following week by 2.5 mg and thereafter by 5 mg up to a total of 20mg. All women were provided standard nutritional instruction for three meals and four snacks daily.	**IG_{INS}:** Initial insulin dose of 0.7 unit/kg of body weight at admission given subcutaneously 3 times daily and increased weekly as necessary. All women were provided standard nutritional instruction for three meals and four snacks daily.	Number of clinic visits attended: mean±SD **IG_{GLY}:** 11±5 **IG_{INS}:** 12±6 Number of measurements of glucose/day: **IG_{GLY}:** 4±2 **IG_{INS}** 4±2 Serum c-peptide **IG_{INS}:** 3.8±2.3 **IG_{GLY}:** 3.4±1.5	**IG_{GLY}:** 8 women (4%) did not achieve good glycemic control and were switched to insulin.

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

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Author, Year	Maternal hypoglycemia	Glycemic control/ separation	Perineal injury	Maternal Wt change/ separation	Induction/ Delivery Mode	Preeclampsia/ PIH	Death	Depression/Anxiety	QOL (ante & postpartum)
Treatment Comparison									
Langer 2000[42] Langer 2005[47]	Number with blood glucose < 40 mg/dL: **IG_{GLY}:** 4 **IG_{INS}:** 41 (p=0.03) None had more than 6% of measurements below this value None reported severe symptoms with hypoglycemia	During treatment: blood glucose mg/dL, mean±SD <u>Fasting</u> **IG_{GLY}:** 98±13 **IG_{INS}:** 96±16 <u>Preprandial</u> **IG_{GLY}:** 95±15 **IG_{INS}:** 97±14 <u>Postprandial</u> **IG_{GLY}:** 113±22 **IG_{INS}:** 112±15 <u>Mean</u> **IG_{GLY}:** 105±16 **IG_{INS}:** 105±18 <u>Glycosylated Hemoglobin (%)</u> **IG_{GLY}:** 5.5±0.7 **IG_{INS}:** 5.4±0.6 None were sig diff	NR	Weight gain lb, mean±SD **IG_{GLY}:** 21±17 **IG_{INS}:** 21±15 Weight measured prior to pregnancy and week prior to delivery.	Cesarean **IG_{GLY}:** 23% **IG_{INS}:** 24%	Preeclampsia **IG_{GLY}:** 6% **IG_{INS}:** 6%	NR	NR	NR

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

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Author, Year	Stillbirth	Neonatal death	Shoulder dystocia/ BPI	Clavicle FX	Respiratory distress	Hyperbilirubinemia/ jaundice	Hypoglycemia/ Hypocalcemia	NICU admission for treatment	Birth weight
Treatment Comparison									
Langer 2000[42] Langer 2005[47]	N (%) **IG_{GLY}:** 1(0.5) **IG_{INS}:** 1(0.5) p=0.99	N (%) **IG_{GLY}:** 1(0.5) **IG_{INS}:** 1(0.5) p=0.99	NR	NR	N (%) **IG_{GLY}:** 4(2) **IG_{INS}:** 6(3) p=0.52 Needed support	N (%) **IG_{GLY}:** 12(6) **IG_{INS}:** 8(4) p=0.36 Defined: ≥ 12 mg/dL	Hypoglycemia N (%) **IG_{GLY}:** 18(9) **IG_{INS}:** 12(6) p=0.25 Defined: 2 consecutive values ≤ 40 mg/dL Hypocalcemia N (%) **IG_{GLY}:** 2(1) **IG_{INS}:** 2(1) p=0.99 Defined: ≤ 7.0 mg/dL	N (%) **IG_{GLY}:** 12(6) **IG_{INS}:** 14(7) p=0.68	g, mean±SD **IG_{GLY}:** 3256±543 **IG_{INS}:** 3194±598 p=0.28

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	%LGA/ macrosomia	Other Outcomes	MV Analysis	Adverse Effects	Comments	Quality rating
Treatment Comparison						
Langer 2000[42] Langer 2005[47]	N (%) **IG_{GLY}:** 14(7) **IG_{INS}:** 9(4) p=0.26 Defined as >4000g %LGA ≤95 mg/dL on OGTT $_{IGGLY}$: 8.8% $_{IGINS}$: 7.7% >95 mg/dL on OGTT $_{IGGLY}$: 18.4% $_{IGINS}$: 17.8% p=0.01 for the difference between low and high fasting glucose Defined as ≥90th %ile in their population	Congenital anomaly N (%) **IG_{GLY}:** 5(2) **IG_{INS}:** 4(2) p=0.74		None reported severe symptoms such as: confusion, poor coordination, double vision, headache, or combativeness, or inability to treat themselves with hypoglycemia (<40 mg/dL).	Glyburide not detected in cord blood of any infant.	Good

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Type of trial	Length of trial	Study Setting	Primary Study Objectives/ Outcomes	Inclusion/ Exclusion Criteria	N, Subjects	BMI	Race/ Ethnicity	Gravidity/ Parity	Age
Bancroft 2000[38]	RCT		2 specialist diabetes clinics in the UK.	To determine whether less intensive monitoring of blood glucose levels during pregnancy is feasible. Frequency of admission to specialty care baby unit; perinatal morbidity; maternal inconvenience.	**Inclusion**: Blood glucose levels-Fasting < 7.0 mmol/L and between 7.8-11.0 mmol/L 2 hrs after 75 g OGTT. **Exclusion**: NR	N=68 **$IG_{DietgluM}$:** 32 **IG_{Diet}:**36	Mean(SD) **$IG_{DietgluM}$**: 31.2(6.7) **IG_{Diet}**: 27.5(6.1)	N(%) **$IG_{DietgluM}$**: Asian 10(31) Caucasian 22(69) **IG_{Diet}**: Asian 11(31) Caucasian 25(69)	Parity Median (range) **$IG_{DietgluM}$**: 2(0-6) **IG_{Diet}**: 1(0-9)	At delivery Mean(SD) **$IG_{DietgluM}$:** 29.7(6.23) **IG_{Diet}:** 31.9(5.17)

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Screening Test/ Mode of Diagnosis	Test preparation	Screening test results	Gestational age at screening	Previous GDM or macrosomic infant	Intervention	Control	Follow-up Measures Surveillance	Insulin required
Bancroft 2000[38]	One step: 75 g OGTT < 7.0 mmol/L fasting and 7.8 to 11.0 mmol/L after 2 hours	NR	HbA1c Mean(SD) **$IG_{DietgluM}$**: 5.3(0.83) **IG_{Diet}**: 5.6(0.96) NS Fasting, mmol/L Median(range) **$IG_{DietgluM}$**: 4.6(3.5-5.8) **IG_{Diet}**: 4.7(3.5-7.0) NS 2 hr glucose **$IG_{DietgluM}$**: 8.5(7.9-10.8) **IG_{Diet}**: 8.9(7.8-11.0) p=0.025	Median (range) **$IG_{DietgluM}$**: 31(24-38) **IG_{Diet}**: 32 (15-37)	NR	**$IG_{DietgluM}$:** Standard dietary advice restricting carbohydrates to 185 g/day; diet sheet listing caloric values of common foods; glucose monitoring 1-2 hrs post meal 5x/week; glycosylated Hb monthly. Insulin introduced if ≥5 measurements > 7.0 mmol/L in 1 week. Care consisted of serial ultrasounds for growth, amniotic fluid levels and Doppler studies of umbilical artery. **IG_{Diet}:** Dietary advice as above. Glycosylated Hb monthly with results not viewed within study period. If clinician became concerned, woman could be withdrawn at any time.	NA	Monthly glycosylated Hb measurements; serial ultrasound.	**$IG_{DietgluM}$: 6 (**19%) **IG_{Diet}:** 0

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

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Author, Year	Maternal hypoglycemia	Glycemic control/ separation	Perineal injury	Maternal Wt change/ separation	Induction/ Delivery Mode	Preeclampsia/ PIH	Death	Depression/Anxiety	QOL (ante & postpartum)
Bancroft 2000[38]	NR	NR	NR	NR	Cesarean section N(%) **$IG_{DietgluM}$**: 10(31) **IG_{Diet}**: 11(31)	NR	None	NR	NR

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

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Author, Year	Stillbirth	Neonatal death	Shoulder dystocia/ BPI	Clavicle FX	Respiratory distress	Hyperbilirubinemia/ jaundice	Hypoglycemia/ Hypocalcemia	NICU admission for treatment	Birth weight
Bancroft 2000[38]	None	None	**$IG_{DietgluM}$:** 0 **IG_{Diet}:** 1	NR	NR	NR	Hypoglycemia N(%) **$IG_{DietgluM}$**: 2(6) **IG_{Diet}**: 6(17) NS (p=NR)	"special care baby unit" N(%) **$IG_{DietgluM}$**: 2(6) **IG_{Diet}**: 6(17) NS (p=NR)	kg, Mean(SD) **$IG_{DietgluM}$:** 3.58(0.55) **IG_{Diet}:** 3.62(0.55) NS (p=NR)

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	%LGA/ macrosomia	Other Outcomes	MV Analysis	Adverse Effects	Comments	Quality rating
Bancroft 2000[38]	LGA N(%) **$IG_{DietgluM}$**: 8(25) **IG_{Diet}**: 7(19) Defined: >90th %ile for gestation			F/U on N=28 in each group Postnatal diabetes N(%) **$IG_{DietgluM}$**: 0 **IG_{Diet}**: 2(7) Postnatal impaired glucose tolerance N(%) **$IG_{DietgluM}$**: 2(7) **IG_{Diet}**: 3(11)		Fair

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Type of trial	Length of trial	Study Setting	Primary Study Objectives/ Outcomes	Inclusion/ Exclusion Criteria	N, Subjects	BMI	Race/ Ethnicity	Gravidity/ Parity	Age
Jovanovic 1999[41]	RCT	Women were diagnosed at 14-32 weeks and enrolled upon failure of dietary and exercise treatment. Followed until 6 weeks postpartum	California	To compare immunologic effects of insulin lispro with those of regular human insulin in patients with gestational diabetes.	**Inclusion**: Diagnosed at 14-32 weeks of gestation who failed to adequately control glucose with diet and exercise (defined as more than 70% of home glucose readings during one week did not meet the following criteria: fasting and preprandial <90mg/dl; 1 hr post-prandial <120 mg/dl). Ultrasound exam documented an anatomically normal fetus. **Exclusion**: Prior insulin treatment; had pregestational diabetes; demonstrated significant concurrent organic disease.	N= 42 **IG_{INSana}:** 19 **IG_{INSreg}:** 23	Mean±SEM **IG_{INSana}:** 31.5±1.1 **IG_{INSreg}:** 33.3±1.2 NS	Caucasian, n **IG_{INSana}:** 2 **IG_{INSreg}:** 0 Hispanic, N **IG_{INSana}:** 17 **IG_{INSreg}:** 23	Mean±SEM Parity **IG_{INSana}:** 1.4±0.3 **IG_{INSreg}:** 1.7±0.3 NS Gravidity **IG_{INSana}:** 1.8±0.2 **IG_{INSreg}:** 2.4±0.3 NS	Mean±SEM **IG_{INSana}:** 34.2±1.3 **IG_{INSreg}:** 29.8±1.0 p<0.01

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Screening Test/ Mode of Diagnosis	Test preparation	Screening test results	Gestational age at screening	Previous GDM or macrosomic infant	Intervention	Control	Follow-up Measures Surveillance	Insulin required
Jovanovic 1999[41]	Diagnosed at 14-32 weeks of gestation who failed to adequately control glucose with diet and exercise (defined as more than 70% of home glucose readings during one week did not meet the following criteria: fasting and preprandial <90mg/dl; 1 hr post-prandial <120 mg/dl). Ultrasound exam documented an anatomically normal fetus.	NR	NR	At enrollment, Mean±SEM **IG_{INSana}:** 27.3±1.4 **IG_{INSreg}:** 25.6±1.3 NS	Previous GDM, N **IG_{INSana}:** 1 **IG_{INSreg}:** 1	Patients were instructed to administer a recommended dosage of insulin lispro five minutes prior to three meals a day. Also received NPH insulin in the morning and evening. Self blood glucose monitoring at 0-30 minutes prior to meal and at 1 hour after the start of the meal. Test meal 20% of each woman's calculated caloric need. Insulin lispro injected 5 min, prior to test meal and plasma glucose, insulin, and c-peptide measured at 1, 2, and 3 hours after the meal.	Same as intervention group, but patients received regular human insulin instead of insulin lispro. For test meal, regular insulin injected 30 min prior to test meal.	Weekly visits to adjust insulin dosages, diet and exercise prescriptions. HbA_{1C} and insulin antibodies at week 6, delivery, and 6 weeks postpartum. Fetal well being monitored with ultrasounds and non-stress tests.	Per protocol

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Maternal hypoglycemia	Glycemic control/ separation	Perineal injury	Maternal Wt change/ separation	Induction/ Delivery Mode	Preeclampsia/ PIH	Death	Depression/Anxiety	QOL (ante & postpartum)
Jovanovic 1999[41]	# of episodes at breakfast±SEM **IG_{INSana}:** 0.65±0.13 **IG_{INSreg}:** 0.93±1.04 p=0.025	Area-under-the-curve with test meal Glucose **IG_{INSana}**: 23.4 **IG_{INSreg}:** 51.5 p=0.025 C-peptide **IG_{INSana}:** 3.0 **IG_{INSreg}:** 10.5 p<0.001	NR	NR	Cesarean section, N(%) **IG_{INSana}:** 7(36.8) **IG_{INSreg}:** 6(27.3) NS	NR	NR	NR	NR

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Stillbirth	Neonatal death	Shoulder dystocia/ BPI	Clavicle FX	Respiratory distress	Hyperbilirubinemia/ jaundice	Hypoglycemia/ Hypocalcemia	NICU admission for treatment	Birth weight
Jovanovic 1999[41]	NR	NR	NR	NR	NR	NR	None	NR	grams, Mean±SEM **IG_{INSana}:** 3098±202 **IG_{INSreg}:** 3169±78 NS (p=NR)

Author, Year	%LGA/ macrosomia	Other Outcomes	MV Analysis	Adverse Effects	Comments	Quality rating
Jovanovic 1999[41]	None			NR		Fair

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Type of trial	Length of trial	Study Setting	Primary Study Objectives/ Outcomes	Inclusion/ Exclusion Criteria	N, Subjects	BMI	Race/ Ethnicity	Gravidity/ Parity	Age
Nachum 1999[43]	RCT	NR	University-affiliated hospital, Israel Enrolled 9/93-12/97	To compare perinatal outcome and glycemic control using two insulin regimens.	**Inclusion**: Singleton pregnancy in which insulin treatment initiated prior to 35 wks gestation. Diagnosed by 100-g OGTT with ≥2 serum glucose concentrations ≥5.9, 10.6, 9.2, 8.1 mmol/l at 0, 1, 2, and 3 hrs respectively.	N=274 **IG_{INS4X} :** 138 **IG_{INS2X} :** 136	**IG_{INS4X}:** 27.9±2.6 **IG_{INS2X}:** 27.8±2.7	Jewish/Non-Jewish **IG_{INS4X}:** 78/60 **IG_{INS2X}:** 75/61	**IG_{INS4X}:** 3.5±1.7 **IG_{INS2X}:** 3.4±1.8	**IG_{INS4X}:** 33±5 **IG_{INS2X}:** 33±5

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Screening Test/ Mode of Diagnosis	Test preparation	Screening test results	Gestational age at screening	Previous GDM or macrosomic infant	Intervention	Control	Follow-up Measures Surveillance	Insulin required
Nachum 1999[43]	Diagnosed by 100-g OGTT with ≥2 serum glucose concentrations ≥5.9, 10.6, 9.2, 8.1 mmol/l at 0, 1, 2, and 3 hrs respectively (NDDG criteria).	NR	NR	At diagnosis **IG_{INS4X}:** 25.9±7.1 **IG_{INS2X}:** 26.3±7.2 Initiated treatment **IG_{INS4X}:** 27.4±6.8 **IG_{INS2X}:** 28.0±6.9	NR	**IG_{INS4X}:** Received four doses of insulin daily. Three doses containing regular insulin were given 30 min prior to meal. The fourth dose containing intermediate insulin was given before bedtime. Dietary recommendations included: 0.13-0.15 Mj/kg ideal body weight; 3 meals and 3 snacks daily; 55% carbohydrate, 20% protein, 25% fat; increased complex and decreased refined carbohydrates.	**CG_{INS2X}:** A morning dose containing 2/3 of the total daily insulin and afternoon dose contained 1/3 total daily insulin. Morning dose comprised 1/3 regular insulin and 2/3 intermediate insulin. The afternoon dose comprised equal amounts of regular and intermediate insulin. Dietary recommendations same as IG_{INS4X}.	F/U telephone calls as needed. Home glucose monitoring and hemoglobin A_{1C} monthly.	100% both groups by design

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Maternal hypoglycemia	Glycemic control/ separation	Perineal injury	Maternal Wt change/ separation	Induction/ Delivery Mode	Preeclampsia/ PIH	Death	Depression/Anxiety	QOL (ante & postpartum)
Nachum 1999[43]	Severe N(%) **IG_{INS4X}:**1(0.7) **IG_{INS2X}:** 1(0.7) Diff (95%CI):0 Defined: Severe enough to independently take oral glucose and requiring help from another person,	Adequate* N(%) **IG_{INS4X}:** 126(91) **IG_{INS2X}:** 101(74) Diff (95%CI): 17(18 to 26) *Defined: mean capillary glucose < 5.8 mmol/L Hb_{A1C} (%) **IG_{INS4X}**: 5.5 (1.0) **IG_{INS2X}**: 5.8 (1.0) Diff (95%CI): -0.3(-0.2 to -0.4)	NR	Weight gain, kg **IG_{INS4X}**: 11.4±3.5 **IG_{INS2X}:** 10.7±3.6 Diff (95%CI): -0.7(-1.5 to 0.1)	Cesarean N(%) **IG_{INS4X}:** 39(28) **IG_{INS2X}:** 38(28) Diff (95%CI):0	N(%) **IG_{INS4X}:** 11(8) **IG_{INS2X}:** 12(9) Diff (95%CI): -1 (-11 to 9) Defined: NR	NR	NR	NR

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Stillbirth	Neonatal death	Shoulder dystocia/ BPI	Clavicle FX	Respiratory distress	Hyperbilirubinemia/ jaundice	Hypoglycemia/ Hypocalcemia	NICU admission for treatment	Birth weight
Nachum 1999[43]	NR	Perinatal Mortality, N(%) **IG_{INS4X}:** 0 **IG_{INS2X}:** 1(0.7) NS	NR	NR	NR	N(%) **IG_{INS4X}**: 15(11) **IG_{INS2X}**: 29(21) p=0.02 RR: 0.51(0.29 to 0.91) Defined: > 205 mmol/L at ≥34 weeks or >137 mmol/L at < 34 weeks	N(%) Hypoglycemia **IG_{INS4X}:** 1(0.7) **IG_{INS2X}:** 8(5.9) p=0.02 RR: 0.12(0.02 to 0.97) Defined:<1.9 mmol/L in term infants and <1.4 mmol/L in preterm infants ≥ 2 occasions. Hypocalcemia **IG_{INS4X}:** 1(0.7) **IG_{INS2X}:** 0 NS Defined: < 2.0 mmol/L	NR	g (SD) **IG_{INS4X}:** 3437(587) **IG_{INS2X}:** 3436(672) NS

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	%LGA/ macrosomia	Other Outcomes	MV Analysis	Adverse Effects	Comments	Quality rating
Nachum 1999[43]	N(%) LGA, ≥90th %ile **IG_{INS4X}:** 36(26) **IG_{INS2X}:** 41(30) NS Macrosomia, ≥4000g **IG_{INS4X}:** 22(16) **IG_{INS2X}:** 26(19) NS	N(%) Anomalies **IG_{INS4X}:** 1(0.7) **IG_{INS2X}:** 2(1.5) NS Overall neonatal morbidity **IG_{INS4X}:** 24(17) **IG_{INS2X}:** 40(29) RR 0.59(0.38 to 0.92)		NR		Fair

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Type of trial	Length of trial	Study Setting	Primary Study Objectives/ Outcomes	Inclusion/ Exclusion Criteria	N, Subjects	BMI	Race/ Ethnicity	Gravidity/ Parity	Age
de Veciana 1995[40]	RCT	NR	Medical center in California.	Comparing the efficacy of of postprandial and preprandial monitoring in achieving glycemic control in women with gestational diabetes. Perinatal outcomes	**Inclusion**: Diagnosed with gestational diabetes requiring insulin at or before 30 weeks gestation; singleton pregnancy; 50 g GCT > 140 mg/dL but < 190 mg/dL, then 3 hr OGTT by NDDG criteria. **Exclusion**: History of diabetes prior to pregnancy; pre-existing hypertension, renal disease, or autoimmune disorders.	N=66 **IG_{pre}:** 33 **IG_{post}:** 33	**IG_{pre}:** 29.0±3.2 **IG_{post}:** 28.4±3.8 NS (p=NR)	**IG_{pre}, N** Hispanic: 27 White: 4 Black/Asian: 2 **IG_{post}, N** Hispanic: 29 White: 3 Black/Asian: 1 NS (p=NR)	**IG_{pre}:** 4.3±3.0 **IG_{post}:** 3.6±2.2 NS (p=NR)	**IG_{pre}:** 31±6 **IG_{post}:** 29±5 NS (p=NR)

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Screening Test/ Mode of Diagnosis	Test preparation	Screening test results	Gestational age at screening	Previous GDM or macrosomic infant	Intervention	Control	Follow-up Measures Surveillance	Insulin required
de Veciana 1995[40]	Women with RF (>120% ideal body weight, ≥35 yrs, glycosuria on dipstick urinalysis (≥2+), history of diabetes in first-degree relative, previous unexplained stillbirth or miscarriage) were screened at initial prenatal visit. All others were screened between 24-28 weeks. Step 1: One-hour 50-g GCT > 140 mg/dL, but <190 mg/dL; those >190 mg/dL started insulin immediately. Step 2: 3-	Fasting	50-g OCT, 1 hr **IG_{pre}:** 216±56 **IG_{post}:** 214±67 NS (p=NR) Fasting at 100-g OGTT **IG_{pre}:** 137±38 **IG_{post}:** 145±50 NS (p=NR)	At diagnosis **IG_{pre}:** 22.9±7.5 **IG_{post}:** 21.8±6.5 NS (p=NR) Initiated insulin **IG_{pre}:** 24.3±5.2 **IG_{post}:** 25.1±5.1 NS (p=NR)	NR	**IG_{pre}**-Preprandial Monitoring: Required daily monitoring of fasting, preprandial and bedtime blood glucose levels. Diet: 30-35 kcal/kg of ideal body weight divided into 3 meals and 1-3 snacks; 40-45% carbohydrate; intake adjusted according to weight and blood glucose levels. Received split-dose insulin (Regular/NPH)	**IG_{post}**-Postprandial Monitoring: Required daily monitoring of blood glucose levels before breakfast and one hour *after* each meal. Diet: Same as IG_{pre} Insulin: Same as IG_{pre}	Evaluated weekly by perinatal-diabetes team (OB, dietician, nurse educator, counselor) unless complications required more frequent visits.	NR

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

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	hour 100-g OGTT with ≥ 2 abnormal glucose values (fasting > 105 mg/dL, 1 hr > 190 mg/dL, 2 hrs > 165 mg/dL, 3 hrs > 145 mg/dL). Those with elevated fasting initiated insulin immediately, others were managed with diet until fasting >105 mg/dL or postprandial (1hr) >140 mg/dL.								

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Maternal hypoglycemia	Glycemic control/ separation	Perineal injury	Maternal Wt change/ separation	Induction/ Delivery Mode	Preeclampsia/ PIH	Death	Depression/Anxiety	QOL (ante & postpartum)
de Veciana 1995[40]	NR	Successful management, % **IG_{pre}:** 86±4.1 **IG_{post}:** 88±5.2 NS Insulin dose units/day **IG_{pre}**: 76.8±21.4 **IG_{post}**: 100.4±29.5 p=0.003 Final glycosylated Hb% **IG_{pre}:** 8.1±2.2 **IG_{post}**: 6.5±1.4 p=0.006 Change in glycosylated Hb% **IG_{pre}:** -0.6±1.6 **IG_{post}:** -3.0±2.2 p<0.001	**IG_{pre}:** 8(24) **IG_{post}:** 3(9) p=0.16 RR 2.7(0.8 to 9.4) Defined: 3rd or 4th degree lacerations	Gain, kg **IG_{pre}:** 10.7±5.4 **IG_{post}:** 10.5±5.4 NS	Cesarean, N(%) **IG_{pre}:** 13(39) **IG_{post}:** 8(24) p=0.29 RR1.6 (0.8 to 3.4) For CPD **IG_{pre}:** 12(36) **IG_{post}:** 4(12) p=0.04 RR 3.0 (1.1 to 8.3)	N (%) **IG_{pre}:** 2(6) **IG_{post}:** 2(6) NS Defined: NR	NR	NR	NR

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Stillbirth	Neonatal death	Shoulder dystocia/ BPI	Clavicle FX	Respiratory distress	Hyperbilirubinemia/ jaundice	Hypoglycemia/ Hypocalcemia	NICU admission for treatment	Birth weight
de Veciana 1995[40]	N (%) **IG_{pre}:** 1(3) **IG_{post}:** 0 NS	NR	N (%) **IG_{pre}:** 6(18) **IG_{post}:** 1(3) p=0.10 RR 6.0 (0.8 to 47.1) Defined: ≥1 maneuvers required to facilitate vaginal delivery	NR	Transient tachypnea **IG_{pre}:** 2(6) **IG_{post}:** 2(6) NS	N (%) **IG_{pre}:** 4(12) **IG_{post}:** 3(9) NS Defined: serum bilirubin >10 mg/dL if full-term or >15 mg/dL if delivered prior to 37 weeks	Hypoglycemia, N(%) **IG_{pre}:** 7(21) **IG_{post}:** 1(3) p=0.05 RR 7.0 (0.9 to 53.8) Defined: ≤30 mg/dL	NR	grams **IG_{pre}:** 3848±434 **IG_{post}:** 3469±668 p=0.01

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	%LGA/ macrosomia	Other Outcomes	MV Analysis	Adverse Effects	Comments	Quality rating
de Veciana 1995[40]	LGA, N(%) **IG_{pre}:** 14(42) **IG_{post}:** 4(12) p=0.01 RR 3.5 (1.3 to 9.5) Defined: ≥ 90%ile for California population Macrosomia **IG_{pre}:** 12(36) **IG_{post}:** 3(9) p=0.01 RR 4.1 (1.3-13.2) Defined: ≥4000g	NR		NR		Fair

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Type of trial	Length of trial	Study Setting	Primary Study Objectives/ Outcomes	Inclusion/ Exclusion Criteria	N, Subjects	BMI	Race/ Ethnicity	Gravidity/ Parity	Age
Bartha, 2000[45]	Prospective cohort study, comparison groups are women with early and late GDM diagnosis	March 1996-March 1998	Puerto Real, Spain	Gestational hypertension, pre-eclampsia, polyhydramnios, PTL, fetal anomalies, oligohydramnios, gylcemic control, delivery mode, 1&5 min Apgars, SGA, macrosomia, hypolgycemia (fetal), perinatal death	Inclusion: 3986 women who presented consecutive-ly to the antenatal clinic in the University Hospital of Puerto Real, Spain Exclusion: delivery data not available	3968 screened, 183 of 235 GDM patients included in analyses, data unavailable for 52 of the 235 since they delivered outside the university hospital (retention rate 77%)	Pregestational BMI **E**: 29.1 (6.9) **L**: 25.3 (3.8) p=0.00006 Gestational BMI **E**: 31.8 (6.5) **L**: 29.0 (3.8) p=0.001	NR	Nulliparous **E**: 36 (55.4%) **L**: 94 (55.3%) p=NS	**E**: 33.6 (5.4) **L**: 32.6 (5.3) p=NS

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Screening Test/ Mode of Diagnosis	Test preparation	Screening test results	Gestational age at screening	Previous GDM or macrosomic infant	Intervention	Control	Follow-up Measures Surveillance	Insulin required
Bartha, 2000[45]	Two-step: 50 g GCT (cut off >=140), 100 g GTT (NDDG)	None	235/3968 (5.9%) diagnosed with GDM, 65 diagnosed early (first screen), 170 diagnosed late (24-28 weeks)	50 g GCT at first antenatal visit, GTT if positive, repeated at 24-28 wks if negative. Mean (SD) gestational age (weeks) at hospitalization: **E**: 18.1 (6.5) **L**: 33.1 (3.9) p<0.000001	NR	NA	NA	Women were hospitalized after diagnosis to assess glycemic profile, diet therapy if preprandial glc <105 mg/CL and 2 hour postprandial glc <120 mg/CL, otherwise insulin begun; fetal growth, glycemic control and test of fetal well-being monitored (visits at 16, 20, 24, 32, 34, 36, 38, 40 wks gestation)	**E**: 22 (33.9%) **L**: 12 (7.1%) p<0.00001

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Maternal hypoglycemia	Glycemic control/ separation	Perineal injury	Maternal Wt change/ separation	Induction/ Delivery Mode	Preeclampsia/ PIH	Death	Depression/Anxiety	QOL (ante & postpartum)
Bartha, 2000[45]	NR	Fasting **E**: 91 (16) **L**: 80 (14) p<0.00001 2hr pp breakfast **E**: 105 (29) **L**: 96 (21) p=0.03 2hr pp lunch **E:** 103 (19) **L**: 92 (16) p=0.00009 2hr pp dinner **E**: 103 (26) **L**: 94 (17) p=0.01 mean glycemic profile **E**: 97 (15) **L**: 88 (10) p=0.00002	NR	Total weight gain: **E**: 7 (4) **L**: 10 (4) p<0.000001	Induction NR Vaginal **E**: 38 (76%) **L**:107 (81%) p=NS CS fetal distress **E**: 1 (8%) **L**: 2 (8%) p=NS CS CPD **E**: 4 (33%) **L**: 12 (46%) p=NS CS failed induction **E**: 1 (8%) **L**: 1 (4%) p=NS	(not defined) Gestational hypertension **E**: 1 (2%) **L**: 5 (3%) p=NS Pre-eclampsia **E**: 2 (3%) **L**: 0 (0%) p=0.07 Chronic htn **E**: 7 (11%) **L**: 4 (2%) p=0.01 Superimposed pre-eclampsia **E**: 2 (3%) **L**: 1 (1%) p=NS Hypertension (total) **E**: 12 (19%) **L**: 10 (6%) p=0.006	none reported	NR	NR

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	Stillbirth	Neonatal death	Shoulder dystocia/ BPI	Clavicle FX	Respiratory distress	Hyperbilirubinemia/ jaundice	Hypoglycemia/ Hypocalcemia	NICU admission for treatment	Birth weight
Bartha, 2000[45]	Perinatal death **E**: 3 (6%) **I:** 0 (0%) p=0.02 One stillbirth at 24 weeks gestation occurred to a woman with a prior fetal loss. The second stillbirth at 35 weeks was toa women with chronic hypertension who used lithium for cyclic psychosis. The third case was a stillbirth at 38 weeks gestation. No fetal anomalies noted in any of the stillborn fetuses. The first two of the above three patients received insulin.	None	NR	NR	NR	NR	Hypoglycemia (not defined) **E**: 4 (8%) **L**: 0 (0%) p=0.005	Special care unit admission (reason not specified) **E**: 5 (10%) **L**: 14 (11%) p=NS	**E**: 3420 +/- 643 g **I**: 3281 +/- 581 g p=NS

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 1. Trials of Treatment for Gestational Diabetes Mellitus – Key Question 3

Author, Year	%LGA/ macrosomia	Other Outcomes	MV Analysis	Adverse Effects	Comments	Quality rating
Bartha, 2000[45]	Macrosomia (>4000g) **E**: 7 (14%) **L**: 11 (8.3%) p=NS	The E and L groups did not differ significantly in proportion of twin gestations, previous spontaneous abortion, previous cesarean delivery nor in proportion of hydramnios, preterm labor, fetal anomalies, vaginal births, preterm births, 5-min Apgar < 7, 1 min Apgar < 6, small for gestational age, meconium passage, or low birth weight (2500g) or in gestational age at delivery. They differed in diagnosis of oligohydramnios: **E**= 0, **I** =11 (6.5%), p=0.02.	None	NR		Fair

RCT-randomized controlled trial; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test; IG-intervention group; CG-control group; NR-not reported; BMI-Body mass index; GCT-glucose challenge test; RF-risk factors; CHO-carbohydrate; OB-obstetrical; abnl-abnormal; pp-postprandial; SD-standard deviation; LGA-large for gestational age.

Appendix C: Table 2. Trials Addressing Harms of Screening – Key Question 4

Author/ Year	Type of trial	Length of trial	Study Setting	Primary Study Objectives/Outcomes	Inclusion/ Exclusion Criteria	N, Subjects	BMI	Race/ Ethnicity
Rumbold, 2002[49]	Prospective cohort, survey study	NR	Women's and Children's Hospital, Adelaide, Australia	To survey women about their experiences of being screened for GDM and effect of screening on QOL	**Inclusion:** Any English-speaking women, aged 18 or older, attending the hopsital for antenatal care. **Exclusion:** Pre-existing diabetes	N=209, 158 enrolled prescreening, 51 women with positive GCT enrolled after screening	Mean, SD **GCT neg:** 27 (5) **GCT pos, OGTT neg:** 29 (6) **GDM:** 30 (7) p=NS	N (%) **GCT neg:** Caucasian 141 (94) Asian 3(2) Aboriginal 0 Other 6 (4) **GCT pos, OGTT neg:** Caucasian 29 (78) Asian 5(14) Aboriginal 0 Other 3 (8) **GDM**: Caucasian 20 (80) Asian 3(12) Aboriginal 1(4) Other 1 (4) p=NS

EPDS-Edinburgh Postnatal Depression Scale; QOL-quality of life; GDM-gestational diabetes mellitus; DM-diabetes mellitus; SD-standard deviation; GCT-glucose tolerance test; neg-negative screen; pos-positive screen; OGTT-oral glucose tolerance test; GIP-glucose intolerance of pregnancy; GTT-glucose tolerance test; WHO-World Health Organization; NS-not significant; -appro-approximate; NR-not reported; C&C-Carpenter and Coustan criteria.

Appendix C: Table 2. Trials Addressing Harms of Screening – Key Question 4

Author/ Year	Parity	Age	Screening Test/ Mode of Diagnosis	Screening test results	Gestational age at screening	Instruments	Anxiety	Depression (EPDS ≥ 12)
Rumbold, 2002[49]	N (%) **GCT neg:** 0: 69 (46) 1 to 3: 79 (53) ≥4: 2(1) **GCT pos, OGTT neg:** 0: 19 (51) 1 to 3: 18 (49) >4: 0(0) **GDM:** 0: 10 (40) 1 to 3: 14 (56) >4: 1(4) p=NS	Mean (SD) **GCT neg:** 28 (5) **GCT pos, OGTT neg:** 30(4) **GDM/GIP:** 30(4) p<0.05 for GCT neg vs GCT pos/OGTT neg p<0.001 for GCT neg vs. GDM	**Hospital protocol:** 50 g GCT at 24-28 wks, 75 g GTT if screen positive, used 1985 WHO criteria for GDM and glucose intolerance of pregnancy	Of 158 women enrolled prescreening, data available for 135. **GCT neg:** 124/135 **GCT pos:** 11/135 **GTT pos:** 7/11 (64%) 7/135 (5%) Of 51 women enrolled after GCT pos: **OGTT pos:** 18/51 (35%)	24-28 weeks	Spielberger State-Trait Anxiety Inventory; Edinburgh postnatal depression scale; SF-36; mother's perception of health and concern felt for health of newborn; adequacy of info given about test results; overall experience of being screened. Instruments were administered before screening, after screening, and late in pregnancy (at approx 36 wks)	Mean (SD) **Before screening** 10 (3) **After screening** **GCT neg:** 11(3) **GCT pos:** 11 (4) p=NS **Late in pregnancy (approx 36 wks)** **GCT neg:** 11(4) **GCT pos, OGTT neg:** 12 (4) **GDM/GIP:** 11 (4) p=NS	N (%) **Before screening** 33 (21) **After screening** **GCT neg:** 21(17) GCT pos: 11 (18) p=NS **Late in pregnancy (approx 36 wks)** **GCT neg:** 17 (18) **GCT pos, OGTT neg:** 6 (21) **GDM/GIP:** 4 (19) p=NS

EPDS-Edinburgh Postnatal Depression Scale; QOL-quality of life; GDM-gestational diabetes mellitus; DM-diabetes mellitus; SD-standard deviation; GCT-glucose tolerance test; neg-negative screen; pos-positive screen; OGTT-oral glucose tolerance test; GIP-glucose intolerance of pregnancy; GTT-glucose tolerance test; WHO-World Health Organization; NS-not significant; -appro-approximate; NR-not reported; C&C-Carpenter and Coustan criteria.

Appendix C: Table 2. Trials Addressing Harms of Screening – Key Question 4

Author/ Year	SF-36 health status by domain			SF-36 Health Rating	Maternal Health perception	Other	Experience of screening	Quality rating
Rumbold, 2002[49]	Mean (SD) Social functioning **<u>After screening</u>** **GCT neg:** 76(19) **GCT pos:** 76 (20) p=NS **<u>Late in pregnancy</u> (approx 36 wks)** **GCT neg:** 75(21) **GCT pos, OGTT neg:** 66 (25) **GDM/GIP:** 69 (21) p<0.05 for neg GCT vs. pos GCT, neg OGTT	Vitality **<u>After screening</u>** **GCT neg**: 48 (19) **GCT pos**: 53 (17) p<0.05 **<u>Late in pregnancy</u>** (approx 36 wks) **GCT neg**: 47 (19) **GCT pos, OGTT neg**: 49 (16) **GDM/GIP**: 56 (17) p<0.05 for GCT neg vs. GDM/GIP	General Health Perceptions **<u>After screening</u>** **GCT neg**: 76 (17) **GCT pos**: 70 (18) p<0.05 **<u>Late in pregnancy</u>** (approx 36 wks) **GCT neg:** 75(21) **GCT pos, OGTT neg:** 69(18) **GDM/GIP:** 71(13) p=NS	Change in health compared to 1 yr ago After screening, GCT neg women were more likely than GCT pos women to say their health was much better than 1 year ago. N (%) **GCT neg**: 14 (11) **GCT pos**: 1 (2) p<0.05 No differences between groups late in pregnancy.	N (%) **<u>After screening</u>** **GCT neg:** Excellent 21 (17) Very good 8(63) *Fair 23 (19) Poor 1 (1) **GCT pos:** Excellent 8 (13) Very good 30 (48) *Fair 23 (37) Poor 1(2) *p≤ 0.01 **<u>Late in pregnancy</u>** **GCT neg vs.GCT false pos vs. GDM/GIP.** p=NS No differences in concern for baby's health at either assessment.	Request screening in future pregnancy- **GCT neg:** Yes 65 (52) No 20(16) Unsure 15 (12) **GCT pos:** Yes 32 (52) No 14 (23) Unsure 16 (26) p=NS **GCT pos, OGTT neg:** Yes 18 (62) No 5 (17) Unsure 5 (17) **GDM/GIP:** Yes 7(33) No 6 (29) Unsure 7 (33) p=NS	N (%) **GCT neg:** pos 96 (72)* neg 6(5) unsure 19(15)* **GCT pos:** pos 35 (57) neg 2(3) unsure 25 (40) *p<0.01 **GCT pos, OGTT neg:** pos 17 (59) neg 1(4) unsure 9 (31) **GDM/GIP** pos 11 (52) neg 3 (19) unsure 6 (29) p=NS	Fair

EPDS-Edinburgh Postnatal Depression Scale; QOL-quality of life; GDM-gestational diabetes mellitus; DM-diabetes mellitus; SD-standard deviation; GCT-glucose tolerance test; neg-negative screen; pos-positive screen; OGTT-oral glucose tolerance test; GIP-glucose intolerance of pregnancy; GTT-glucose tolerance test; WHO-World Health Organization; NS-not significant; -appro-approximate; NR-not reported; C&C-Carpenter and Coustan criteria.

Appendix C: Table 2. Trials Addressing Harms of Screening – Key Question 4

Author/ Year	Type of trial	Length of trial	Study Setting	Primary Study Objectives/Outcomes	Inclusion/ Exclusion Criteria	N, Subjects	BMI	Race/ Ethnicity
Spirito, 1989[50]	Cross-sectional study	NR	Women and Infants Hospital of Rhode Island	Evaluate psychological impact of diagnosis of GDM, examine relationship between psychological status and metabolic control in GDM	**Inclusion:** English-speaking women with GDM referred to Woman and Infants hospital **Exclusion:** None noted	N=108 **GDM**: 68 **Controls**: 50	NR	% **GDM:** White 87 Non-white 13 **Controls:** White 90 Non-white 10 p=NS

EPDS-Edinburgh Postnatal Depression Scale; QOL-quality of life; GDM-gestational diabetes mellitus; DM-diabetes mellitus; SD-standard deviation; GCT-glucose tolerance test; neg-negative screen; pos-positive screen; OGTT-oral glucose tolerance test; GIP-glucose intolerance of pregnancy; GTT-glucose tolerance test; WHO-World Health Organization; NS-not significant; -appro-approximate; NR-not reported; C&C-Carpenter and Coustan criteria.

Appendix C: Table 2. Trials Addressing Harms of Screening – Key Question 4

Author/ Year	Parity	Age	Screening Test/ Mode of Diagnosis	Screening test results	Gestational age at screening	Instruments	Anxiety	Depression (EPDS ≥ 12)
Spirito, 1989[50]	NR	Mean (SD) **GDM:** 28.5 (5.4) **Controls:** 27.3 (4.7) p=NS	3 hr GTT C&C criteria	NA	28 weeks	Profile of Mood States-Bipolar Form Mean (SD) Gestational age at administration **GDM** 35.5 (2.5) **Controls** 35.0 (4.0) p=NS	NA	NA

EPDS-Edinburgh Postnatal Depression Scale; QOL-quality of life; GDM-gestational diabetes mellitus; DM-diabetes mellitus; SD-standard deviation; GCT-glucose tolerance test; neg-negative screen; pos-positive screen; OGTT-oral glucose tolerance test; GIP-glucose intolerance of pregnancy; GTT-glucose tolerance test; WHO-World Health Organization; NS-not significant; -appro-approximate; NR-not reported; C&C-Carpenter and Coustan criteria.

Appendix C: Table 2. Trials Addressing Harms of Screening – Key Question 4

Author/ Year	SF-36 health status by domain			SF-36 Health Rating	Maternal Health perception	Other	Experience of screening	Quality rating
Spirito, 1989[50]	NA			NA	NA	NA	NA	Profile of Mood States Bipolar Form subscales.No significant differences between women with and without GDM. Results from this form were not predictive of blood glucose parameters.

EPDS-Edinburgh Postnatal Depression Scale; QOL-quality of life; GDM-gestational diabetes mellitus; DM-diabetes mellitus; SD-standard deviation; GCT-glucose tolerance test; neg-negative screen; pos-positive screen; OGTT-oral glucose tolerance test; GIP-glucose intolerance of pregnancy; GTT-glucose tolerance test; WHO-World Health Organization; NS-not significant; -appro-approximate; NR-not reported; C&C-Carpenter and Coustan criteria.

Appendix C: Table 2. Trials Addressing Harms of Screening – Key Question 4

Author/ Year	Type of trial	Length of trial	Study Setting	Primary Study Objectives/Outcomes	Inclusion/ Exclusion Criteria	N, Subjects	BMI	Race/ Ethnicity
Daniells, 2003[51]	Prospective cohort, survey study	One year (Nov 2000-Nov 2001)	Wollongong, Australia	Examine anxiety levels at the beginning of the 3rd trimester, 36 wks, and 6 wks postpartum in women diagnosed with GDM compared to controls	**Inclusion**: Able to read and write English, singleton pregnancy, no previous history of GDM, tested after 26 wks gestation, seen in clinic within 1 wk of diagnosis and before 32 wks gestation	N=100 **GDM**: 50 **Controls**: 50	Mean (SD) **GDM:** 27.4 (7.2) **Controls:** 24.6 (3.8) p=0.02	Percent Australian born **GDM:** 66 **Control:** 86 p=0.02

EPDS-Edinburgh Postnatal Depression Scale; QOL-quality of life; GDM-gestational diabetes mellitus; DM-diabetes mellitus; SD-standard deviation; GCT-glucose tolerance test; neg-negative screen; pos-positive screen; OGTT-oral glucose tolerance test; GIP-glucose intolerance of pregnancy; GTT-glucose tolerance test; WHO-World Health Organization; NS-not significant; -appro-approximate; NR-not reported; C&C-Carpenter and Coustan criteria.

Appendix C: Table 2. Trials Addressing Harms of Screening – Key Question 4

Author/ Year	Parity	Age	Screening Test/ Mode of Diagnosis	Screening test results	Gestational age at screening	Instruments	Anxiety	Depression (EPDS ≥ 12)
Daniells, 2003[51]	Mean (SD) **GDM:** 0.9 (1.1) **Controls:** 0.7 (1.2) p=NS	Mean (SD) **GDM:** 31.4 (5.0) **Controls:** 29.0 (4.8) p=0.02	2 hr 75 g GTT given in a fasting state, GDM diagnosed if fasting glucose ≥ 5.5 mmol/l (99mg%) and/or 2 hr glucose ≥ 8.0 mmol/l (144 mg%)	NA	26+ Mean (SD) **GDM:** 28.4 (1.8) **Control:** 28.2 (0.6) p=NS	Mental Health Inventory-5 (MHI-5), Speilberger State-Trait anxiety Inventory (STAI), six questions regarding attiitudes towards testing rated on Likert scale	State anxiety (STAI) Mean (SD) **GDM:** Week 30 - 40.6 (13.3) **Control:** Week 30 - 34.2 (9.9) p=0.007 Women with GDM had higher state ofanxiety at week 30. No significant difference at weeks 36 and 6 wks postpartum. No differences in trait anxiety at 30 or 36 wks or postpartum.	NA

EPDS-Edinburgh Postnatal Depression Scale; QOL-quality of life; GDM-gestational diabetes mellitus; DM-diabetes mellitus; SD-standard deviation; GCT-glucose tolerance test; neg-negative screen; pos-positive screen; OGTT-oral glucose tolerance test; GIP-glucose intolerance of pregnancy; GTT-glucose tolerance test; WHO-World Health Organization; NS-not significant; -appro-approximate; NR-not reported; C&C-Carpenter and Coustan criteria.

Appendix C: Table 2. Trials Addressing Harms of Screening – Key Question 4

Author/ Year	SF-36 health status by domain			SF-36 Health Rating	Maternal Health perception	Other	Experience of screening	Quality rating
Daniells, 2003[51]	NA			Profile of Mood States Bipolar Form subscales.No significant differences between women with and without GDM. Results from this form were not predictive of blood glucose parameters.	NA	Fair	NA	Profile of Mood States Bipolar Form subscales.No significant differences between women with and without GDM. Results from this form were not predictive of blood glucose parameters.

EPDS-Edinburgh Postnatal Depression Scale; QOL-quality of life; GDM-gestational diabetes mellitus; DM-diabetes mellitus; SD-standard deviation; GCT-glucose tolerance test; neg-negative screen; pos-positive screen; OGTT-oral glucose tolerance test; GIP-glucose intolerance of pregnancy; GTT-glucose tolerance test; WHO-World Health Organization; NS-not significant; -appro-approximate; NR-not reported; C&C-Carpenter and Coustan criteria.

Appendix C: Table 3. Trials of Adverse Effects of Treatment for Gestational Diabetes Mellitus – Key Question 5

Study USPSTF Quality	Type of trial	Length of trial	Study Setting	Primary Study Objectives/ Outcomes	Inclusion/ Exclusion Criteria	N, Subjects	Weight	Race/ Ethnicity	Gravidity/ Parity	Age
Study unique to KQ5										
Langer, 1994[56] Fair	Cohort	NR	Urban residents, low SES, attending maternal health clinics in San Antonio, TX	To determine the effect of intensified treatment on emotional status of women who are newly diagnosed with gestational diabetes mellitus.	**Inclusion**: English-speaking patients newly diagnosed with gestational diabetes mellitus.	N=301 **IG_{Diet}**: 69 **IG_{INS}**: 137 **CG**: 95	% **IG_{Diet}:** Obese 20.3 Non-obese 79.7 **IG_{INS}:** Obese 50.4 Non-obese 49.6 **CG:** Obese 26.3 Non-obese 73.7 p<0.0003 Diet and control vs. insulin	**%** **IG_{Diet}:** White 23.2 Hispanic 75.4 Black 1.4 **IG_{INS}:** White 20.4 Hispanic 76.6 Black 2.9 **CG:** White 13.5 Hispanic 81.2 Black 5.3 NS	Parity, % **IG_{Diet}:** Primipara 37.7 Multipara 62.3 **IG_{INS}:** Primipara 24.8 Multipara 75.2 **CG:** Primipara 34.8 Multipara 65.2 NS	**IG_{Diet}:** 29±6.7 **IG_{INS}:** 29.5±6.1 **CG:** 24.6±6 CG vs IG_{Diet} & IG_{INS}, p<0.001

NS-not significant; IG-intervention group; CG-control group; INS-insulin; NR-not reported; wk(s)-week(s); SD-standard deviation; RCT-randomized control trial; f/u-follow up; WHO-World Health Organization; GDM-gestational diabetes mellitus; GCT-glucose challenge test; OGTT-oral glucose tolerance test; QID-four times daily; RR-relative risk; EPDS-Edinburgh post-natal depression scale; yrs-years; hr-hour; C&C-Carpenter & Coustan

Appendix C: Table 3. Trials of Adverse Effects of Treatment for Gestational Diabetes Mellitus – Key Question 5

Study USPSTF Quality	Screening Test/ Mode of Diagnosis (1 or more steps)	Test preparation	Screening test results	Gestational age at diagnosis	Previous macrosomic infant	Previous fetal death	Gestational Age at Delivery
Study unique to KQ5							
Langer, 1994[56] Fair	Diagnosed using the National Diabetes Data Group glucose threshold. One or more elevated values were considered abnormal.	NR	NR	wk, mean±SD **IG_{Diet}:** 28.0±5.3 **IG_{INS}:** 27.0±7.7 NS	% **IG_{Diet}:** 28.9 **IG_{INS}:** 32.1 **CG:** 5.3 p<0.001 CG vs. diet and insulin	% **IG_{Diet}:** 8.7 **IG_{INS}:** 7.2 **CG:** 2.1 NS	wks, mean±SD **IG_{Diet}:** 39.4±1.9 **IG_{INS}:** 39.0±2.0 **CG:** 39.0±3 NS

NS-not significant; IG-intervention group; CG-control group; INS-insulin; NR-not reported; wk(s)-week(s); SD-standard deviation; RCT-randomized control trial; f/u-follow up; WHO-World Health Organization; GDM-gestational diabetes mellitus; GCT-glucose challenge test; OGTT-oral glucose tolerance test; QID-four times daily; RR-relative risk; EPDS-Edinburgh post-natal depression scale; yrs-years; hr-hour; C&C-Carpenter & Coustan

Appendix C: Table 3. Trials of Adverse Effects of Treatment for Gestational Diabetes Mellitus – Key Question 5

Study USPSTF Quality	Intervention	Control	Depression/Anxiety
Study unique to KQ5			
Langer, 1994[56] Fair	Women who are newly diagnosed with gestational diabetes. Women were first directed to try to achieve blood glucose control through diet if: Fasting <95 mg/dL; 2 hr postprandial <120mg/dL; mean glucose <100mg/dL. If diet did not control glucose levels, women were assigned to the insulin control group. They were instructed to take 3 injections/day of regular and intermediate insulin. Subjects were monitored through weekly clinic visits. Profile of Mood States-Bipolar Form administered at 37-38 weeks gestation.	Non-diabetic controls who were high-risk subjects recruited from the same maternal health clinics. Profile of Mood States-Bipolar Form administered 37-38 weeks gestation.	**Mean±SD** Composed-Anxious **IG_{Diet}:** 47±9.25 **IG_{INS}:** 46.7±9.5 **CG:** 47.2±7.6 Agreeable-Hostile **IG_{Diet}:** 41.7±8.3 **IG_{INS}:** 42.0±9.0 **CG:** 40.3±8.9 Elated-Depressed **IG_{Diet}:** 45.1±7.5 **IG_{INS}:** 45.5±8.3 **CG:** 43.9±9.0 Confident-Unsure **IG_{Diet}:** 45.6±8.2 **IG_{INS}:** 47.9±7.1 **CG:** 48.3±8.0 Energetic-Tired **IG_{Diet}:** 46.9±6.6 **IG_{INS}:** 47.8±6.7 **CG:** 45.8±6.7 Clearheaded-Confused **IG_{Diet}:** 46.0±10 **IG_{INS}:** 48.0±9.4 **CG:** 48.7±9.6 No significant differences

NS-not significant; IG-intervention group; CG-control group; INS-insulin; NR-not reported; wk(s)-week(s); SD-standard deviation; RCT-randomized control trial; f/u-follow up; WHO-World Health Organization; GDM-gestational diabetes mellitus; GCT-glucose challenge test; OGTT-oral glucose tolerance test; QID-four times daily; RR-relative risk; EPDS-Edinburgh post-natal depression scale; yrs-years; hr-hour; C&C-Carpenter & Coustan

Appendix C: Table 3. Trials of Adverse Effects of Treatment for Gestational Diabetes Mellitus – Key Question 5

Study USPSTF Quality	Type of trial	Length of trial	Study Setting	Primary Study Objectives/ Outcomes	Inclusion/ Exclusion Criteria	N, Subjects	Weight	Race/ Ethnicity	Gravidity/ Parity	Age
Treatment vs. no treatment										
Crowther 2005[39] ACHOIS Good	RCT	Screened 16-30 weeks f/u 3 mos. Post-partum	18 centers: 14 Australia; 4 UK Initiated prior to change in WHO criteria Recruitment 9/93-6/03	To assess whether treatment of GDM reduces perinatal complications; or has an effect on maternal outcomes; mood; or quality-of-life	**Inclusion**: Singleton or twin pregnancy 16-30 weeks gestation; RF for GDM or 50-g GCT (≥7.8 mmol/l) AND 75-g OGTT (24-34 weeks gestation) 2-hr plasma glucose 7.8-11.0 mmol/l with fasting plasma glucose <7.8 mmol/l **Exclusion**: Previously treated GDM; active chronic disease (except essential hypertension)	N=1,000 **IG:** 490 **CG:** 510	Body Mass Index* Median (Interquartile Range) **IG:** 26.8 (23.3-31.2) **CG**: 26.0 (22.9-30.9) *weight in kilograms divided by the square of the height in meters.	**IG:** 73% White 19% Asian 9% Other **CG**: 78% White 14% Asian 8% Other	Primiparous N (%) **IG:** 212 (43%) **CG:** 251 (49%)	Mean (SD) **IG:** 30.9 (5.4) **CG:** 30.1(5.5)

NS-not significant; IG-intervention group; CG-control group; INS-insulin; NR-not reported; wk(s)-week(s); SD-standard deviation; RCT-randomized control trial; f/u-follow up; WHO-World Health Organization; GDM-gestational diabetes mellitus; GCT-glucose challenge test; OGTT-oral glucose tolerance test; QID-four times daily; RR-relative risk; EPDS-Edinburgh post-natal depression scale; yrs-years; hr-hour; C&C-Carpenter & Coustan

Appendix C: Table 3. Trials of Adverse Effects of Treatment for Gestational Diabetes Mellitus – Key Question 5

Study USPSTF Quality	Screening Test/ Mode of Diagnosis (1 or more steps)	Test preparation	Screening test results	Gestational age at diagnosis	Previous macrosomic infant	Previous fetal death	Gestational Age at Delivery
Treatment vs. no treatment							
Crowther 2005[39] ACHOIS Good	Two steps Step 1: RF or 50-g GCT (≥7.8 mmol/l) 1-hr cut-off (93% were positive with 50-g) Step 2: 75 g OGTT	50-g GCT NR 75 g OGTT 48 hr normal diet; 8 hr overnight fast	Median (Interquartile range) **GCT, mmol/l** **IG:** 8.8 (8.2-9.7) **CG:** C: 8.8 (8.3-9.7) **75-g OGTT, mmol/l** **IG:** 8.6 (8.1-9.3) **CG:** 8.5 (8.1-9.1)	At entry Median (Interquartile range) **IG:** 29.1 weeks (28.2-30.0) **CG:** 29.2 weeks (28.2-30.0)	NR	Previous pregnancy ending in perinatal death **IG**: 12/278 (4%) **CG**: 7/259 (3%)	Median weeks (Interquartile Range) **IG**: 39.0 (38.1-40.0) **CG**: 39.3 (38.3-40.4)

NS-not significant; IG-intervention group; CG-control group; INS-insulin; NR-not reported; wk(s)-week(s); SD-standard deviation; RCT-randomized control trial; f/u-follow up; WHO-World Health Organization; GDM-gestational diabetes mellitus; GCT-glucose challenge test; OGTT-oral glucose tolerance test; QID-four times daily; RR-relative risk; EPDS-Edinburgh post-natal depression scale; yrs-years; hr-hour; C&C-Carpenter & Coustan

Appendix C: Table 3. Trials of Adverse Effects of Treatment for Gestational Diabetes Mellitus – Key Question 5

Study USPSTF Quality	Intervention	Control	Depression/Anxiety
Treatment vs. no treatment			
Crowther 2005[39] ACHOIS Good	**IG:** Replicated clinical care in which universal screening and treatment for GDM are available Received a slip indicating a diagnosis of glucose intolerance and the plan for intervention Intervention was individualized dietary advice from dietician; instructions to self-monitor glucose QID until within specified range for 2 weeks; insulin initiated if not in range and titrated to glucose range	**CG:** Replicated clinical care in which screening for GDM was not available Received a slip indicating they did not have gestational diabetes A proportion (not fewer than one in 5) had normal OGTT results assigned to routine care to help maintain blinding Glucose monitoring and insulin initiated at the discretion of the attending clinician	Depression Adj RR 0.46 (0.29-0.73) p=0.001 Defined as: Likely depressed (EPDS score >12) at 3 months post-partum Anxiety score Adj mean diff -0.3 (-0.9-0.4; p=0.41)

NS-not significant; IG-intervention group; CG-control group; INS-insulin; NR-not reported; wk(s)-week(s); SD-standard deviation; RCT-randomized control trial; f/u-follow up; WHO-World Health Organization; GDM-gestational diabetes mellitus; GCT-glucose challenge test; OGTT-oral glucose tolerance test; QID-four times daily; RR-relative risk; EPDS-Edinburgh post-natal depression scale; yrs-years; hr-hour; C&C-Carpenter & Coustan

Appendix C: Table 3. Trials of Adverse Effects of Treatment for Gestational Diabetes Mellitus – Key Question 5

Study USPSTF Quality	Type of trial	Length of trial	Study Setting	Primary Study Objectives/ Outcomes	Inclusion/ Exclusion Criteria	N, Subjects	Weight	Race/ Ethnicity	Gravidity/ Parity	Age
Treatment comparison										
Langer 2000[42] Good	RCT	Screened 11-33 weeks F/U to postpartum	Inner-city maternal health clinics in San Antonio, TX	To assess whether glyburide is an effective alternative to insulin for control of hyperglycemia during pregnancy; glycemic control; maternal and neonatal complications.	**Inclusion**: Singleton pregnancy 11-33 weeks; 50-g GCT > 130 mg/dL at 1 hr. AND 100-g OGTT with ≥ 2 abnormal glucose values by C&C criteria. Those with fasting plasma glucose <95 mg/dL were initially treated with diet and enrolled if levels increased to ≥95 mg/dL or postprandial levels were ≥ 120 mg/dL. **Exclusion**: NR	N=404 **IG_{GLY}:** 201 **IG_{INS}:** 203		83% Hispanic 12% White 5% Black	Nulliparity N (%) **IG_{GLY}:** 56 (28) **IG_{INS}:** 59 (29)	yrs, Mean±SD **IG_{GLY}:**29±7 **IG_{INS}:** 30±6

NS-not significant; IG-intervention group; CG-control group; INS-insulin; NR-not reported; wk(s)-week(s); SD-standard deviation; RCT-randomized control trial; f/u-follow up; WHO-World Health Organization; GDM-gestational diabetes mellitus; GCT-glucose challenge test; OGTT-oral glucose tolerance test; QID-four times daily; RR-relative risk; EPDS-Edinburgh post-natal depression scale; yrs-years; hr-hour; C&C-Carpenter & Coustan

Appendix C: Table 3. Trials of Adverse Effects of Treatment for Gestational Diabetes Mellitus – Key Question 5

Study USPSTF Quality	Screening Test/ Mode of Diagnosis (1 or more steps)	Test preparation	Screening test results	Gestational age at diagnosis	Previous macrosomic infant	Previous fetal death	Gestational Age at Delivery
Treatment comparison							
Langer 2000[42] Good	Step 1: 50-g GCT > 130 mg/dL Step 2: 100-g OGTT with ≥ 2 abnormal glucose values by C&C criteria.	Fasting for OGTT	Screening plasma glucose mg/dL,mean±SD **IG_{GLY}:** 169±28 **IG_{INS}:** 169±31 OGTT mg/dL,mean±SD Fasting **IG_{GLY}:** 97±14 **IG_{INS}:** 98±16 1 hr **IG_{GLY}:** 197±31 **IG_{INS}:** 201±30 2 hr **IG_{GLY}:** 174±31 **IG_{INS}:** 174±29 3 hr **IG_{GLY}:** 140±37 **IG_{INS}:** 134±37	wks, mean±SD **IG_{GLY}:**24±7 **IG_{INS}:** 25±7	Previous GDM N(%) **IG_{GLY}:** 24(12) **IG_{INS}:** 22(11) Previous macrosomic infant N(%) **IG_{GLY}:** 36(18) **IG_{INS}:** 45(22)	NR	weeks, mean ± SD **IG_{INS}**: 38.5+ 2.1 **IG_{GLY}**:38.7+ 1.6

NS-not significant; IG-intervention group; CG-control group; INS-insulin; NR-not reported; wk(s)-week(s); SD-standard deviation; RCT-randomized control trial; f/u-follow up; WHO-World Health Organization; GDM-gestational diabetes mellitus; GCT-glucose challenge test; OGTT-oral glucose tolerance test; QID-four times daily; RR-relative risk; EPDS-Edinburgh post-natal depression scale; yrs-years; hr-hour; C&C-Carpenter & Coustan

Appendix C: Table 3. Trials of Adverse Effects of Treatment for Gestational Diabetes Mellitus – Key Question 5

Study USPSTF Quality	Intervention	Control	Depression/Anxiety
Treatment comparison			
Langer 2000[42] Good	**IG_{GLY}:** Initial oral dose of 2.5 mg of glyburide in the morning, when indicated the dose increased the following week by 2.5 mg and thereafter by 5 mg up to a total of 20mg. All women were provided standard nutritional instruction for three meals and four snacks daily.	**IG_{INS}:** Initial insulin dose of 0.7 unit/kg of body weight at admission given subcutaneously 3 times daily and increased weekly as necessary. All women were provided standard nutritional instruction for three meals and four snacks daily.	NR

NS-not significant; IG-intervention group; CG-control group; INS-insulin; NR-not reported; wk(s)-week(s); SD-standard deviation; RCT-randomized control trial; f/u-follow up; WHO-World Health Organization; GDM-gestational diabetes mellitus; GCT-glucose challenge test; OGTT-oral glucose tolerance test; QID-four times daily; RR-relative risk; EPDS-Edinburgh post-natal depression scale; yrs-years; hr-hour; C&C-Carpenter & Coustan

Appendix C: Table 3. Trials of Adverse Effects of Treatment for Gestational Diabetes Mellitus – Key Question 5

Study USPSTF Quality	Type of trial	Length of trial	Study Setting	Primary Study Objectives/ Outcomes	Inclusion/ Exclusion Criteria	N, Subjects	Weight	Race/ Ethnicity	Gravidity/ Parity	Age
Jovanovic 1999[41] Fair	RCT	Women were diagnosed at 14-32 weeks and enrolled upon failure of dietary and exercise treatment. Followed until 6 weeks postpartum	California	To compare immunologic effects of insulin lispro with those of regular human insulin in patients with gestational diabetes.	**Inclusion**: Diagnosed at 14-32 weeks of gestation who failed to adequately control glucose with diet and exercise (defined as more than 70% of home glucose readings during one week did not meet the following criteria: fasting and preprandial <90mg/dl; 1 hr post-prandial <120 mg/dl). Ultrasound exam documented an anatomically normal fetus. **Exclusion**: Prior insulin treatment; had pregestational diabetes; demonstrated significant concurrent organic disease.	N= 42 **IG_{INSana}:** 19 **IG_{INSreg}:** 23	**IG_{INSana}**: 76.3kg ± 2.9 **IG_{INSreg}**: 78.5kg ± 2.5 NS	Caucasian, n **IG_{INSana}:** 2 **IG_{INSreg}:** 0 Hispanic, N **IG_{INSana}:** 17 **IG_{INSreg}:** 23	Mean±SEM Parity **IG_{INSana}:** 1.4±0.3 **IG_{INSreg}:** 1.7±0.3 NS Gravidity **IG_{INSana}:** 1.8±0.2 **IG_{INSreg}:** 2.4±0.3 NS	Mean±SEM **IG_{INSana}:** 34.2±1.3 **IG_{INSreg}:** 29.8±1.0 p<0.01

NS-not significant; IG-intervention group; CG-control group; INS-insulin; NR-not reported; wk(s)-week(s); SD-standard deviation; RCT-randomized control trial; f/u-follow up; WHO-World Health Organization; GDM-gestational diabetes mellitus; GCT-glucose challenge test; OGTT-oral glucose tolerance test; QID-four times daily; RR-relative risk; EPDS-Edinburgh post-natal depression scale; yrs-years; hr-hour; C&C-Carpenter & Coustan

Appendix C: Table 3. Trials of Adverse Effects of Treatment for Gestational Diabetes Mellitus – Key Question 5

Study USPSTF Quality	Screening Test/ Mode of Diagnosis (1 or more steps)	Test preparation	Screening test results	Gestational age at diagnosis	Previous macrosomic infant	Previous fetal death	Gestational Age at Delivery
Jovanovic 1999[41] Fair	Diagnosed at 14-32 weeks of gestation who failed to adequately control glucose with diet and exercise (defined as more than 70% of home glucose readings during one week did not meet the following criteria: fasting and preprandial <90mg/dl; 1 hr post-prandial <120 mg/dl). Ultrasound exam documented an anatomically normal fetus.	NR	NR	At enrollment, Mean±SEM **IG_{INSana}:** 27.3±1.4 **IG_{INSreg}:** 25.6±1.3 NS	Previous GDM, N **IG_{INSana}:** 1 **IG_{INSreg}:** 1	NR	Weeks **IG_{INSana}:** 38.8±0.3 **IG_{INSreg}:** 38.8±0.2

NS-not significant; IG-intervention group; CG-control group; INS-insulin; NR-not reported; wk(s)-week(s); SD-standard deviation; RCT-randomized control trial; f/u-follow up; WHO-World Health Organization; GDM-gestational diabetes mellitus; GCT-glucose challenge test; OGTT-oral glucose tolerance test; QID-four times daily; RR-relative risk; EPDS-Edinburgh post-natal depression scale; yrs-years; hr-hour; C&C-Carpenter & Coustan

Appendix C: Table 3. Trials of Adverse Effects of Treatment for Gestational Diabetes Mellitus – Key Question 5

Study USPSTF Quality	Intervention	Control	Depression/Anxiety
Jovanovic 1999[41] Fair	Patients were instructed to administer a recommended dosage of insulin lispro five minutes prior to three meals a day. Also received NPH insulin in the morning and evening. Self blood glucose monitoring at 0-30 minutes prior to meal and at 1 hour after the start of the meal. Test meal 20% of each woman's calculated caloric need. Insulin lispro injected 5 min, prior to test meal and plasma glucose, insulin, and c-peptide measured at 1, 2, and 3 hours after the meal.	Same as intervention group, but patients received regular human insulin instead of insulin lispro. For test meal, regular insulin injected 30 min prior to test meal.	NR

NS-not significant; IG-intervention group; CG-control group; INS-insulin; NR-not reported; wk(s)-week(s); SD-standard deviation; RCT-randomized control trial; f/u-follow up; WHO-World Health Organization; GDM-gestational diabetes mellitus; GCT-glucose challenge test; OGTT-oral glucose tolerance test; QID-four times daily; RR-relative risk; EPDS-Edinburgh post-natal depression scale; yrs-years; hr-hour; C&C-Carpenter & Coustan

Appendix C: Table 3. Trials of Adverse Effects of Treatment for Gestational Diabetes Mellitus – Key Question 5

Study USPSTF Quality	Type of trial	Length of trial	Study Setting	Primary Study Objectives/ Outcomes	Inclusion/ Exclusion Criteria	N, Subjects	Weight	Race/ Ethnicity	Gravidity/ Parity	Age
Bancroft 2000[38] Fair	RCT		2 specialist diabetes clinics in the UK.	To determine whether less intensive monitoring of blood glucose levels during pregnancy is feasible. Frequency of admission to specialty care baby unit; perinatal morbidity; maternal inconvenience.	**Inclusion**: Blood glucose levels-Fasting < 7.0 mmol/L and between 7.8-11.0 mmol/L 2 hrs after 75 g OGTT. **Exclusion**: NR	N=68 **$IG_{DietgluM}$:** 32 **IG_{Diet}:**36		N(%) **$IG_{DietgluM}$**: Asian 10(31) Caucasian 22(69) **IG_{Diet}**: Asian 11(31) Caucasian 25(69)	Parity Median (range) **$IG_{DietgluM}$**: 2(0-6) **IG_{Diet}**: 1(0-9)	At delivery Mean(SD) **$IG_{DietgluM}$:** 29.7(6.23) **IG_{Diet}:** 31.9(5.17)

NS-not significant; IG-intervention group; CG-control group; INS-insulin; NR-not reported; wk(s)-week(s); SD-standard deviation; RCT-randomized control trial; f/u-follow up; WHO-World Health Organization; GDM-gestational diabetes mellitus; GCT-glucose challenge test; OGTT-oral glucose tolerance test; QID-four times daily; RR-relative risk; EPDS-Edinburgh post-natal depression scale; yrs-years; hr-hour; C&C-Carpenter & Coustan

Appendix C: Table 3. Trials of Adverse Effects of Treatment for Gestational Diabetes Mellitus – Key Question 5

Study USPSTF Quality	Screening Test/ Mode of Diagnosis (1 or more steps)	Test preparation	Screening test results	Gestational age at diagnosis	Previous macrosomic infant	Previous fetal death	Gestational Age at Delivery
Bancroft 2000[38] Fair	One step: 75 g OGTT < 7.0 mmol/L fasting and 7.8 to 11.0 mmol/L after 2 hours	NR	HbA1c Mean(SD) **$IG_{DietgluM}$**: 5.3(0.83) **IG_{Diet}**: 5.6(0.96) NS Fasting, mmol/L Median(range) **$IG_{DietgluM}$**: 4.6(3.5-5.8) **$IG_{Diet:}$** 4.7(3.5-7.0) NS 2 hr glucose **$IG_{DietgluM:}$** 8.5(7.9-10.8) **IG_{Diet}:** 8.9(7.8-11.0) p=0.025	At entry Median (range) **$IG_{DietgluM}$**: 31(24-38) **IG_{Diet}**: 32 (15-37)	NR		

NS-not significant; IG-intervention group; CG-control group; INS-insulin; NR-not reported; wk(s)-week(s); SD-standard deviation; RCT-randomized control trial; f/u-follow up; WHO-World Health Organization; GDM-gestational diabetes mellitus; GCT-glucose challenge test; OGTT-oral glucose tolerance test; QID-four times daily; RR-relative risk; EPDS-Edinburgh post-natal depression scale; yrs-years; hr-hour; C&C-Carpenter & Coustan

Appendix C: Table 3. Trials of Adverse Effects of Treatment for Gestational Diabetes Mellitus – Key Question 5

Study USPSTF Quality	Intervention	Control	Depression/Anxiety
Bancroft 2000[38] Fair	**$IG_{DietgluM}$:** Standard dietary advice restricting carbohydrates to 185 g/day; diet sheet listing caloric values of common foods; glucose monitoring 1-2 hrs post meal 5x/week; glycosylated Hb monthly. Insulin introduced if ≥5 measurements > 7.0 mmol/L in 1 week. Care consisted of serial ultrasounds for growth, amniotic fluid levels and Doppler studies of umbilical artery. **IG_{Diet}:** Dietary advice as above. Glycosylated Hb monthly with results not viewed within study period. If clinician became concerned, woman could be withdrawn at any time.	NA	NR

NS-not significant; IG-intervention group; CG-control group; INS-insulin; NR-not reported; wk(s)-week(s); SD-standard deviation; RCT-randomized control trial; f/u-follow up; WHO-World Health Organization; GDM-gestational diabetes mellitus; GCT-glucose challenge test; OGTT-oral glucose tolerance test; QID-four times daily; RR-relative risk; EPDS-Edinburgh post-natal depression scale; yrs-years; hr-hour; C&C-Carpenter & Coustan

Appendix C: Table 3. Trials of Adverse Effects of Treatment for Gestational Diabetes Mellitus – Key Question 5

Study USPSTF Quality	Type of trial	Length of trial	Study Setting	Primary Study Objectives/ Outcomes	Inclusion/ Exclusion Criteria	N, Subjects	Weight	Race/ Ethnicity	Gravidity/ Parity	Age
Nachum 1999[43] Fair	RCT	NR	University-affiliated hospital, Israel Enrolled 9/93-12/97	To compare perinatal outcome and glycemic control using two insulin regimens.	**Inclusion**: Singleton pregnancy in which insulin treatment initiated prior to 35 wks gestation. Diagnosed by 100-g OGTT with ≥2 serum glucose concentrations ≥5.9, 10.6, 9.2, 8.1 mmol/l at 0, 1, 2, and 3 hrs respectively.	N=274 **IG_{INS4X} :** 138 **IG_{INS2X} :** 136	kg(SD) **IG_{INS4X}** : 73(15) **IG_{INS2X}** : 72(15)	Jewish/Non-Jewish **IG_{INS4X}:** 78/60 **IG_{INS2X}:** 75/61	**IG_{INS4X}:** 3.5±1.7 **IG_{INS2X}:** 3.4±1.8	**IG_{INS4X}:** 33±5 **IG_{INS2X}:** 33±5

NS-not significant; IG-intervention group; CG-control group; INS-insulin; NR-not reported; wk(s)-week(s); SD-standard deviation; RCT-randomized control trial; f/u-follow up; WHO-World Health Organization; GDM-gestational diabetes mellitus; GCT-glucose challenge test; OGTT-oral glucose tolerance test; QID-four times daily; RR-relative risk; EPDS-Edinburgh post-natal depression scale; yrs-years; hr-hour; C&C-Carpenter & Coustan

Appendix C: Table 3. Trials of Adverse Effects of Treatment for Gestational Diabetes Mellitus – Key Question 5

Study USPSTF Quality	Screening Test/ Mode of Diagnosis (1 or more steps)	Test preparation	Screening test results	Gestational age at diagnosis	Previous macrosomic infant	Previous fetal death	Gestational Age at Delivery
Nachum 1999[43] Fair	Diagnosed by 100-g OGTT with ≥2 serum glucose concentrations ≥5.9, 10.6, 9.2, 8.1 mmol/l at 0, 1, 2, and 3 hrs respectively (NDDG criteria).	NR	NR	At diagnosis **IG_{INS4X}:** 25.9±7.1 **IG_{INS2X}:** 26.3±7.2 Initiated treatment **IG_{INS4X}:** 27.4±6.8 **IG_{INS2X}:** 28.0±6.9	NR	NR	Weeks(SD) **IGI_{NS4X}**: 38.9(1.6) **IG_{INS2X}**: 38.6(1.9)

NS-not significant; IG-intervention group; CG-control group; INS-insulin; NR-not reported; wk(s)-week(s); SD-standard deviation; RCT-randomized control trial; f/u-follow up; WHO-World Health Organization; GDM-gestational diabetes mellitus; GCT-glucose challenge test; OGTT-oral glucose tolerance test; QID-four times daily; RR-relative risk; EPDS-Edinburgh post-natal depression scale; yrs-years; hr-hour; C&C-Carpenter & Coustan

Appendix C: Table 3. Trials of Adverse Effects of Treatment for Gestational Diabetes Mellitus – Key Question 5

Study USPSTF Quality	Intervention	Control	Depression/Anxiety
Nachum 1999[43] Fair	**IG_{INS4X}:** Received four doses of insulin daily. Three doses containing regular insulin were given 30 min prior to meal. The fourth dose containing intermediate insulin was given before bedtime. Dietary recommendations included: 0.13-0.15 Mj/kg ideal body weight; 3 meals and 3 snacks daily; 55% carbohydrate, 20% protein, 25% fat; increased complex and decreased refined carbohydrates.	**CG_{INS2X}:** A morning dose containing 2/3 of the total daily insulin and afternoon dose contained 1/3 total daily insulin. Morning dose comprised 1/3 regular insulin and 2/3 intermediate insulin. The afternoon dose comprised equal amounts of regular and intermediate insulin. Dietary recommendations same as IG_{INS4X}.	NR

NS-not significant; IG-intervention group; CG-control group; INS-insulin; NR-not reported; wk(s)-week(s); SD-standard deviation; RCT-randomized control trial; f/u-follow up; WHO-World Health Organization; GDM-gestational diabetes mellitus; GCT-glucose challenge test; OGTT-oral glucose tolerance test; QID-four times daily; RR-relative risk; EPDS-Edinburgh post-natal depression scale; yrs-years; hr-hour; C&C-Carpenter & Coustan

Appendix C: Table 3. Trials of Adverse Effects of Treatment for Gestational Diabetes Mellitus – Key Question 5

Study USPSTF Quality	Type of trial	Length of trial	Study Setting	Primary Study Objectives/ Outcomes	Inclusion/ Exclusion Criteria	N, Subjects	Weight	Race/ Ethnicity	Gravidity/ Parity	Age
de Veciana 1995[40] Fair	RCT	NR	Medical center in California.	Comparing the efficacy of of postprandial and preprandial monitoring in achieving glycemic control in women with gestational diabetes. Perinatal outcomes	**Inclusion**: Diagnosed with gestational diabetes requiring insulin at or before 30 weeks gestation; singleton pregnancy; 50 g GCT > 140 mg/dL but < 190 mg/dL, then 3 hr OGTT by NDDG criteria. **Exclusion**: History of diabetes prior to pregnancy; pre-existing hypertension, renal disease, or autoimmune disorders.	N=66 **IG_{pre}:** 33 **IG_{post}:** 33	**IG_{pre}**: 79kg±13 **IG_{post}**: 77kg±13	**IG_{pre}, N** Hispanic: 27 White: 4 Black/Asian: 2 **IG_{post}, N** Hispanic: 29 White: 3 Black/Asian: 1 NS (p=NR)	**IG_{pre}:** 4.3±3.0 **IG_{post}:** 3.6±2.2 NS (p=NR)	**IG_{pre}:** 31±6 **IG_{post}:** 29±5 NS (p=NR)

NS-not significant; IG-intervention group; CG-control group; INS-insulin; NR-not reported; wk(s)-week(s); SD-standard deviation; RCT-randomized control trial; f/u-follow up; WHO-World Health Organization; GDM-gestational diabetes mellitus; GCT-glucose challenge test; OGTT-oral glucose tolerance test; QID-four times daily; RR-relative risk; EPDS-Edinburgh post-natal depression scale; yrs-years; hr-hour; C&C-Carpenter & Coustan

Appendix C: Table 3. Trials of Adverse Effects of Treatment for Gestational Diabetes Mellitus – Key Question 5

Study USPSTF Quality	Screening Test/ Mode of Diagnosis (1 or more steps)	Test preparation	Screening test results	Gestational age at diagnosis	Previous macrosomic infant	Previous fetal death	Gestational Age at Delivery
de Veciana 1995[40] Fair	Women with RF (>120% ideal body weight, ≥35 yrs, glycosuria on dipstick urinalysis (≥2+), history of diabetes in first-degree relative, previous unexplained stillbirth or miscarriage) were screened at initial prenatal visit. All others were screened between 24-28 weeks. Step 1: One-hour 50-g GCT > 140 mg/dL, but <190 mg/dL; those >190 mg/dL started insulin immediately. Step 2: 3-hour 100-g OGTT with ≥ 2 abnormal glucose values (fasting > 105 mg/dL, 1 hr > 190 mg/dL, 2 hrs > 165 mg/dL, 3 hrs > 145 mg/dL). Those with elevated fasting initiated insulin immediately, others were managed with diet until fasting >105 mg/dL or postprandial (1hr) >140 mg/dL.	Fasting	50-g OCT, 1 hr **IG_{pre}:** 216±56 **IG_{post}:** 214±67 NS (p=NR) Fasting at 100-g OGTT **IG_{pre}:** 137±38 **IG_{post}:** 145±50 NS (p=NR)	At diagnosis **IG_{pre}:** 22.9±7.5 **IG_{post}:** 21.8±6.5 NS (p=NR) Initiated insulin **IG_{pre}:** 24.3±5.2 **IG_{post}:** 25.1±5.1 NS (p=NR)	NR	NR	Weeks **IG_{pre}**: 37.6±3.8 **IG_{post}**: 37.9±1.4 NS

NS-not significant; IG-intervention group; CG-control group; INS-insulin; NR-not reported; wk(s)-week(s); SD-standard deviation; RCT-randomized control trial; f/u-follow up; WHO-World Health Organization; GDM-gestational diabetes mellitus; GCT-glucose challenge test; OGTT-oral glucose tolerance test; QID-four times daily; RR-relative risk; EPDS-Edinburgh post-natal depression scale; yrs-years; hr-hour; C&C-Carpenter & Coustan

Appendix C: Table 3. Trials of Adverse Effects of Treatment for Gestational Diabetes Mellitus – Key Question 5

Study USPSTF Quality	Intervention	Control	Depression/Anxiety
de Veciana 1995[40] Fair	**IG_{pre}**-Preprandial Monitoring: Required daily monitoring of fasting, preprandial and bedtime blood glucose levels. Diet: 30-35 kcal/kg of ideal body weight divided into 3 meals and 1-3 snacks; 40-45% carbohydrate; intake adjusted according to weight and blood glucose levels. Received split-dose insulin (Regular/NPH)	**IG_{post}**-Postprandial Monitoring: Required daily monitoring of blood glucose levels before breakfast and one hour *after* each meal. Diet: Same as IG_{pre} Insulin: Same as IG_{pre}	NR

NS-not significant; IG-intervention group; CG-control group; INS-insulin; NR-not reported; wk(s)-week(s); SD-standard deviation; RCT-randomized control trial; f/u-follow up; WHO-World Health Organization; GDM-gestational diabetes mellitus; GCT-glucose challenge test; OGTT-oral glucose tolerance test; QID-four times daily; RR-relative risk; EPDS-Edinburgh post-natal depression scale; yrs-years; hr-hour; C&C-Carpenter & Coustan

Appendix D: Excluded Studies

Reference	Reason for Exclusion
Aberg A, Rydhstroem H, Frid A. Impaired glucose tolerance associated with adverse pregnancy outcome: a population-based study in southern Sweden. American Journal of Obstetrics & Gynecology 184(2):77-83, 2001.	Excluded for Study Design
Aberg A, Westbom L. Association between maternal pre-existing or gestational diabetes and health problems in children. Acta Paediatrica 90(7):746 -50, 2001.	Does not address one of the key questions
Adams KM, Li H, Nelson RL, Ogburn PL, Jr., Danilenko-Dixon DR. Sequelae of unrecognized gestational diabetes. Am J Obstet Gynecol 1998; 178(6):1321-1332.	Excluded for Study Design
Agardh CD, Aberg A, Norden NE. Glucose levels and insulin secretion during a 75 g glucose challenge test in normal pregnancy. Journal of Internal Medicine 240(5):303-9, 1996.	No information on yield (prevalence), sensitivity/specificity or reliability
Agarwal MM, Dhatt GS, Punnose J, Koster G. Gestational diabetes in a high-risk population: using the fasting plasma glucose to simplify the diagnostic algorithm. European Journal of Obstetrics, Gynecology, & Reproductive Biology 75(1):37-41, 2005.	Does not address morbidity and/or mortality
Agarwal MM, Dhatt GS, Punnose J, Koster G. Gestational diabetes: a reappraisal of HBA1c as a screening test. Acta Obstet Gynecol Scand 2005; 84(12):1159-1163.	Did not use designated diagnostic test or diagnostic criteria
Agarwal MM, Dhatt GS, Punnose J, Koster G. Gestational diabetes: dilemma caused by multiple international diagnostic criteria. Diabet Med 2005; 22(12):1731-1736.	Prevalence outside U.S.
Agarwal MM, Hughes PF, Ezimokhai M. Screening for gestational diabetes in a high-risk population using fasting plasma glucose. International Journal of Gynaecology & Obstetrics 68(2):147-8, 2000.	Excluded for Study Design
Agarwal MM, Hughes PF, Punnose J, Ezimokhai M. Fasting plasma glucose as a screening test for gestational diabetes in a multi-ethnic, high-risk population. Diabetic Medicine 17(10):720 -6, 2000.	Does not address morbidity and/or mortality
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):149-153.	Does not address one of the key questions
Agrawal RK, Lui K, Gupta JM. Neonatal hypoglycaemia in infants of diabetic mothers. Journal of Paediatrics & Child Health 36(4):354-6, 2000.	Excluded for Study Design
Al Mahroos S, Nagalla DS, Yousif W, Sanad H. A population-based screening for gestational diabetes mellitus in non-diabetic women in Bahrain. Annals of Saudi Medicine 25(2):129-33, 2005;-Apr.	Did not use designated diagnostic test or diagnostic criteria
Alberico S, Strazzanti C, De Santo D, De Seta F, Lenardon P, Bernardon M et al. Gestational diabetes: universal or selective screening? Journal of Maternal-Fetal & Neonatal Medicine 16(6):331-7, 2004.	Natural history only
Baliutaviciene D, Petrenko V, Zalinkevicius R. Selective or universal diagnostic testing for gestational diabetes mellitus. International Journal of Gynaecology & Obstetrics 78(3):207-11, 2002.	Excluded for Study Design

Appendix D: Excluded Studies (continued)

Reference	Reason for Exclusion
Barahona MJ, Sucunza N, Garcia-Patterson A, Hernandez M, Adelantado JM, Ginovart G et al. Period of gestational diabetes mellitus diagnosis and maternal and fetal morbidity. Acta Obstetricia et Gynecologica Scandinavica 84(7):622-7, 2005.	Excluded for Study Design
Barden A, Singh R, Walters BN, Ritchie J, Roberman B, Beilin LJ. Factors predisposing to pre-eclampsia in women with gestational diabetes. Journal of Hypertension 22(12):2371 -8, 2004.	Excluded for Study Design
Bartha JL, Martinez-Del-Fresno P, Comino-Delgado R. Early diagnosis of gestational diabetes mellitus and prevention of diabetes-related complications. European Journal of Obstetrics, Gynecology, & Reproductive Biology 75(1):37-41, 2003.	Excluded for Study Design
Beischer NA, Wein P, Sheedy MT, Steffen B. Identification and treatment of women with hyperglycaemia diagnosed during pregnancy can significantly reduce perinatal mortality rates. Australian & New Zealand Journal of Obstetrics & Gynaecology 36(3):239-47, 1996.	Did not use designated diagnostic test or diagnostic criteria
Benjamin F, Wilson SJ, Deutsch S, Seltzer VL, Droesch K, Droesch J. Effect of advancing pregnancy on the glucose tolerance test and on the 50-g oral glucose load screening test for gestational diabetes. Obstetrics & Gynecology 68(3):362-5, 1986.	Prevelence only data
Berger H, Crane J, Farine D, Armson A, De La RS, Keenan-Lindsay L et al. Screening for gestational diabetes mellitus. J Obstet Gynaecol Can 2002; 24(11):894-912.	Non-systematic review
Berkowitz GS, Roman SH, Lapinski RH, Alvarez M. Maternal characteristics, neonatal outcome, and the time of diagnosis of gestational diabetes. American Journal of Obstetrics & Gynecology 167(4 Pt 1):976-82, 1992.	Excluded for Study Design
Berkus MD, Langer O, Piper JM, Luther MF . Efficiency of lower threshold criteria for the diagnosis of gestational diabetes. Obstet Gynecol 1995; 86(6):892-896.	Does not address one of the key questions
Berkus MD, Langer O. Glucose tolerance test: degree of glucose abnormality correlates with neonatal outcome. Obstet Gynecol 1993; 81(3):344-348.	Does not address one of the key questions
Bertini AM, Silva JC, Taborda W, Becker F, Lemos Bebber FR, Zucco Viesi JM et al. Perinatal outcomes and the use of oral hypoglycemic agents. Journal of Perinatal Medicine 33(6):519-23, 2005.	Poor Quality
Bhattacharya SM. Fasting or two-hour postprandial plasma glucose levels in early months of pregnancy as screening tools for gestational diabetes mellitus developing in later months of pregnancy. Journal of Obstetrics & Gynaecology Research 30(4):333-6, 2004.	Excluded for Study Design
Bhattacharya SM. Glucose screening test results in first and early third trimester of pregnancy: is there any correlation? Journal of Obstetrics & Gynaecology Research 28(6):304-7, 2002.	Excluded for Study Design, Does not address morbidity and/or mortality
Bito T, NyariT, KovacsL, Pal A. Oral glucose tolerance testing at gestational weeks < or =16 could predict or exclude subsequent gestational diabetes mellitus during the current pregnancy in high risk group. Eur J Obstet Gynecol Reprod Biol 2005; 121 (1):51-55.	Not generalizable to US population

Appendix D: Excluded Studies (continued)

Reference	Reason for Exclusion
Bo S, Menato G, Signorile A, Bardelli C, Lezo A, Gallo ML et al. Obesity or diabetes: what is worse for the mother and for the baby? Diabetes & Metabolism 29(2 Pt 1):175-8, 2003.	Excluded for Study Design
Boriboonhirunsarn D, Sunsaneevithayakul P, Nuchangrid M. Incidence of gestational diabetes mellitus diagnosed before 20 weeks of gestation. Journal of the Medical Association of Thailand 87(9):1017 - 21, 2004.	Does not address morbidity and/or mortality
Buchanan TA, Xiang AH, Kjos SL, Trigo E, Lee WP, Peters RK. Antepartum predictors of the development of type 2 diabetes in Latino women 11-26 months after pregnancies complicated by gestational diabetes. Diabetes 1999; 48(12):2430-2436.	Does not address one of the key questions
Buchbinder A, Miodovnik M, Khoury J, Sibai BM. Is the use of insulin lispro safe in pregnancy?. Journal of Maternal-Fetal & Neonatal Medicine 11(4):232-7, 2002.	Non-systematic review
Calle-Pascual AL, Bagazgoitia J, Calle JR, Charro A, Maranes JP. Use of insulin lispro in pregnancy. Diabetes, Nutrition & Metabolism - Clinical & Experimental 13(3):173-7, 2000.	Non-systematic review
Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. Am J Obstet Gynecol 1982; 144(7):768-773.	No information on yield (prevalence), sensitivity/specificity or reliability
Carr CA. Evidence-based diabetes screening during pregnancy. J Midwifery Womens Health 2001; 46(3):152-158.	Non-systematic review
Catalano PM, Thomas A, Huston-Presley L, Amini SB. Increased fetal adiposity: a very sensitive marker of abnormal in utero development. American Journal of Obstetrics & Gynecology 189(6):1698 -704, 2003.	Does not address one of the key questions
Chan BC, Lao TT. Gestational diabetes mellitus in women in the fourth decade--is treatment worthwhile? Gynecologic & Obstetric Investigation 60(2):112-6, 2005.	Excluded for Study Design
Chen X, Scholl TO, Stein TP. Association of elevated serum ferritin levels and the risk of gestational diabetes mellitus in pregnant women: the camden study. Diabetes Care 2006; 29(5):1077-1082.	Does not address one of the key questions
Cheung NW, Byth K. Population health significance of gestational diabetes. Diabetes Care 2003; 26(7):2005-2009.	Does not address one of the key questions
Contreras-Soto J, Forsbach G, Vazquez-Rosales J, Alvarez-Garcia C, Garcia G. Noninsulin dependent diabetes mellitus and pregnancy in Mexico. International Journal of Gynaecology & Obstetrics 34(3):205-10, 1991.	Did not use established screening criteria, Prevalence outside U.S.
Conway DL, Gonzales O, Skiver D. Use of glyburide for the treatment of gestational diabetes: the San Antonio experience. Journal of Maternal-Fetal & Neonatal Medicine 15(1):51-5, 2004.	Excluded for Study Design
Coomarasamy A, Connock M, Thornton J, Khan KS. Accuracy of ultrasound biometry in the prediction of macrosomia: a systematic quantitative review. BJOG 2005; 112(11):1461-1466.	Does not address one of the key questions
Coustan DR, Imarah J. Prophylactic insulin treatment of gestational diabetes reduces the incidence of macrosomia, operative delivery, and birth trauma . American Journal of Obstetrics & Gynecology 150(7):836-42, 1984.	Excluded for Study Design
Coustan DR. Management of gestational diabetes mellitus: a self-fulfilling prophecy? JAMA 1996; 275(15):1199-1200.	Editorials, comments and letters

Appendix D: Excluded Studies (continued)

Reference	Reason for Exclusion
Culligan PJ, Myers JA, Goldberg RP, Blackwell L, Gohmann SF, Abell TD. Elective cesarean section to prevent anal incontinence and brachial plexus injuries associated with macrosomia--a decision analysis. Int Urogynecol J Pelvic Floor Dysfunct 2005; 16(1):19-28.	Does not address one of the key questions
Cundy T, Gamble G, Townend K, Henley PG, MacPherson P, Roberts AB. Perinatal mortality in Type 2 diabetes mellitus. Diabetic Medicine 2000; 17 (1):33-39.	Excluded for Study Design
Dabelea D, Snell-Bergeon JK, Hartsfield CL, Bischoff KJ, Hamman RF, McDuffie RS. Increasing prevalence of gestational diabetes mellitus (GDM) over time and by birth cohort: Kaiser Permanente of Colorado GDM Screening Program. Diabetes Care 2005; 28(3):579-584.	Prevalence only data
Dang K, Homko C, Reece EA. Factors associated with fetal macrosomia in offspring of gestational diabetic women. J Matern Fetal Med 2000; 9(2):114-117.	Does not address one of the key questions
Davey RX, Hamblin PS. Selective versus universal screening for gestational diabetes mellitus: an evaluation of predictive risk factors. Medical Journal of Australia 174(3):118-21, 2001.	Excluded for Study Design
De M, X. Perinatal complications of gestational diabetes: the influence of the timing of the diagnosis. European Journal of Obstetrics, Gynecology, & Reproductive Biology 75(1):37-41, 1984.	Excluded for Study Design
de Sereday MS, Damiano MM, Gonzalez CD, Bennett PH. Diagnostic criteria for gestational diabetes in relation to pregnancy outcome. J Diabetes Complications 2003; 17 (3):115-119.	Does not report sensitivity and specificity criterion to assess specified health outcomes
Deerochanawong C, Putiyanun C, Wongsuryrat M, Serirat S, Jinayon P. Comparison of National Diabetes Data Group and World Health Organization criteria for detecting gestational diabetes mellitus. Diabetologia 1996; 39 (9):1070-1073.	Does not report sensitivity and specificity criterion to assess specified health outcomes
Di Cianni G, Benzi L, Bottone P, Volpe L, Orsini P, Murru S et al. Neonatal outcome and obstetric complications in women with gestational diabetes: effects of maternal body mass index. International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity 1996;(5):445-449.	Excluded for Study Design
Di Cianni G, Miccoli R, Volpe L, Lencioni C, Ghio A, Giovannitti MG et al. Maternal triglyceride levels and newborn weight in pregnant women with normal glucose tolerance. Diabetic Medicine 22(1):21-5, 2005.	Does not address one of the key questions
Di Cianni G, Volpe L, Lencioni C, Miccoli R, Cuccuru I, Ghio A et al. Prevalence and risk factors for gestational diabetes assessed by universal screening. Diabetes Research & Clinical Practice 62(2):131-7, 2003.	Excluded for Study Design, Prevalence outside U.S.
Dong ZG, Beischer NA, Wein P, Sheedy MT. Value of early glucose tolerance testing in women who had gestational diabetes in their previous pregnancy. Australian & New Zealand Journal of Obstetrics & Gynaecology 33(4):350-7, 1993.	Excluded for Study Design
Dornan T, Hollis S. Critical appraisal of published research evidence: treatment of gestational diabetes. Diabet Med 2001; Suppl 3:1-5.	Editorials, comments and letters
Dornhorst A, Frost G. The principles of dietary management of gestational diabetes: reflection on current evidence. J Hum Nutr Diet 2002; 15(2):145-156.	Non-systematic review
Dornhorst A. A comparison of glyburide and insulin in women with gestational diabetes mellitus. Diabetic Medicine Suppl 3:12-4, 2001.	Editorials, comments and letters

Appendix D: Excluded Studies (continued)

Reference	Reason for Exclusion
Drexel H, Bichler A, Sailer S, Breier C, Lisch HJ, Braunsteiner H et al. Prevention of perinatal morbidity by tight metabolic control in gestational diabetes mellitus. Diabetes Care 1988; 11(10):761-768.	Excluded for Study Design
El Sayed YY, Lyell DJ. New therapies for the pregnant patient with diabetes. Diabetes Technology & Therapeutics 3(4):635-40, 2001.	Non-systematic review
Erem C, Cihanyurdu N, Deger O, Karahan C, Can G, Telatar M. Screening for gestational diabetes mellitus in northeastern Turkey (Trabzon City). European Journal of Epidemiology 18(1):39-43, 2003.	Excluded for Study Design
Ertunc D, Tok E, Dilek U, Pata O, Dilek S. The effect of carbohydrate intolerance on neonatal birth weight in pregnant women without gestational diabetes mellitus. Annals of Saudi Medicine 24(4):280-3, 2004;-Aug.	Does not address one of the key questions
Esakoff TF, Cheng YW, Caughey AB. Screening for gestational diabetes: different cut-offs for different ethnicities? Am J Obstet Gynecol. 2005; 193 (3 Pt 2):1040-1044.	Does not report sensitivity and specificity criterion to assess specified health outcomes
Fedele D, Lapolla A. A protocol of screening of gestational diabetes mellitus. Annali Dell'Istituto Superiore di Sanita 33(3):383-7, 1997.	Prevelence only data
Feig DS, Chen E, Naylor CD. Self-perceived health status of women three to five years after the diagnosis of gestational diabetes: a survey of cases and matched controls. Am J Obstet Gynecol 1998; 178(2):386-393.	Poor Quality
Feig DS, Razzaq A, Sykora K, Hux JE, Anderson GM. Trends in deliveries, prenatal care, and obstetrical complications in women with pregestational diabetes: a population-based study in Ontario, Canada, 1996-2001. Diabetes Care 2006; 29(2):232-235.	Does not address one of the key questions
Ferrara A, Hedderson MM, Quesenberry CP, Selby JV. Prevalence of gestational diabetes mellitus detected by the national diabetes data group or the carpenter and coustan plasma glucose thresholds. Diabetes Care 25(9):1625-30, 2002.	Prevelence only data
Ferrara A, Kahn HS, Quesenberry CP, Riley C, Hedderson MM. An increase in the incidence of gestational diabetes mellitus: Northern California, 1991-2000. Obstetrics & Gynecology 103(3):526 -33, 2004.	Prevelence only data
Fink K, Clark B. Screening for gestational diabetes mellitus. American Family Physician 69(5):1187-8, 2004.	Does not address one of the key questions
Fotinos C, Dodson S, French L. Clinical inquiries. Does tight control of blood glucose in pregnant women with diabetes improve neonatal outcomes?. Journal of Family Practice 53(10):838 -41, 2004.	Non-systematic review
Gabbe SG, Mestman JG, Freeman RK, Anderson GV, Lowensohn RI. Management and outcome of class A diabetes mellitus. Am J Obstet Gynecol 1977; 127(5):465-469.	Excluded for Study Design
Garcia-Patterson A, Erdozain L, Ginovart G, Adelantado JM, Cubero JM, Gallo G et al. In human gestational diabetes mellitus congenital malformations are related to pre-pregnancy body mass index and to severity of diabetes. Diabetologia 2004; 47(3):509-514.	Excluded for Study Design
Garcia-Patterson A, Martin E, Ubeda J, Maria MA, de Leiva A, Corcoy R. Evaluation of light exercise in the treatment of gestational diabetes. Diabetes Care 24(11):2006 -7, 2001.	Excluded for Study Design

Appendix D: Excluded Studies (continued)

Reference	Reason for Exclusion
Garner P, Okun N, Keely E, Wells G, Perkins S, Sylvain J, Belcher J. A randomized controlled trial of strict glycemic control and tertiary level obstetric care versus routine obstetric care in the management of gestational diabetes: a pilot study. Am J Obstet Gynecol. 177 (1):190-195, 1997.	Did not use established screening criteria
Gezer A, Esen F, Mutlu H, Ozturk E, Ocak V. Prognosis of patients with positive screening but negative diagnostic test for gestational diabetes. Archives of Gynecology & Obstetrics 266 (4):201-4, 2002.	Excluded for Study Design
Gillman MW, Rifas-Shiman S, Berkey CS, Field AE, Colditz GA. Maternal gestational diabetes, birth weight, and adolescent obesity. Pediatrics 111(3):e221 -6, 2003.	Excluded for Study Design
Giuffrida FM, Castro AA, Atallah AN, Dib SA. Diet plus insulin compared to diet alone in the treatment of gestational diabetes mellitus: a systematic review. Braz J Med Biol Res 2003; 36(10):1297-1300.	Poor Quality
Glueck CJ, Bornovali S, Pranikoff J, Goldenberg N, Dharashivkar S, Wang P. Metformin, pre-eclampsia, and pregnancy outcomes in women with polycystic ovary syndrome. Diabetic Medicine 21(8):829-36, 2004.	Does not address one of the key questions
Glueck CJ, Goldenberg N, Pranikoff J, Loftspring M, Sieve L, Wang P. Height, weight, and motor-social development during the first 18 months of life in 126 infants born to 109 mothers with polycystic ovary syndrome who conceived on and continued metformin through pregnancy. Human Reproduction 2004;19(6):1323-1330.	Does not address one of the key questions
Glueck CJ, Wang P, Goldenberg N, Sieve-Smith L. Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. Human Reproduction 17(11):2858 -64, 2002.	Does not address one of the key questions
Gokcel A, Bagis T, Killicadag EB, Tarim E, Guvener N. Comparison of the criteria forgestational diabetes mellitus by NDDG and Carpenter and Coustan, and the outcomes of pregnancy. Journal of Endocrinological Investigation 25(4):357-61, 2002.	Excluded for Study Design
Gonzalez C, Santoro S, Salzberg S, Di Girolamo G, Alvarinas J. Insulin analogue therapy in pregnancies complicated by diabetes mellitus. Expert Opinion on Pharmacotherapy 6(5):735 -42, 2005.	Non-systematic review
Gray-Donald K, Robinson E, Collier A, David K, Renaud L, Rodrigues S. Intervening to reduce weight gain in pregnancy and gestational diabetes mellitus in Cree communities: an evaluation. CMAJ Canadian Medical Association Journal 163(10):1247-51, 2000.	Excluded for Study Design
Greene MF. Oral hypoglycemic drugs for gestational diabetes. New England Journal of Medicine 343(16):1178-9, 2000.	Editorials, comments and letters
Griffin ME, Coffey M, Johnson H, Scanlon P, Foley M, Stronge J et al. Universal vs. risk factor-based screening for gestational diabetes mellitus: detection rates, gestation at diagnosis and outcome. Diabetic Medicine 17(1):26-32, 2000.	Poor Quality
Gruendhammer M, Brezinka C, Lechleitner M. The number of abnormal plasma glucose values in the oral glucose tolerance test and the feto-maternal outcome of pregnancy. European Journal of Obstetrics, Gynecology, & Reproductive Biology 75(1):37-41, 2003.	Excluded for Study Design
Hadden D. Evidence-based screening for gestational diabetes? Diabetic Medicine 17(5):402-4, 2000.	Editorials, comments and letters

Appendix D: Excluded Studies (continued)

Reference	Reason for Exclusion
Hague WM, Davoren PM, Oliver J, Rowan J. Contraindications to use of metformin. Metformin may be useful in gestational diabetes. BMJ 326(7392):762; author reply 762, 2003.	Editorials, comments and letters
HAPO Study Cooperative Research Group. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. International Journal of Gynaecology & Obstetrics 78(1):69-77, 2002.	Excluded for Study Design
Harlass FE, Brady K, Read JA. Reproducibility of the oral glucose tolerance test in pregnancy. American Journal of Obstetrics & Gynecology 164(2):564-8, 1991.	Poor Quality
Hassan A. Screening of pregnant women for gestational diabetes mellitus. Journal of Ayub Medical College, Abbottabad: JAMC 17(2):54-8, 2005;-Jun.	Does not address morbidity and/or mortality
Hedderson MM, Ferrara A, Sacks DA. Gestational diabetes mellitus and lesser degrees of pregnancy hyperglycemia: association with increased risk of spontaneous preterm birth. Obstetrics & Gynecology 102(4):850-6, 2003.	Excluded for Study Design
Hellmuth E, Damm P, Molsted-Pedersen L. Oral hypoglycaemic agents in 118 diabetic pregnancies. Diabetic Medicine 17(7):507-11, 2000.	Does not address morbidity and/or mortality
Hill JC, Krishnaveni GV, Annamma I, Leary SD, Fall CH. Glucose tolerance in pregnancy in South India: relationships to neonatal anthropometry. Acta Obstetricia et Gynecologica Scandinavica 84(2):159-65, 2005.	Does not address morbidity and/or mortality
Hiramatsu Y, Masuyama H, Mizutani Y, Kudo T, Oguni N, Oguni Y. Heavy-for-date infants: their backgrounds and relationship with gestational diabetes. Journal of Obstetrics & Gynaecology Research 26(3):193-8, 2000.	Excluded for Study Design
Homko CJ, Reece EA. To screen or not to screen for gestational diabetes mellitus. The clinical quagmire. Clinics in Perinatology 28(2):407-17, 2001.	Non-systematic review
Homko CJ, Sivan E, Reece AE. Is there a role for oral antihyperglycemics in gestational diabetes and type 2 diabetes during pregnancy? Treat Endocrinol 2004; 3(3):133-139.	Non-systematic review
Homko CJ, Sivan E, Reece EA. The impact of self-monitoring of blood glucose on self-efficacy and pregnancy outcomes in women with diet-controlled gestational diabetes. Diabetes Educator 28(3):435-43, 2002;-Jun.	Not one of the included treatments
Hong PL, Benjamin F, Deutsch S. First prenatal visit glucose screening. American Journal of Perinatology 6(4):433-6, 1989.	Did not use designated diagnostic test or diagnostic criteria
Hughes PF, Agarwal M, Newman P, Morrison J. Screening for gestational diabetes in a multi-ethnic population. Diabetes Research & Clinical Practice 28(1):73-8, 1995.	Natural history only
Hughes PF, Agarwal M, Newman P, Morrison J. Screening for gestational diabetes in a multi-ethnic population. Diabetes Research & Clinical Practice 28(1):73-8, 1995.	Natural history only
Hunger-Dathe W, Volk K, Braun A, Samann A, Muller UA, Peiker G et al. Perinatal morbidity in women with undiagnosed gestational diabetes in northern thuringia in Germany. Experimental & Clinical Endocrinology & Diabetes 113(3):160-6, 2005.	Excluded for Study Design

Appendix D: Excluded Studies (continued)

Reference	Reason for Exclusion
Jacobson GF, Ramos GA, Ching JY, Kirby RS, Ferrara A, Field DR. Comparison of glyburide and insulin for the management of gestational diabetes in a large managed care organization. Am J Obstet Gynecol 2005; 193(1):118-124.	Excluded for Study Design
Jensen DM, Damm P, Sorensen B, Molsted-Pedersen L, Westergaard JG, Klebe J et al. Clinical impact of mild carbohydrate intolerance in pregnancy: a study of 2904 nondiabetic Danish women with risk factors for gestational diabetes mellitus. American Journal of Obstetrics & Gynecology 185(2):413-9, 2001.	Excluded for Study Design
Jensen DM, Damm P, Sorensen B, Molsted-Pedersen L, Westergaard JG, Korsholm L et al. Proposed diagnostic thresholds for gestational diabetes mellitus according to a 75-g oral glucose tolerance test. Maternal and perinatal outcomes in 3260 Danish women. Diabetic Medicine 1920;(1):51-7, 2003.	Excluded for Study Design
Jensen DM, Damm P, Sorensen B, Molsted-Pedersen L, Westergaard JG, Ovesen P et al. Pregnancy outcome and prepregnancy body mass index in 2459 glucose-tolerant Danish women. American Journal of Obstetrics & Gynecology 189(1):239-44, 2003.	Excluded for Study Design
Jensen DM, Molsted-Pedersen L, Beck-Nielsen H, Westergaard JG, Ovesen P, Damm P. Screening for gestational diabetes mellitus by a model based on risk indicators: a prospective study. Am J Obstet Gynecol 2003; 189(5):1383-1388.	Does not address one of the key questions
Jensen DM, Sorensen B, Feilberg-Jorgensen N, Westergaard JG, Beck-Nielsen H. Maternal and perinatal outcomes in 143 Danish women with gestational diabetes mellitus and 143 controls with a similar risk profile. Diabetic Medicine 17(4):281-6, 2000.	Excluded for Study Design
Jimenez-Moleon JJ, Bueno-Cavanillas A, Luna-Del-Castillo JD, Lardelli-Claret P, Garcia-Martin M , Galvez-Vargas R. Predictive value of a screen for gestational diabetes mellitus: influence of associated risk factors. Acta Obstetricia et Gynecologica Scandinavica 79(11):991-8, 2000.	Does not address one of the key questions
Jimenez-Moleon JJ, Bueno-Cavanillas A, Luna-del-Castillo JD, Garcia-Martin M, Lardelli-Claret P, Galvez-Vargas R. Impact of different levels of carbohydrate intolerance on neonatal outcomes classically associated with gestational diabetes mellitus. European Journal of Obstetrics, Gynecology, & Reproductive Biology 75(1):37-41, 2002.	Excluded for Study Design
Jimenez-Moleon JJ, Bueno-Cavanillas A, Luna-Del-Castillo JD, Garcia-Martin M, Lardelli-Claret P, Galvez-Vargas R. Prevalence of gestational diabetes mellitus: variations related to screening strategy used. European Journal of Endocrinology 146(6):831-7, 2002.	Prevalence outside U.S.
Jimenez-Moleon JJ, Bueno-Cavanillas A, Luna-Del-Castillo JD, Lardelli-Claret P, Garcia-Martin M, Galvez-Vargas R. Predictive value of a screen for gestational diabetes mellitus: influence of associated risk factors. Acta Obstetricia et Gynecologica Scandinavica 79(11):991-8, 2000.	Excluded for Study Design
Joffe GM, Esterlitz JR, Levine RJ, Clemens JD, Ewell MG, Sibai BM et al. The relationship between abnormal glucose tolerance and hypertensive disorders of pregnancy in healthy nulliparous women. Calcium for Preeclampsia Prevention (CPEP) Study Group. Am J Obstet Gynecol 1998; 179(4):1032-1037.	Does not address one of the key questions

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Reference	Reason for Exclusion
Jorgensen LG, Schytte T, Brandslund I, Stahl M, Petersen PH, Andersen B. Fasting and post-glucose load--reference limits for peripheral venous plasma glucose concentration in pregnant women. Clinical Chemistry & Laboratory Medicine 41(2):187-99, 2003.	Did not use designated diagnostic test or diagnostic criteria
Jovanovic L, Knopp RH, Brown Z, Conley MR, Park E, Mills JL et al. Declining insulin requirement in the late first trimester of diabetic pregnancy. Diabetes Care 2001; 24(7):1130-1136.	Does not address one of the key questions
Jovanovic L, Knopp RH, Kim H, Cefalu WT, Zhu XD, Lee YJ et al. Elevated pregnancy losses at high and low extremes of maternal glucose in early normal and diabetic pregnancy: evidence for a protective adaptation in diabetes. Diabetes Care 28(5):1113-7, 2005.	Does not address one of the key questions
Kalter H. The non-teratogenicity of gestational diabetes. Paediatr Perinat Epidemiol 1998; 12(4):456-458.	Excluded for Study Design
Kerbel D, Glazier R, Holzapfel S, Yeung M, Lofsky S. Adverse effects of screening for gestational diabetes: a prospective cohort study in Toronto, Canada. J Med Screen 1997; 4(3):128-132.	Poor Quality
Keshavarz M, Cheung NW, Babaee GR, Moghadam HK, Ajami ME, Shariati M. Gestational diabetes in Iran: incidence, risk factors and pregnancy outcomes. Diabetes Research & Clinical Practice 69(3):279-86, 2005.	Natural history only
Kitzmiller JL, Elixhauser A, Carr S, Major CA, de Veciana M, Dang-Kilduff L et al. Assessment of costs and benefits of management of gestational diabetes mellitus. Diabetes Care 1998; 21 Suppl 2:B123-B130 .	Does not address one of the key questions
Kjos SL, Buchanan TA. Gestational diabetes mellitus. N Engl J Med 1999; 341(23):1749-1756.	Non-systematic review
Kjos SL, Schaefer-Graf U, Sardesi S, Peters RK, Buley A, Xiang AH et al. A randomized controlled trial using glycemic plus fetal ultrasound parameters versus glycemic parameters to determine insulin therapy in gestational diabetes with fasting hyperglycemia. Diabetes Care 24(11):1904 -10, 2001.	Does not address one of the key questions
Knopp RH, Magee MS, Raisys V, Benedetti T, Bonet B. Hypocaloric diets and ketogenesis in the management of obese gestational diabetic women. J Am Coll Nutr 1991; 10(6):649-667.	Excluded for Study Design
Ko GT, Chan JC, Tsang LW, Yeung VT, Chow CC, Cockram CS. Outcomes of screening for diabetes in high-risk Hong Kong Chinese subjects. Diabetes Care 23(9):1290-4, 2000.	Does not address one of the key questions
Kremer CJ, Duff P. Glyburide for the treatment of gestational diabetes . American Journal of Obstetrics & Gynecology 190;(5):1438-1439.	Excluded for Study Design
Kumar KM. Current diagnostic criteria and their impact on outcome and management. Journal of the Indian Medical Association 100(3):149-52, 2002.	Editorials, comments and letters
Kvetny J, Poulsen HF. Incidence of gestational hypertension in gestational diabetes mellitus. Archives of Gynecology & Obstetrics 267(3):153-7, 2003.	Natural history only
Kyle CV, Cundy TF. Screening for gestational diabetes mellitus: can we be more efficient? Australian & New Zealand Journal of Obstetrics & Gynaecology 41(3):285-90, 2001.	Excluded for Study Design, No information on yield (prevalence), sensitivity/specificity or reliability

Appendix D: Excluded Studies (continued)

Reference	Reason for Exclusion
Landon MB, Thom E, Spong CY, Gabbe SG, Leindecker S, Johnson F et al. A planned randomized clinical trial of treatment for mild gestational diabetes mellitus. Journal of Maternal-Fetal & Neonatal Medicine 11(4):226-31, 2002.	Does not address one of the key questions
Langer O, Anyaegbunam A, Brustman L, Divon M. Management of women with one abnormal oral glucose tolerance test value reduces adverse outcome in pregnancy. American Journal of Obstetrics & Gynecology 161(3):593-9, 1989.	Does not address one of the key questions
Langer O, Brustman L, Anyaegbunam A, Mazze R. The significance of one abnormal glucose tolerance test value on adverse outcome in pregnancy. Am J Obstet Gynecol 1987; 157(3):758-763.	Does not address one of the key questions
Langer O, Rodriguez DA, Xenakis EM, McFarland MB , Berkus MD, Arrendondo F. Intensified versus conventional management of gestational diabetes. Am J Obstet Gynecol 1994; 170(4):1036-1046.	Excluded for Study Design
Langer O, Yogev Y, Most O, Xenakis EM. Gestational diabetes: the consequences of not treating. American Journal of Obstetrics & Gynecology 192;(4):989-997.	Excluded for Study Design
Langer O, Yogev Y, Xenakis EM, Brustman L. Overweight and obese in gestational diabetes: the impact on pregnancy outcome. American Journal of Obstetrics & Gynecology 192;(6):1768-1776.	Excluded for Study Design
Lanni S, Barrett D. The predictive value of the 1-h 50-g glucose screen for diagnosing gestational diabetes mellitus in a high-risk population. Journal of Maternal-Fetal & Neonatal Medicine 15(6):375-9, 2004.	Excluded for Study Design
Lao TT, Tam KF. Gestational diabetes diagnosed in third trimester pregnancy and pregnancy outcome. Acta Obstetricia et Gynecologica Scandinavica 80(11):1003-8, 2001.	Did not use designated diagnostic test or diagnostic criteria
Lao TT, Wong KY. Perinatal outcome in large-for-gestational-age infants. Is it influenced by gestational impaired glucose tolerance? Journal of Reproductive Medicine 47(6):497-502, 2002.	Excluded for Study Design
Lauenborg J, Hansen T, Jensen DM, Vestergaard H, Molsted-Pedersen L, Hornnes P et al. Increasing incidence of diabetes after gestational diabetes: a long-term follow-up in a Danish population. Diabetes Care 2004; 27(5):1194-1199.	Does not address one of the key questions
Lauszus FF, Rasmussen OW, Henriksen JE, Klebe JG , Jensen L, Lauszus KS et al. Effect of a high monounsaturated fatty acid diet on blood pressure and glucose metabolism in women with gestational diabetes mellitus. European Journal of Clinical Nutrition 55(6):436-43, 2001.	Did not use designated diagnostic test or diagnostic criteria
Lavin JP, Barden TP, Miodovnik M. Clinical experience with a screening program for gestational diabetes. Am J Obstet Gynecol 1981; 141(5):491-494.	Does not address one of the key questions
Leipold H, Worda C, Gruber CJ, Kautzky-Willer A, Husslein PW, Bancher-Todesca D. Large-for-gestational-age newborns in women with insulin-treated gestational diabetes under strict metabolic control. Wien Klin Wochenschr 2005; 117(15-16):521-525.	Did not use designated diagnostic test or diagnostic criteria
Lemen PM, Wigton TR, Miller-McCarthey AJ, Cruikshank DP. Screening for gestational diabetes mellitus in adolescent pregnancies. Am J Obstet Gynecol 1998; 178(6):1251-1256.	Does not address one of the key questions

Appendix D: Excluded Studies (continued)

Reference	Reason for Exclusion
Li DF, Wong VC, O'Hoy KM, Yeung CY, Ma HK. Is treatment needed for mild impairment of glucose tolerance in pregnancy? A randomized controlled trial. British Journal of Obstetrics & Gynaecology 94(9):851-4, 1987.	Poor Quality
Livingston RC, Bachman-Carter K, Frank C, Mason WB. Diabetes mellitus in Tohon O'odham pregnancies. Diabetes Care 16(1):318-21, 1993.	Excluded for Study Design
Lu GC, Rouse DJ, DuBard M, Cliver S, Kimberlin D, Hauth JC. The effect of the increasing prevalence of maternal obesity on perinatal morbidity. Am J Obstet Gynecol 2001; 185(4):845-849.	Excluded for Study Design
Lucas MJ, Lowe TW, Bowe L, McIntire DD. Class A1 gestational diabetes: a meaningful diagnosis? Obstet Gynecol 1993; 82(2):260-265.	Excluded for Study Design
MacNeill S, Dodds L, Hamilton DC, Armson BA, VandenHof M. Rates and risk factors for recurrence of gestational diabetes. Diabetes Care 2001; 24(4):659-662.	Does not address one of the key questions
Magee MS, Walden CE, Benedetti TJ, Knopp RH. Influence of diagnostic criteria on the incidence of gestational diabetes and perinatal morbidity. JAMA 1993; 269(5):609-615.	Excluded for Study Design
Manassakorn J, Wankrue P, Tantisirin P, Cheunwatana P, Intramax L. Oral glucose tolerance test at each trimester of pregnancy. Journal of the Medical Association of Thailand 71(1):25-8, 1988.	Does not address morbidity and/or mortality, Does not address one of the key questions
Mannucci E, Bardini G, Rotella CM. Effect of lower diagnostic thresholds on estimates of prevalence of impaired fasting glucose (IFG). Diabetic Medicine 22(3):353-4, 2005.	Editorials, comments and letters
Marquette GP, Klein VR, Niebyl JR. Efficacy of screening for gestational diabetes. Am J Perinatol 1985; 2(1):7-9.	Does not address morbidity and/or mortality
Massion C, O'Connor PJ, Gorab R, Crabtree BF, Nakamura RM, Coulehan JL. Screening for gestational diabetes in a high-risk population. J Fam Pract 1987; 25(6):569-575.	No information on yield (prevalence), sensitivity/specificity or reliability
Mazze RS, Langer O. Primary, secondary, and tertiary prevention. Program for diabetes in pregnancy. Diabetes Care 11(3):263-8, 1988.	Natural history only
McDonald GW, Fisher GF, Burnham C. Reproducibility of the oral glucose tolerance test. Diabetes 1965; 14:473-480.	Does not address one of the key questions
McIntyre HD, Begg LM, Parry AF, Oats J. Audit of maternal and fetal outcomes in women treated for glucose intolerance during pregnancy. Australian & New Zealand Journal of Obstetrics & Gynaecology 42(2):131-7, 2002.	Excluded for Study Design
McIntyre HD, Cheung NW, Oats JJ, Simmons D. Gestational diabetes mellitus: from consensus to action on screening and treatment. Medical Journal of Australia 183(6):288-9, 2005.	Editorials, comments and letters
Mecacci F, Carignani L, Cioni R, Bartoli E, Parretti E, La Torre P et al. Maternal metabolic control and perinatal outcome in women with gestational diabetes treated with regular or lispro insulin: comparison with non-diabetic pregnant women. Eur J Obstet Gynecol Reprod Biol 2003; 111(1):19-24.	Poor Quality

Appendix D: Excluded Studies (continued)

Reference	Reason for Exclusion
Mello G, Parretti E, Mecacci F, Lucchetti R, Cianciulli D, Lagazio C et al. Anthropometric characteristics of full-term infants: effects of varying degrees of "normal" glucose metabolism. Journal of Perinatal Medicine 25(2):197-204, 1997.	Does not address one of the key questions
Mello G, Parretti E, Mecacci F, Lucchetti R, Lagazio C, Pratesi M et al. Risk factors for fetal macrosomia: the importance of a positive oral glucose challenge test.[see comment]. European Journal of Endocrinology 137(1):27-33, 1997.	Natural history only
Meyer WJ, Carbone J, Gauthier DW, Gottmann DA. Early gestational glucose screening and gestational diabetes. Journal of Reproductive Medicine 41(9):675-9, 1996.	No information on yield (prevalence), sensitivity/specificity or reliability
Miyakoshi K, Tanaka M, Matsumoto T, Hattori Y, Ueno K, Teranishi T et al. Hypertensive disorders in Japanese women with gestational glucose intolerance. Diabetes Research & Clinical Practice 64(3):201-5, 2004.	Excluded for Study Design
Miyakoshi K, Tanaka M, Ueno K, Uehara K, Ishimoto H, Yoshimura Y. Cutoff value of 1 h, 50 g glucose challenge test for screening of gestational diabetes mellitus in a Japanese population. Diabetes Research & Clinical Practice 60(1):63-7, 2003.	Excluded for Study Design, No information on yield (prevalence), sensitivity/specificity or reliability
Montoro MN, Kjos SL, Chandler M, Peters RK, Xiang AH, Buchanan TA. Insulin resistance and preeclampsia in gestational diabetes mellitus. Diabetes Care 2005; 28(8):1995-2000.	Does not address one of the key questions
Moses RG, Griffiths RD. Can a diagnosis of gestational diabetes be an advantage to the outcome of pregnancy? J Soc Gynecol Investig 1995; 2(3):523-525.	Excluded for Study Design
Moses RG, Mackay MT. Gestational diabetes: Is there a relationship between leg length and glucose tolerance? Diabetes Care 2004; 27(5):1033-1035.	Does not address one of the key questions
Moses RG, Moses J, Davis WS. Gestational diabetes: do lean young caucasian women need to be tested? Diabetes Care 1998; 21(11):1803-1806.	Does not address one of the key questions
Nahum GG, Huffaker BJ. Correlation between first- and early third-trimester glucose screening test results. Obstetrics & Gynecology 76(4):709-13, 1990.	Poor Quality
Nahum GG, Wilson SB, Stanislaw H. Early-pregnancy glucose screening for gestational diabetes mellitus. Journal of Reproductive Medicine 47(8):656-62, 2002.	Did not use designated diagnostic test or diagnostic criteria
Naylor CD, Sermer M, Chen E, Farine D. Selective screening for gestational diabetes mellitus. Toronto Trihospital Gestational Diabetes Project Investigators. N Engl J Med 1997; 337(22):1591-1596.	Excluded for Study Design
Naylor JL, Schraer CD, Mayer AM, Lanier AP, Treat CA, Murphy NJ. Diabetes among Alaska Natives: a review. International Journal of Circumpolar Health 62(4):363-87, 2003.	Non-systematic review
Nielsen IK, Vinther S, Birch K, Lange AP . Random blood glucose sampling as an early antenatal screening test for diabetes mellitus. Diabetes Research 8(1):31-3, 1988.	No information on yield (prevalence), sensitivity/specificity or reliability

Appendix D: Excluded Studies (continued)

Reference	Reason for Exclusion
Nordin NM, Wei JW, Naing NN, Symonds EM. Comparison of maternal-fetal outcomes in gestational diabetes and lesser degrees of glucose intolerance. Journal of Obstetrics & Gynaecology Research 32(1):107-14, 2006.	Excluded for Study Design
Olefsky JM, Reaven GM. Insulin and glucose responses to identical oral glucose tolerance tests performed forty-eight hours apart. Diabetes 1974; 23(5):449-453.	Excluded for Study Design
Omori Y, Minei S, Uchigata Y, Shimizu M , Sanaka M, Honda M et al. Comparison of diagnostic criteria of IGT, borderline, and GDM. Blood glucose curve and IRI response. Diabetes 40 Suppl 2:30-4, 1991.	No information on yield (prevalence), sensitivity/specificity or reliability
Oppermann W, Camerini-Davalos RA. Early diabetes during pregnancy. Diabetes Care 3(3):465-7, 1980;-Jun.	Excluded for Study Design
Ostlund I, Hanson U, Bjorklund A, Hjertberg R, Eva N, Nordlander E et al. Maternal and fetal outcomes if gestational impaired glucose tolerance is not treated. Diabetes Care 2003; 26(7):2107-2111.	Excluded for Study Design
Ostlund I, Hanson U. Repeated random blood glucose measurements as universal screening test for gestational diabetes mellitus. Acta Obstetricia et Gynecologica Scandinavica 83(1):46-51, 2004.	Did not use designated diagnostic test or diagnostic criteria
O'Sullivan JB, Charles D, MAHAN CM, Dandrow RV. Gestational diabetes and perinatal mortality rate. American Journal of Obstetrics & Gynecology 116(7):901-4, 1973.	Natural history only
O'Sullivan JB, Mahan CM. Criteria for the oral glucose tolerance test in pregnancy. Diabetes 1964; 13:278-285.	Does not address one of the key questions
O'Sullivan JB. Establishing criteria for gestational diabetes. Diabetes Care 3(3):437-9, 1980;-Jun.	Poor Quality
O'Sullivan JB. Gestational diabetes. Unsuspected, asymptomatic diabetes in pregnancy. New England Journal of Medicine 264:1082-5, 1961.	Prevelence only data
Peled Y, Perri T, Chen R, Pardo J, Bar J, Hod M. Gestational diabetes mellitus--implications of different treatment protocols. Journal of Pediatric Endocrinology 17(6):847-52, 2004.	Excluded for Study Design
Pennison EH, Egerman RS. Perinatal outcomes in gestational diabetes: a comparison of criteria for diagnosis. American Journal of Obstetrics & Gynecology 184(6):1118-21, 2001.	Excluded for Study Design, No information on yield (prevalence), sensitivity/specificity or reliability
Pettitt DJ, Bennett PH, Hanson RL, Narayan KM, Knowler WC. Comparison of World Health Organization and National Diabetes Data Group procedures to detect abnormalities of glucose tolerance during pregnancy. Diabetes Care 1994; 17(11):1264-1268.	Natural history only
Pettitt DJ, Bennett PH, Hanson RL, Narayan KM, Knowler WC. Comparison of World Health Organization and National Diabetes Data Group procedures to detect abnormalities of glucose tolerance during pregnancy. Diabetes Care 1994; 17(11):1264-1268.	Poor Quality
Pettitt DJ, Bennett PH, Saad MF, Charles MA, Nelson RG, Knowler WC. Abnormal glucose tolerance during pregnancy in Pima Indian women. Long-term effects on offspring. Diabetes 1991; 40 Suppl 2:126-130.	Does not address one of the key questions

Appendix D: Excluded Studies (continued)

Reference	Reason for Exclusion
Pettitt DJ, Knowler WC, Baird HR, Bennett PH. Gestational diabetes: infant and maternal complications of pregnancy in relation to third-trimester glucose tolerance in the Pima Indians. Diabetes Care 1980; 3(3):458-464.	Natural history only
Phung H, Bauman A, Tran M, Young L, McDonald J, Michell L et al. Factors that influence special care nursery admissions to a district hospital in South-western Sydney. Journal of Paediatrics & Child Health 41(3):119-24, 2005.	Excluded for Study Design
Poyhonen-Alho M, Teramo K, Kaaja R. Treatment of gestational diabetes with short- or long-acting insulin and neonatal outcome: a pilot study. Acta Obstetricia et Gynecologica Scandinavica 81(3):258-9, 2002.	Did not use designated diagnostic test or diagnostic criteria
Poyhonen-Alho M, Teramo K, Kaaja R. Treatment of gestational diabetes with short- or long-acting insulin and neonatal outcome: a pilot study. Acta Obstetricia et Gynecologica Scandinavica 81(3):258-9, 2002.	Did not use designated diagnostic test or diagnostic criteria
Ramadhani TA, Canfield MA, Waller DK, Case AP. Medical records vs. interview responses: a comparative analysis of selected variables for linked birth defect cases. Birth Defects Research 70(9):592-6, 2004.	Excluded for Study Design
Ramirez-Torres MA, Rodriguez-Pezino J, Zambrana-Castaneda M, Lira-Plascencia J, Parra A. Gestational diabetes mellitus and glucose intolerance among Mexican pregnant adolescents. Journal of Pediatric Endocrinology 16(3):401-5, 2003.	Does not address morbidity and/or mortality, No information on yield (prevalence), sensitivity/specificity or reliability
Ratzon N, Greenbaum C, Dulitzky M, Ornoy A. Comparison of the motor development of school-age children born to mothers with and without diabetes mellitus. Phys Occup Ther Pediatr 2000; 20(1):43-57.	Does not address one of the key questions
Ray JG. Screening and active management reduced perinatal complications more than routine care in gestational diabetes. ACP J Club 2005; 143(3):65.	Editorials, comments and letters
Reece EA. Synopsis of the North American Diabetes in Pregnancy Study Group Conference in Little Rock, Arkansas, May 2003. Journal of Maternal-Fetal & Neonatal Medicine 15(1):1-5, 2004.	Editorials, comments and letters
Ricart W, Bach C, Fernandez-Real JM, Sabria J. Major fetal complications in optimised progestational diabetes mellitus. Diabetologia 43(8):1077 -8, 2000.	Editorials, comments and letters
Ricart W, Lopez J, Mozas J, Pericot A, Sancho MA, Gonzalez N et al. Body mass index has a greater impact on pregnancy outcomes than gestational hyperglycaemia. Diabetologia 2005; 48(9):1736-1742.	Natural history only
Ricart W, Lopez J, Mozas J, Pericot A, Sancho MA, Gonzalez N et al. Potential impact of American Diabetes Association (2000) criteria for diagnosis of gestational diabetes mellitus in Spain. Diabetologia 48(6):1135-41, 2005.	Natural history only
Rizzo TA, Dooley SL, Metzger BE, Cho NH, Ogata ES, Silverman BL. Prenatal and perinatal influences on long-term psychomotor development in offspring of diabetic mothers. Am J Obstet Gynecol 1995; 173(6):1753-1758.	Excluded for Study Design
Roberts RN, Moohan JM, Foo RL, Harley JM, Traub AI, Hadden DR. Fetal outcome in mothers with impaired glucose tolerance in pregnancy. Diabet Med 1993; 10(5):438-443.	Excluded for Study Design

Appendix D: Excluded Studies (continued)

Reference	Reason for Exclusion
Rouse DJ, Owen J, Goldenberg RL, Cliver SP. The effectiveness and costs of elective cesarean delivery for fetal macrosomia diagnosed by ultrasound. JAMA 1996; 276(18):1480-1486.	Does not address one of the key questions
Rouse DJ, Owen J. Prophylactic cesarean delivery for fetal macrosomia diagnosed by means of ultrasonography--A Faustian bargain? Am J Obstet Gynecol 1999; 181(2):332-338.	Does not address one of the key questions
Rudge MV, Calderon IM, Ramos MD, Abbade JF, Rugolo LM. Perinatal outcome of pregnancies complicated by diabetes and by maternal daily hyperglycemia not related to diabetes. A retrospective 10-year analysis. Gynecologic & Obstetric Investigation 50(2):108-12, 2000.	Excluded for Study Design
Rust OA, Bofill JA, Andrew ME, Kincaid TA, Stubbs TM, Miller EH et al. Lowering the threshold for the diagnosis of gestational diabetes. Am J Obstet Gynecol 1996; 175(4 Pt 1):961-965.	Excluded for Study Design
Sacks DA, Abu-Fadil S, Greenspoon JS, Fotheringham N. Do the current standards for glucose tolerance testing in pregnancy represent a valid conversion of O'Sullivan's original criteria? Am J Obstet Gynecol 1989; 161(3):638-641.	Does not address one of the key questions
Sacks DA, Abu-Fadil S, Greenspoon JS, Fotheringham N. How reliable is the fifty-gram, one-hour glucose screening test? Am J Obstet Gynecol 1989; 161(3):642-645.	Poor Quality
Sacks DA, Abu-Fadil S, Karten GJ, Forsythe AB, Hackett JR. Screening for gestational diabetes with the one-hour 50-g glucose test. Obstetrics & Gynecology 70(1):89-93, 1987.	No information on yield (prevalence), sensitivity/specificity or reliability
Sacks DA, Chen W, Wolde-Tsadik G, Buchanan TA. Fasting plasma glucose test at the first prenatal visit as a screen for gestational diabetes. Obstetrics & Gynecology 101(6):1197-203, 2003.	Did not use established screening criteria
Sacks DA, Greenspoon JS, Abu-Fadil S, Henry HM, Wolde-Tsadik G, Yao JF. Toward universal criteria for gestational diabetes: the 75-gram glucose tolerance test in pregnancy. Am J Obstet Gynecol 1995; 172(2 Pt 1):607-614.	Does not address one of the key questions
Sacks DA, Liu AI, Wolde-Tsadik G, Amini SB, Huston-Presley L, Catalano PM. What proportion of birth weight is attributable to maternal glucose among infants of diabetic women? American Journal of Obstetrics & Gynecology 194;(2):501-507.	Excluded for Study Design
Saldana TM, Siega-Riz AM, Adair LS, Savitz DA, Thorp JM, Jr. The association between impaired glucose tolerance and birth weight among black and white women in central North Carolina. Diabetes Care 26(3):656-61, 2003.	Natural history only
Sameshima H, Kamitomo M, Kajiya S, Kai M, Furukawa S, Ikenoue S. Early glycemic control reduces large-for-gestational-age infants in 250 Japanese gestational diabetes pregnancies. American Journal of Perinatology 17(7):371-6, 2000.	Excluded for Study Design
Santini DL, Ales KL. The impact of universal screening for gestational glucose intolerance on outcome of pregnancy. Surg Gynecol Obstet 1990; 170(5):427-436.	Excluded for Study Design
Sarkar S, Watman J, Seigel WM, Schaeffer HA. A prospective controlled study of neonatal morbidities in infants born at 36 weeks or more gestation to Women with diet-controlled gestational diabetes (GDM-class Al). J Perinatol 2003; 23(3):223-228.	Does not address one of the key questions

Appendix D: Excluded Studies (continued)

Reference	Reason for Exclusion
Schafer-Graf UM, Dupak J, Vogel M, Dudenhausen JW, Kjos SL, Buchanan TA et al. Hyperinsulinism, neonatal obesity and placental immaturity in infants born to women with one abnormal glucose tolerance test value. J Perinat Med 1998; 26(1):27-36.	Does not address one of the key questions
Schmidt MI, Duncan BB, Reichelt AJ, Branchtein L, Matos MC, Costa e Forti 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):1151-1155.	Natural history only
Schwartz ML, Ray WN, Lubarsky SL. The diagnosis and classification of gestational diabetes mellitus: is it time to change our tune? Am J Obstet Gynecol 1999; 180 (6 Pt 1):1560-1571.	Does not report sensitivity and specificity criterion to assess specified health outcomes
Schytte T, Jorgensen LG, Brandslund I, Petersen PH, Andersen B. The clinical impact of screening for gestational diabetes. Clin Chem Lab Med 2004; 42(9):1036-1042.	Did not use designated diagnostic test or diagnostic criteria
Scott DA, Loveman E, McIntyre L, Waugh N . Screening for gestational diabetes: a systematic review and economic evaluation. Health Technol Assess 2002; 6(11):1-161.	SER used as source document
Sermer M, Naylor CD, Farine D, Kenshole AB, Ritchie JW, Gare DJ et al. The Toronto Tri-Hospital Gestational Diabetes Project. A preliminary review. Diabetes Care 1998; 21 Suppl 2:B33-B42.	Did not use designated diagnostic test or diagnostic criteria
Sermer M, Naylor CD, Gare DJ, Kenshole AB, Ritchie JW, Farine D et al. Impact of increasing carbohydrate intolerance on maternal-fetal outcomes in 3637 women without gestational diabetes. The Toronto Tri-Hospital Gestational Diabetes Project. Am J Obstet Gynecol 1995; 173(1):146-156.	Did not use designated diagnostic test or diagnostic criteria
Sermer M, Naylor CD, Gare DJ, Kenshole AB, Ritchie JW, Farine D et al. Impact of time since last meal on the gestational glucose challenge test. The Toronto Tri-Hospital Gestational Diabetes Project. Am J Obstet Gynecol 1994; 171(3):607-616.	No information on yield (prevalence), sensitivity/specificity or reliability
Shamsuddin K, Mahdy ZA, Siti R, I, Jamil MA, Rahimah MD. Risk factor screening for abnormal glucose tolerance in pregnancy. Int J Gynaecol Obstet 2001; 75(1):27-32.	Does not address one of the key questions
Sheffield JS, Butler-Koster EL, Casey BM, McIntire DD, Leveno KJ. Maternal diabetes mellitus and infant malformations. Obstetrics & Gynecology 100(5 Pt 1):925-30, 2002.	Excluded for Study Design
Silverman BL, Rizzo T, Green OC, Cho NH , Winter RJ, Ogata ES et al. Long-term prospective evaluation of offspring of diabetic mothers. Diabetes 1991; 40 Suppl 2:121-125.	Does not address one of the key questions
Simmons D, Thompson CF, Conroy C, Scott DJ. Use of insulin pumps in pregnancies complicated by type 2 diabetes and gestational diabetes in a multiethnic community. Diabetes Care 24(12):2078 -82, 2001.	Did not use designated diagnostic test or diagnostic criteria
Simmons D, Thompson CF, Conroy C. Incidence and risk factors for neonatal hypoglycaemia among women with gestational diabetes mellitus in South Auckland. Diabetic Medicine 17(12):830-4, 2000.	Excluded for Study Design
Simpson RW, Kast SJ. Management of gestational diabetes with a conservative insulin protocol. Medical Journal of Australia 172(11):537-40, 2000.	Did not use designated diagnostic test or diagnostic criteria

Appendix D: Excluded Studies (continued)

Reference	Reason for Exclusion
Siribaddana SH, Deshabandu R, Rajapakse D, Silva K, Fernando DJ. The prevalence of gestational diabetes in a Sri Lankan antenatal clinic. Ceylon Medical Journal 43(2):88-91, 1998.	Prevalence outside U.S.
Sjogren B, Robeus N, Hansson U. Gestational diabetes: a case-control study of women's experience of pregnancy, health and the child. J Psychosom Res 1994; 38(8):815-822.	Poor Quality
Skitek M. Screening for gestational diabetes mellitus. Clinical Chemistry & Laboratory Medicine 43(6):664-6, 2005.	Editorials, comments and letters
Soonthornpun S, Soonthornpun K, Aksonteing J, Thamprasit A. A comparison between a 75-g and 100-g oral glucose tolerance test in pregnant women. International Journal of Gynaecology & Obstetrics 81(2):169-73, 2003.	No information on yield (prevalence), sensitivity/specificity or reliability
Southwick RD, Wigton TR. Screening for gestational diabetes mellitus in adolescent Hispanic Americans. Journal of Reproductive Medicine 45(1):31-4, 2000.	Excluded for Study Design
Stamilio DM, Olsen T, Ratcliffe S, Sehdev HM, Macones GA. False-positive 1-hour glucose challenge test and adverse perinatal outcomes. Obstetrics & Gynecology 103(1):148-56, 2004.	Excluded for Study Design
Suhonen L, Teramo K. Hypertension and pre-eclampsia in women with gestational glucose intolerance. Acta Obstet Gynecol Scand 1993; 72(4):269-272.	Excluded for Study Design
Sunsaneevithayakul P, Boriboohirunsarn D, Sutanthavibul A, Ruangvutilert P, Kanokpongsakdi S, Singkiratana D et al. Risk factor-based selective screening program for gestational diabetes mellitus in Siriraj Hospital: result from clinical practice guideline. Journal of the Medical Association of Thailand 86(8):708-14, 2003.	Excluded for Study Design
Super DM, Edelberg SC, Philipson EH, Hertz RH, Kalhan SC. Diagnosis of gestational diabetes in early pregnancy. Diabetes Care 14(4):288-94, 1991.	Did not use designated diagnostic test or diagnostic criteria
Sutton L, Sayer GP, Bajuk B, Richardson V, Berry G, Henderson-Smart DJ. Do very sick neonates born at term have antenatal risks? 2. Infants ventilated primarily for lung disease. Acta Obstetricia et Gynecologica Scandinavica 80(10):917-25, 2001.	Excluded for Study Design
Svare JA, Hansen BB, Molsted-Pedersen L. Perinatal complications in women with gestational diabetes mellitus. Acta Obstet Gynecol Scand 2001; 80(10):899-904.	Excluded for Study Design
Tanir HM, Sener T, Gurer H, Kaya M. A ten-year gestational diabetes mellitus cohort at a university clinic of the mid-Anatolian region of Turkey. Clinical & Experimental Obstetrics & Gynecology 32(4):241-4, 2005.	Excluded for Study Design
Taylor JS, Kacmar JE, Nothnagle M, Lawrence RA. A systematic review of the literature associating breastfeeding with type 2 diabetes and gestational diabetes. J Am Coll Nutr 2005; 24(5):320-326.	Does not address one of the key questions
Tuffnell DJ, West J, Walkinshaw SA. Treatments for gestational diabetes and impaired glucose tolerance in pregnancy. Cochrane Database of Systematic Reviews 2006;(1).	SER used as source document
Turok DK, Ratcliffe SD, Baxley EG. Management of gestational diabetes mellitus. American Family Physician 68(9):1767 -72, 2003.	Non-systematic review

Appendix D: Excluded Studies (continued)

Reference	Reason for Exclusion
Vaidyanathan B, Menon PS. Insulin analogues and management of diabetes mellitus. Indian Journal of Pediatrics 67(6):435-41, 2000.	Excluded for Study Design
van Hoorn J, Dekker G, Jeffries B. Gestational diabetes versus obesity as risk factors for pregnancy-induced hypertensive disorders and fetal macrosomia. Aust N Z J Obstet Gynaecol 2002; 42(1):29-34.	Excluded for Study Design
Vanky E, Salvesen KA, Heimstad R, Fougner KJ, Romundstad P, Carlsen SM. Metformin reduces pregnancy complications without affecting androgen levels in pregnant polycystic ovary syndrome women: results of a randomized study. Human Reproduction 2004;(8):1734-1740.	Does not address one of the key questions
Vidaeff AC, Yeomans ER, Ramin SM. Gestational diabetes: a field of controversy. Obstetrical & Gynecological Survey 58(11):759-69, 2003.	Non-systematic review
Vogel N, Burnand B, Vial Y, Ruiz J, Paccaud F, Hohlfeld P. Screening for gestational diabetes: variation in guidelines. Eur J Obstet Gynecol Reprod Biol 2000; 91(1):29-36.	Does not address one of the key questions
Walkinshaw SA. Dietary regulation for 'gestational diabetes'. Cochrane Database of Systematic Reviews 2006;(1).	Does not address one of the key questions
Walkinshaw SA. Very tight versus tight control for diabetes in pregnancy. Cochrane Database of Systematic Reviews 2006;(1).	Does not address one of the key questions
Watson WJ. Serial changes in the 50-g oral glucose test in pregnancy: implications for screening. Obstetrics & Gynecology 74(1):40-3, 1989.	No information on yield (prevalence), sensitivity/specificity or reliability
Weijers RN, Bekedam DJ, Smulders YM. Determinants of mild gestational hyperglycemia and gestational diabetes mellitus in a large dutch multiethnic cohort. Diabetes Care 25(1):72-7, 2002.	Non-systematic review
Wein P, Dong ZG, Beischer NA, Sheedy MT. Factors predictive of recurrent gestational diabetes diagnosed before 24 weeks' gestation. American Journal of Perinatology 12(5):352-6, 1995.	Excluded for Study Design
Weiner CP, Fraser MM, Burns JM, Schnoor D, Herrig J, Whitaker LA. Cost efficacy of routine screening for diabetes in pregnancy: 1-h versus 2-h specimen. Diabetes Care 1986; 9(3):255-259.	Does not address one of the key questions
Weiss JL, Malone FD, Emig D, Ball RH, Nyberg DA, Comstock CH et al. Obesity, obstetric complications and cesarean delivery rate--a population-based screening study. American Journal of Obstetrics & Gynecology 190;(4):1091-1097.	Does not address one of the key questions
Weissman A, Solt I, Zloczower M, Jakobi P. Hypoglycemia during the 100-g oral glucose tolerance test: incidence and perinatal significance. Obstetrics & Gynecology 105(6):1424 -8, 2005.	Excluded for Study Design
Wen SW, Liu S, Kramer MS, Joseph KS, Levitt C, Marcoux S et al. Impact of prenatal glucose screening on the diagnosis of gestational diabetes and on pregnancy outcomes. American Journal of Epidemiology 152(11):1009 -14; discussion 1015 -6, 2000.	Excluded for Study Design
Wong L, Tan AS. The glucose challenge test for screening gestational diabetes in pregnant women with no risk factors. Singapore Medical Journal 42(11):517-21, 2001.	Does not address morbidity and/or mortality
Wood SL, Jick H, Sauve R. The risk of stillbirth in pregnancies before and after the onset of diabetes. Diabetic Medicine 1920;(9):703-7, 2003.	Excluded for Study Design

Appendix D: Excluded Studies (continued)

Reference	Reason for Exclusion
Wyatt PR, Owolabi T, Meier C, Huang T. Age-specific risk of fetal loss observed in a second trimester serum screening population. American Journal of Obstetrics & Gynecology 192;(1):240-246.	Does not address one of the key questions
Yang X, Hsu-Hage B, Zhang H, Zhang C, Zhang Y, Zhang C. Women with impaired glucose tolerance during pregnancy have significantly poor pregnancy outcomes. Diabetes Care 2002; 25(9):1619-1624.	Natural history only
Yogev Y, Langer O, Brustman L, Rosenn B. Pre-eclampsia and gestational diabetes mellitus: does a correlation exist early in pregnancy? J Matern Fetal Neonatal Med 2004; 15(1):39-43.	Excluded for Study Design
Yogev Y, Langer O, Xenakis EM, Rosenn B. Glucose screening in Mexican-American women. Obstetrics & Gynecology 103(6):1241 -5, 2004.	Prevalence only data
Young C, Kuehl TJ, Sulak PJ, Allen SR. Gestational diabetes screening in subsequent pregnancies of previously healthy patients. American Journal of Obstetrics & Gynecology 182(5):1024 -6, 2000.	Excluded for Study Design