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Systematic Evidence Review
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Screening for Gestational Diabetes Mellitus

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Preface

The Agency for Healthcare Research and Quality (AHRQ) sponsors the development of Systematic Evidence Reviews (SERs) through its Evidence-based Practice Program. With guidance from the third U.S. Preventive Services Task Force* (USPSTF) and input from Federal partners and primary care specialty societies, two Evidence-based Practice Centers—one at the Oregon Health Sciences University and the other at Research Triangle Institute-University of North Carolina—systematically review the evidence of the effectiveness of a wide range of clinical preventive services, including screening, counseling, immunizations, and chemoprevention, in the primary care setting. The SERs—comprehensive reviews of the scientific evidence on the effectiveness of particular clinical preventive services—serve as the foundation for the recommendations of the third USPSTF, which provide age- and risk-factor-specific recommendations for the delivery of these services in the primary care setting. Details of the process of identifying and evaluating relevant scientific evidence are described in the "Methods" section of each SER.

The SERs document the evidence regarding the benefits, limitations, and cost-effectiveness of a broad range of clinical preventive services and will help to further awareness, delivery, and coverage of preventive care as an integral part of quality primary health care.

AHRQ also disseminates the SERs on the AHRQ Web site (http://www.ahrq.gov/uspstfix.htm) and disseminates summaries of the evidence (summaries of the SERs) and recommendations of the third USPSTF in print and on the Web. These are available through the AHRQ Web site (http://www.ahrgq.gov/uspstfix.htm), through the National Guideline Clearinghouse (http://www.ncg.gov), and in print through the AHRQ Publications Clearinghouse (1-800-358-9295).

We welcome written comments on this SER. Comments may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 6010 Executive Blvd., Suite 300, Rockville, MD 20852.

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*The USPSTF is an independent panel of experts in primary care and prevention first convened by the U.S. Public Health Service in 1984. The USPSTF systematically reviews the evidence on the effectiveness of providing clinical preventive services--including screening, counseling, immunization, and chemoprevention--in the primary care setting. AHRQ convened the third USPSTF in November 1998 to update existing Task Force recommendations and to address new topics.

The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services of a particular drug, device, test, treatment, or other clinical service.

Structured Abstract

Context

Gestational diabetes mellitus (GDM) has been associated with increased perinatal morbidity, maternal trauma, and an increase in operative deliveries (cesarean section and forceps or vacuum extraction). Long-term sequelae for the mother with GDM and her offspring have also been reported. A major concern is the association of GDM with fetal macrosomia and its potential for subsequent neonatal birth trauma (e.g., temporary or permanent brachial plexus injury, clavicular fracture). Although universal GDM screening has become routine practice in the United States, it is not clear that such screening has an important impact on maternal and neonatal health outcomes.

Objective

To systematically review the evidence about the benefits and harms of screening pregnant women for gestational diabetes mellitus (GDM).

Data Sources and Study Selection

We systematically searched MEDLINE and the Cochrane Collaboration library from 1994 through December 2001, using the Medical Subject Headings (MeSH) "diabetes, gestational" and combining this term with predefined strategies to identify diagnostic accuracy studies and randomized controlled trials (RCTs) of screening and treatment for pregnant women.

We also conducted focused searches of MEDLINE from 1966 through 1994 to identify older articles of interest. We examined reference lists of textbooks, monographs and review articles; and asked experts in the field. We graded the quality of the articles according to criteria for both internal and external validity.

Data Extraction

The first author abstracted relevant data from the included articles and entered them into a standardized form. A second reviewer checked the accuracy of the tables against the original articles. Using USPSTF criteria, we evaluated the internal and external validity and coherence of the results of each individual study and all the evidence concerning each key question.

Data Synthesis

No well-conducted RCT provides direct evidence for the health benefits of screening for GDM. The impact of hyperglycemia on adverse maternal and fetal health outcomes is probably continuous; the magnitude of any increased risk for the large number of women at lower levels of hyperglycemia is uncertain. The evidence is unclear about the optimal screening and reference diagnostic test and cutpoint for GDM. Although insulin therapy decreases the incidence of fetal macrosomia for those women with higher levels of hyperglycemia, the magnitude of any effect on maternal and neonatal health outcomes is not clear. The evidence is insufficient to determine the magnitude of health benefit for any treatment among the large number of women with GDM at lower levels of hyperglycemia. No properly controlled prospective trials show that antepartum surveillance in patients with GDM is beneficial when compared to those with GDM but who are not monitored. As the magnitude of benefit of

screening and treating GDM is uncertain, so to is the cost-effectiveness of this strategy. We found limited evidence about the potential adverse effects of screening for GDM.

Conclusion

The evidence of screening for GDM is insufficient to determine the extent to which screening has an important impact on maternal and neonatal health outcomes. The balance of benefits versus harms remains in question, especially for the large number of women with lower degrees of hyperglycemia. There is no evidence from prospective trials that screening for GDM is a cost-effective strategy. An RCT of screening is necessary to answer the many remaining questions.

Table of Contents

List of Tables

List of Figures

Chapter 1. Introduction

Epidemiology of Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is defined as glucose intolerance with the onset or first detection during pregnancy.[1,2] GDM occurs in 2% to 5% of all pregnancies, for approximately 135,000 cases annually in the United States.[1] Major risk factors for developing GDM include increasing maternal age, family history of diabetes, increased pregravid body mass index (BMI), and lack of pregravid vigorous exercise.[3]

Observational data reveal that the prevalence of GDM in women with defined low-risk factors, such as being of white ethnic origin, less than 25 years old, and having a BMI less than 25 kilograms per meter of height squared (kg/m^2), ranges from 1.4% to 2.8%.[4-6] The prevalence of GDM in the low-risk group of adolescent or teenage pregnancies ranges from 1.2% to 1.8%.[7-9] The prevalence of GDM in high-risk populations (those with risk factors such as obesity, family history of diabetes, certain ethnic groups) generally ranges from 3.3% to 6.1%.[6,10,11]

Pregnant women demonstrate a range of glucose intolerance, exemplified by normal to slightly or greatly elevated glucose levels. Physiologic changes during pregnancy impair peripheral insulin action, inducing a degree of glucose intolerance that increases as pregnancy progresses. In normal pregnancies, the fasting levels of glucose range from 60 milligrams per decileter (mg/dL) to 90 mg/dL; 1-hour and 2-hour postprandial levels of glucose are less than 140 mg/dL and 120 mg/dL, respectively.[1] Thus, pregnant women demonstrate a spectrum of glucose intolerance exemplified by prolonged postprandial hyperglycemia and hyperinsulinemia, but with mild fasting hypoglycemia.

Markedly elevated maternal glucose levels most often occur in women with pregestational diabetes. These pregnancies are at higher risk for multiple complications affecting both the mother and the fetus than are those among women without existing diabetes. Current therapy improves outcomes for both mother and fetus.[12]

The point on the spectrum of glucose intolerance that defines "gestational diabetes" is controversial. No study has found a threshold that separates those with risk of complications from those with no risk.

Both additional risk of adverse health outcomes from the lower levels of maternal hyperglycemia associated with GDM, detectable primarily by screening in the third trimester, and the magnitude of the benefit from treating that risk are less certain than are data about women with pregestational diabetes. No well-designed randomized controlled trial (RCT) of screening for GDM has been completed, and thus the evidence for screening is indirect.

Prior Recommendations about Screening for Gestational Diabetes Mellitus

National groups disagree about whether to recommend screening for GDM (Table 1).[1,13-17] The American Diabetes Association[17] and the Fourth International Workshop on Gestational Diabetes Mellitus,[16] for example, recommend selective screening (i.e., screening all women with risk factors and no glucose testing of women who do not meet specific criteria). In the mid-1990s, the US Preventive Services Task Force (USPSTF) and earlier the Canadian Task Force on the Periodic Health Examination concluded that the evidence was insufficient to recommend for or against routine screening.[13,14] The USPSTF had also noted that "…Clinicians may decide to screen high-risk pregnant women on other grounds..."(p. 204).[14]

Despite no strong recommendations in favor of universal screening, a 1996 survey by the American College of Obstetricians and Gynecologists (ACOG) showed that 94% of 550 ACOG Fellows in office-based practice reported performing universal screening for GDM.[18] This pattern was seen even though ACOG made no definite recommendation in 1994, stating that "there are no data to support the benefit of screening...and further studies are needed on which to base a recommendation" (p.5).[19] At the same time, the ACOG guidelines stated that selective screening for GDM may be appropriate in some clinical settings (e.g., teen clinics) but that universal screening may be more appropriate in other settings (e.g., in those having a high background prevalence of type 2 diabetes and other risk factors).[18]

The latest ACOG recommendation (issued in 2001), based primarily on consensus and expert opinion, stated that "although universal glucose challenge screening for GDM is the most sensitive approach, there may be pregnant women at low risk who are less likely to benefit from testing" (p. 534).[1] These recommendations were made "despite the lack of population-derived data supporting the benefit of making the diagnosis of GDM" (p. 526).

With the continuing controversy concerning the advisability of GDM screening, the RTI International-University of North Carolina Evidence-based Practice Center (RTI-UNC EPC) undertook this systematic evidence review (SER) to assist the USPSTF in reconsidering its previous conclusions and recommendation. We restricted the SER to screening for GDM in the third trimester of pregnancy, thus excluding both women with known pregestational diabetes and those who are discovered by symptoms earlier in pregnancy. Some women with previously undiscovered pregestational diabetes, however, will inevitably be detected in any screening program for GDM.

Organization of This Report

Chapter 2 of this SER documents our methods for searching and synthesizing the literature and producing this report; in these efforts, we were guided by an analytic framework and six key questions agreed to by the USPSTF. Chapter 3 presents results of our literature search and synthesis. We offer a further discussion of these results and recommendations for future research in Chapter 4. Figures and tables in the text can be found at the end of chapters where they are first called out. Appendix A contains acknowledgments to our peer reviewers, USPSTF liaisons and RTI-UNC EPC staff; Appendix B provides the detailed evidence tables for selected reviewed articles.

Chapter 2. Methods

Analytic Framework and Key Questions

Members of the RTI International-University of North Carolina (UNC) Evidence-based Practice Center (RTI-UNC EPC), together with 2 liaison members of the US Preventive Services Task Force (USPSTF) (see acknowledgments in Appendix A), developed an analytic framework to specify the key questions relevant to the issues of screening for and treatment of gestational diabetes mellitus (GDM). The analytic framework describes the relationships among screening a population at risk (starting on the left of the figure), diagnosing and then treating patients (the middle panels of the figure), and realizing one or more sets of desired outcomes (on the right side of the figure), in this case decreased incidence and severity of maternal and infant morbidity (Figure 1). Numbers in superscripts in the analytic framework correspond to six key questions that guided the literature searches and analysis.

The six key questions for this work are as follows:

- **Key Question No. 1.** What are the health consequences for mothers and infants of screening for gestational diabetes? Both the type and the magnitude of such outcomes are of concern. For mothers, specific outcomes include perineal injuries (such as third or fourth degree lacerations), cesarean section, anesthesia risks, and pregnancy-induced hypertension (PIH). For infants, outcomes of interest include hypoglycemia that requires treatment, hyperbilirubinema that requires treatment, brachial plexus injuries, fractures of the clavicle, admissions to special care nurseries, and stillbirth.

- **Key Question No. 2.** What are the health consequences of untreated gestational diabetes?
- **Key Question No. 3.** What are the accuracy and reliability of GDM screening tests? In this case, accuracy is considered largely in terms of sensitivity and specificity.
- **Key Question No. 4**. What is the efficacy or effectiveness of glycemic control or antepartum testing and surveillance, or both, in terms of maternal and infant outcomes? With respect to glycemia control, 4 intermediate outcomes are of interest: macrosomia, operative delivery, neonatal hypoglycemia, and neonatal hyperbilirubemia (both by biochemical assays). Generally these issues are couched in terms of the outcomes for screened women versus those for women who are not screened; where differences occur, what they are and their magnitude are then the important matters. The same approach holds for comparisons of women who do or do not receive antepartum testing and surveillance.
- **Key Question No. 5**. What are the harms of screening? What are the harms of treatment?
- **Key Question No. 6**. What are the costs and cost-effectiveness of screening and treatment for GDM versus not screening or not treating.

The GDM analytic framework in Figure 1 depicts 2 approaches for connecting screening with improved health outcomes. The first entails direct evidence (Key Question 1) linking screening to the specified maternal outcomes. The second entails more indirect evidence arrived at by piecing together several bodies of evidence (via Key Questions 3, 4, 5) concerning the accuracy and reliability of screening tests and the efficacy or effectiveness of treatment (specifically, glycemic control) or antepartum testing and surveillance. For both screening and

the two treatment interventions (glycemic control or testing and surveillance), costs and cost-effectiveness are relevant concerns (Key Question 6). Finally, Key Question 2 about the impact of untreated GDM provides a context within which to interpret all these issues.

Literature Search and Analysis Strategy

Inclusion/Exclusion Criteria for Admissible Evidence

We developed inclusion criteria for selecting the evidence relevant to answer the key questions (Table 2). We required randomized controlled trials (RCTs) for direct evidence for the efficacy of screening, treatment, and harms associated with treatment. Although we examined evidence of the effects of treatment on intermediate outcomes (i.e., those specified for Key Question 4 – macrosomia, operative delivery, neonatal hypoglycemia or hyperbilirubinemia), we prioritized studies that included health outcomes of the types shown in the boxes on the far right of the analytic framework for both mothers and infants (e.g., maternal trauma, brachial plexus injury, treatment-requiring hypoglycemia). For material on the sensitivity, specificity, and reliability of GDM screening tests, we required that articles provide data by which we could calculate sensitivity and specificity (if not reported directly by the article) and that the studies have used a criterion or reference standard. We allowed any study design for articles relating to harms and costs. All searches started with exploding the term "diabetes, gestational" and then proceeded by adding further terms.

Review of the literature was guided by our key questions and these inclusion criteria. We examined the critical literature from the 1996 USPSTF review[14] and searched MEDLINE and the Cochrane Library for systematic reviews and relevant studies published in English between

January 1, 1994 and December 15, 2001. We also examined the bibliographies of pertinent articles and contacted experts. We especially looked for studies concerning groups whose experience is clearly generalizable to the US population. We also conducted focused searches of MEDLINE from 1966 through 1994 to identify older articles of interest.

Study Selection

The first author reviewed abstracts of all articles found in the searches to determine which ones met inclusion criteria. The second author reviewed all abstracts excluded by the first. The authors retrieved the full text of all articles not excluded by both of these reviewers.

The first author reviewed the full text of all retrieved articles against inclusion criteria and discussed all excluded articles with the second author. They included any article that either author judged to have met the inclusion criteria (see last column in Table 2).

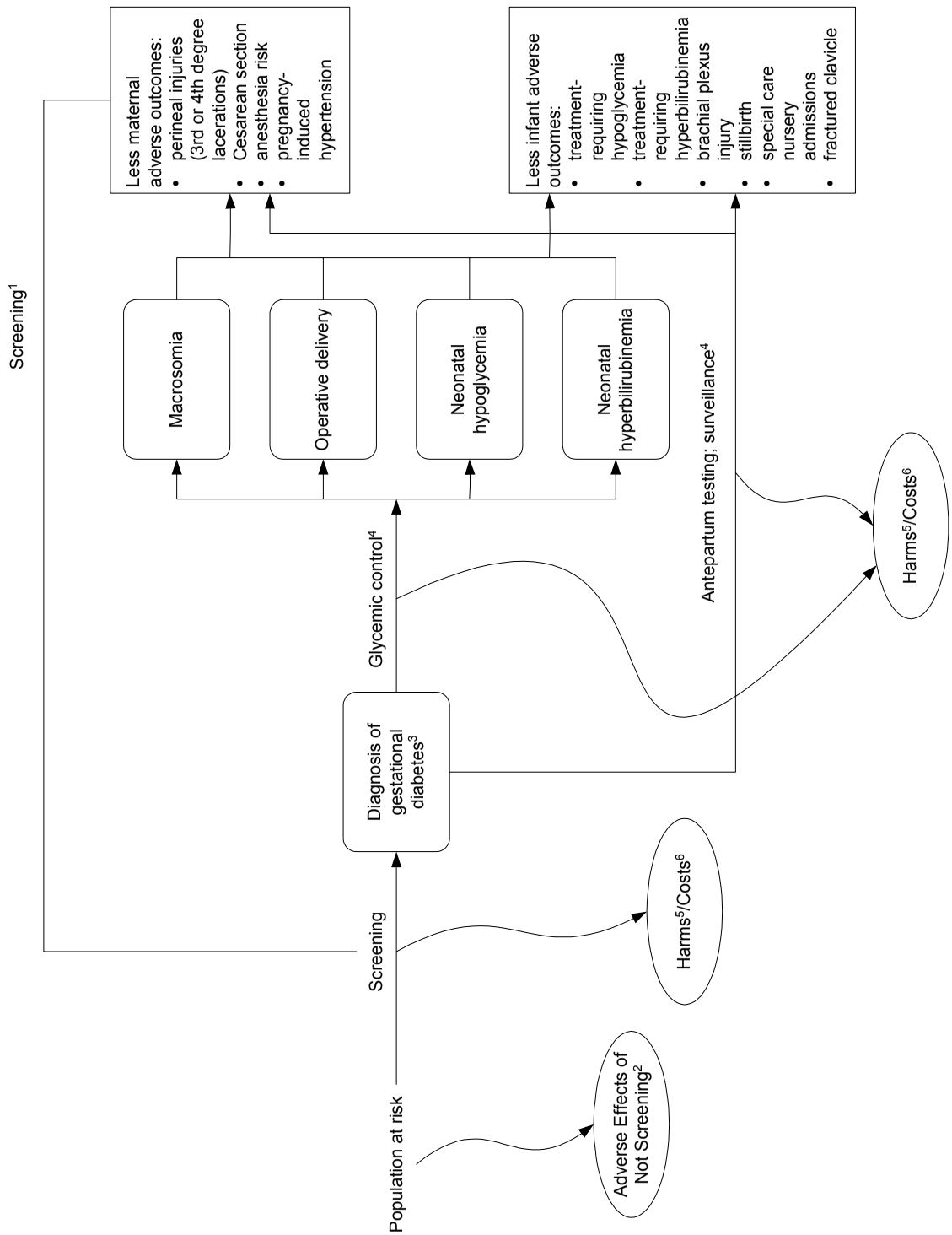
Synthesis of the Literature

The first author abstracted data from all these articles and entered those data into predesigned evidence tables. (Evidence tables appear in Appendix B.) USPSTF criteria was used for judging the quality of individual studies,[20] and both authors agreed to the final grading. Throughout the review, the authors worked closely with the USPSTF liaisons assigned to this topic.

Preparation of this Systematic Evidence Review

The authors presented an initial work plan for this SER and interim reports (including a full draft of this SER) at several meetings of the USPSTF in 2001, receiving feedback at each stage. Throughout the development of the SER, the material was also discussed with the TF liaisons. Finally, we sent the draft SER to multiple external peer reviewers (see Appendix A) and revised the SER as appropriate into this final version.

Figure 1. Screening for Gestational Diabetes: Analytic Framework



Chapter 3. Results

Our presentation of results is arranged chiefly in accordance with the 6 key questions (KQ) introduced in Chapter 2. Specifically, we address the following issues: impact of gestational diabetes mellitus (GDM) screening on maternal or fetal outcomes (KQ No. 1); adverse effects of unrecognized and untreated GDM (KQ No. 2); the accuracy and reliability of various ways to screening for GDM (KQ No. 3); efficacy and effectiveness of various treatments (KQ No. 4), including glycemic control, antepartum testing and surveillance; harms of screening or earlier treatment (KQ No. 5); and costs and cost-effectiveness (KQ No. 6). For KQ No. 3 on treatments, we organize the discussion in terms of the four intermediate health outcomes – macrosomia, operative delivery, neonatal hypoglycemia and neonatal hyperbilirubinemia - specified in the Analytic Framework (Figure 1).

Studies meeting our inclusion criteria that provide data for the sections that follow appear in one or more of the several evidence tables found in Appendix B. Those tables contain abstracted information on the following topics:

- Efficacy of GDM Screening (KQ No. 2)(Evidence Table [ET] 1);
- Impact of treatment for GDM (KQ Nos. 4 and 5) (ET 2) (nine randomized controlled trials (RCTs) of treatment of GDM are highlighted in Table 6, and are not presented in evidence tables);
- Impact of Antepartum Testing and Surveillance (ET 3).

Efficacy of Screening for Gestational Diabetes Mellitus

No properly designed and conducted RCT has examined the benefit of universal or selective screening for GDM compared to routine care without screening (KQ No. 1). The only RCT of the impact of different screening strategies attempted to examine the effects of either universal or selective screening for gestational diabetes on maternal and neonatal outcomes, but it had major methodologic flaws (ET No. 1).[21] In this study, Griffin et al. randomized patients at their first obstetrical visit to either selective screening based on risk factors at 32 weeks gestational age or universal screening between 26 and 28 weeks of gestation.

Uniform diabetic and obstetrical management was performed in all patients diagnosed with GDM; however, the duration of such interventions and gestational age at initiation of the intervention varied significantly between the 2 groups. Insulin therapy was used in fewer of the risk factor-screening group than the universal-screening group (7.4% v. 14.2%, $P > 0.05$). The prevalence of GDM was 2.7% in the universal-screening group and 1.45% in the selective-screening group ($P< 0.03$).

Women found to have GDM in the universal-screening group had improved health outcomes (e.g., spontaneous vaginal deliveries, cesarean delivery, prematurity, pre-eclampsia, and admissions to neonatal intensive care units) when compared to women found to have GDM in the selective group and to a combination of women found not to have diabetes from both screening groups. The investigators did no intention-to-screen analysis and provided no statistical significance information on comparisons of the universal group to the selective group.

We found serious flaws with this study. Besides the lack of an intention to screen analysis, there are problems with the control group that was used. A single “control group” was utilized after the authors combined the non-GDM women from both groups (n = 3,090) because

they found no differences in the outcomes between the 2 groups. In addition, no information is available on women who either refused (31% of 1,889 in the universal-screening group and 32 of 249 in the selective-screening group) or did not complete testing (22 of 333 with a positive glucose challenge test [GCT]). The 2 groups were not comparable in that they differed not only with regard to universal or selective screening but also in the timing of screening. Because of this, any differences in outcomes may be due more to the timing and duration of treatment than to any real effect of a difference in screening. Only 6 cases of fetal macrosomia occurred in this study; all 6 were in those screened at 33 weeks or later. The control group was also not comparable in that the women in that group were significantly younger and lower in weight and body mass index (BMI) when compared to the women in both GDM groups ($P < 0.05$). In addition, this was an unmasked study, so the obstetrical management of the subjects with GDM may have been influenced by the knowledge of the diagnosis. Lastly, the investigators did not use risk factors that have been widely recommended, such as race, ethnicity, or maternal age, as a basis for their selective screening process.

On the whole, this study does not answer the question as to whether universal screening offers benefits beyond selective screening or whether either is more effective than no screening at all. No other published RCT compares screening with no screening or compares universal screening with selective screening.

Retrospective studies comparing screened populations to unscreened control populations have also been flawed and had mixed results.[22,23] Some retrospective analyses that have compared screened populations to unscreened control populations have found no significant differences in macrosomia or in birth trauma.[24,25] These studies cannot definitively exclude a

benefit of screening because women screened for GDM are more likely to be at high risk,[25] and the study populations are not of sufficient size to determine if a true difference exists.

Beischer et al. retrospectively reviewed 116,303 pregnancies screened for GDM at a hospital in Melbourne, Australia between 1971 and 1994.[23] For the period 1971 through 1980, perinatal mortality was higher for infants born to women with GDM than for infants of women without GDM (odds ratio [OR], 2.11; 95% confidence interval [CI], 1.32-3.37). The study found no difference between these groups in perinatal mortality for the periods of 1981-1990 or 1991 through 1994 (OR, 0.96; 95% CI, 0.42-2.22). Perinatal mortality decreased for all GDM women throughout the study period. Among women who delivered between 1991 and 1994, those who were not screened for GDM had a higher perinatal mortality rate than women who were screened after adjustment for gestational age (OR, 2.21; 95% CI, 1.56-3.12). The authors were not able however, to account for the many additional differences between screened and nonscreened women that could confound the results. The data suggest that any previous association between GDM and perinatal mortality may be diminished with present-day obstetrical care. Alternatively, better glycemic control of women with GDM may account for this improved outcome.

In a 1998 preliminary review of The Toronto Tri-Hospital Gestational Diabetes Project (a prospective analytic cohort study conducted in three teaching hospitals), 3 groups of subjects were compared: (1) non-GDM controls (blinded caregivers); (2) women with carbohydrate intolerance who did not meet criteria for GDM by National Diabetes Data Group (NDDG) criteria (caregivers blinded); and (3) women diagnosed with GDM (caregivers given the results and treated the subjects for GDM).[26]

The untreated borderline GDM group had increased rates of macrosomia (28.7%) when compared to the normoglycemic control group (13.7%, $P < 0.001$) and cesarean delivery rate (29.6% compared to the normoglycemic controls [20.2%, $P = 0.03$]). Among women with GDM who received treatment, the birth weights of their infants normalized but the rate of cesarean delivery (33%) remained significantly increased compared with normoglycemic controls, whether macrosomia was present or not. Their increased rate of cesarean delivery persisted after adjustment for multiple maternal risk factors. Other maternal outcomes, such as lacerations, and perinatal outcomes, such as peripheral nerve injuries or fractures, did not differ between the groups.[26]

In this study design, the mild glucose intolerance group with masked caregivers could be viewed as an unscreened group. If maternal or perinatal outcomes in this group differ from those in the treated GDM group (after adjusting for potential confounders), then this difference may potentially be even greater for those who have more extreme glucose intolerance but are unscreened. The fact that health outcomes did not differ between these 2 groups does not, however, answer the question of the efficacy of screening.

This prospective cohort study provides good evidence that pregnant women with mild degrees of carbohydrate intolerance will have more macrosomic infants and cesarean deliveries then normoglycemic pregnant women. It also shows that in a tertiary care setting, treatment of women with GDM can reduce rates of macrosomia, but this decrease does not lead to lower rates of cesarean delivery when compared to those with untreated carbohydrate intolerance or to other important maternal or perinatal outcomes.

One ecologic study found no evidence that a program of universal screening compared with a geographic area without such a program, reduced fetal macrosomia, cesarean delivery, or

other diabetes-related complications.[27] Wen et al. examined the impact of universal screening on the diagnosis of GDM and its complications in Canada between 1984 and 1996. During this period, in all of Canada the diagnosis of women with GDM increased from 0.3% to 2.7% and the proportion with pregestational diabetes fell from 0.7% to 0.4%. A subanalysis of 2 regions of Ontario revealed that the incidence of GDM fell in a region where screening had been discontinued (as of 1989), but it remained high in the region where screening continued. The authors found no temporal trends for fetal macrosomia, cesarean delivery, or other diabetes-related complications, regardless of which screening policy was used. They concluded that universal screening may be of limited benefit. The authors also found that the increased screening for GDM identified cases of decreased severity, suggesting that the additional cases found by universal screening are mild. This study did not include the analysis of potential confounders such as prepregnancy BMI or gestational weight gain.

In summary, no properly controlled trial has examined the benefit of universal or selective screening compared to routine care without screening. No information is available from properly controlled trials that have examined the benefit of universal versus selective screening.

Thus, our review must examine indirect evidence that screening for GDM improves health outcomes. For the USPSTF to recommend screening for GDM, it must have adequate evidence that: (1) untreated GDM causes substantial maternal and/or fetal adverse health outcomes; (2) available screening tests accurately and efficiently detect GDM; and (3) available treatments improve health outcomes, with a magnitude that clearly justifies the harms and effort of screening and treatment. We will examine these issues in turn.

Adverse Health Outcomes from Untreated Gestational Diabetes Mellitus

Eight important adverse health outcomes for offspring have often been considered to be associated with untreated GDM (KQ No. 2). These are (1) increased perinatal mortality, (2) brachial plexus injury or clavicular fracture secondary to fetal macrosomia or increased fetal adiposity resulting in shoulder dystocia, (3) hypoglycemia, (4) hyperbilirubinemia, (5) hypocalcemia, (6) polycythemia, (7) preterm birth, and (8) the later development of diabetes, obesity, or neuropsychiatric disturbances. The 4 adverse maternal outcomes most frequently considered are (1) cesarean delivery, (2) third- and fourth-degree lacerations, (3) pre-eclampsia, and (4) the later development of type 1 or 2 diabetes mellitus.

Determining the existence and magnitude of a causal association between GDM of various degrees and adverse health outcomes is complex. We have only older studies of untreated GDM, at a time when obstetric practice was not as good as today, or more recent studies in which women received some treatment. We examined both types of studies.

Another problem with many studies is that they consider GDM as a dichotomous variable. If the risk of adverse health outcomes increases with the degree of hyperglycemia, as some studies suggest,[28-31] then studies that combine the few women who have higher levels of hyperglycemia with the many women who have lower levels may underestimate or even miss the association altogether.

Offspring Health Outcomes

The literature is scant and mixed about whether untreated GDM, given optimal obstetric care today, is associated with increased perinatal mortality. Although older studies found an

association between untreated GDM and increased perinatal mortality,[32,33] more recent studies have not shown this association (Table 3).[23,34-37] Perinatal mortality has declined in both non-GDM and GDM infants; it is a rare event in both groups.[23] For example, no stillbirths were seen in the 3 large studies including untreated women with GDM since 1985.[35,36,38] The lack of an association between GDM and perinatal mortality in these recent studies may be attributable to the small size of the studies (and concomitant lack of power to find small but real differences), the actual lack of an association, or improved obstetric care. The extent to which GDM is truly associated with perinatal mortality remains unclear.

Fetal morbidity related to macrosomia, commonly defined as fetal weight of 4,000 or 4,500 grams (g) or greater, is a better-documented effect of untreated GDM. As fetal weight increases above 4,000 (and especially 4,500) g, the risk of fetal morbidity due to shoulder dystocia (release maneuvers required for delivery of the shoulders) and brachial plexus injury also increases.

The incidence of fetal macrosomia in GDM pregnancies varies from 10% to 20% and the incidence of large-for-gestational-age (LGA) fetuses (LGA, >90th percentile) ranges from 15% to 35%.[39] The 2 largest and most recent studies of untreated women with GDM found that the percentage of macrosomic infants greater than 4,000 g was between about 19% and 29%.[35,36] Other studies found the incidence of LGA ranges from 22% to 44% (Table 3).[34,38,40] In the general population, the percentage of birth weights greater than 4,000 g is about 10%,[34,41,42,43] and for weights greater than 4,500 g, 1.5%.[6]

Although women with GDM have a higher percentage of macrosomic infants, a larger overall number of macrosomic infants are born to women without GDM.[19,39,44-46] There are risk factors other than GDM for newborn macrosomia. These include a history of a prior macrosomic

infant, maternal prepregnancy weight and pregnancy weight gain, multiparity, male fetus, prolonged gestation, ethnicity, maternal height and birth weight, maternal age less than 17 years, and a positive 50-g glucose challenge test with a negative oral glucose tolerance test (GTT).[47] Maternal obesity is a major risk factor and may explain some of the increased birth weight seen in GDM, as GDM is commonly diagnosed in obese women. Maternal obesity is a greater risk factor for macrosomia than GDM;[47-49] the association between GDM and fetal macrosomia persists but is diminished after controlling for maternal weight.[26,50]

Macrosomia is an intermediate outcome; the important adverse neonatal health outcomes that are linked to macrosomia are brachial plexus injury and clavicular fracture. Brachial plexus injury is a complication of shoulder dystocia and is reported to occur in 4% to 8% of vaginally delivered macrosomic infants[51-53] compared to 0.5 to 1.89 injuries per 1,000 vaginal deliveries (0.2%) for all vaginally delivered infants regardless of fetal weight.[45,53-57] Observational studies have shown an 18- to 21-fold increased risk for birth weights greater than 4,500 g.[45,55,56] Recent observational studies have shown that among infants with a birth weight greater than 4,000 g, the incidence of injury related to shoulder dystocia is 1.6%.[58] An observational study of neonates weighing greater than 4,200 g revealed 11.4% with shoulder dystocia and 1.3% with brachial plexus injury.[59] In studies of birth weight greater than 4,500 g, 5.7% of the neonates had brachial plexus injury,[52] and injury rates of 7% to 11% are reported for infants with birth weights greater than 5,000 g.[49]

Infants of women with both gestational and pregestational diabetes are at increased risk of shoulder dystocia, brachial plexus injury, and clavicular fracture regardless of birth weight.[54,55,60,61] The higher incidence of shoulder dystocia among infants of women with diabetes is theoretically attributable to the fact that macrosomia produced by maternal glucose

intolerance tends to lead to infants with greater total body fat, larger shoulder and upper-extremity circumferences, and smaller head-to-abdominal-circumference ratios than macrosomic infants of mothers without GDM.[62] Three large observational studies report that vaginally born infants of nondiabetic mothers with birth weights of greater than 4,000 g have a 0.6% to 1.1% rate of birth-related brachial plexus injury compared to 2.1% to 5% for infants born to diabetic mothers and of the same birth weight.[53,55,58]

The best (but minimal) data on untreated women with GDM reveal no difference in the rate of brachial plexus injury or clavicular fracture compared with the non-GDM population.[2,35,38,63,64] One study of only 16 patients,[34] however, found increased rates for both of these outcomes above the general population percentage of less than 1%. Recent data suggest that women with higher levels of hyperglycemia treated for GDM may have a 2% increase in brachial plexus injury and 6% increase in clavicular fracture.[34,65]

Most often brachial plexus injuries do not lead to permanent disability. The best studies show that 80% to 90% of brachial plexus injuries resolve by one year of life.[51,52,66,67] Clavicular fracture occurs in 0.3% to 0.7% of all deliveries, and it is increased approximately 10-fold for macrosomic infants. More than 95% of clavicular fractures heal within a few months without residual problems.[56,67-69]

GDM may be a risk factor for other neonatal complications such as preterm birth,[2,42] hypoglycemia, hyperbilirubinemia,[70,71] hypocalcemia, and polycythemia.[36,63,72,73] The evidence is strongest for an association with hypoglycemia, where studies among untreated[36] and treated women with GDM found higher rates of hypoglycemia in their infants. The magnitude of clinically important hypoglycemia is less clear. Also not clear is whether increased surveillance of infants with GDM mothers contributes to the increased finding of hypoglycemia.

The evidence is limited and unclear about whether GDM is associated with preterm birth, hyperbilirubinemia, hypocalcemia, or polycythemia.[2,36,42,70-74] Because of limited evidence and the increased surveillance given to infants of women with GDM, the magnitude of any associated adverse health effects is uncertain but likely small.

Some have suggested that the diagnosis of GDM may have long-term implications for the offspring, such as an increased risk of impaired glucose tolerance, childhood obesity, and neuropsychological disturbances. Several studies have shown higher rates of impaired glucose tolerance in the offspring of diabetic mothers.[75-78] These studies have some problems, however; the offspring of the mothers with GDM were not examined separately,[75] and in two studies, the high underlying genetic predisposition to obesity and diabetes in the study population makes the findings difficult to generalize.[76,77] On the other hand, Beischer et al. identified 38 children with type 1 diabetes whose mothers had oral GTTs performed during pregnancy. Only one of these mothers had GDM compared with 5.6% in the overall hospital population. Blood glucose levels did not differ between the mothers of the children who developed diabetes and the general hospital population.[79] Overall, the data regarding the offspring of women with GDM only are limited and mixed.

Most studies of childhood obesity in the offspring of mothers with GDM have included mothers with known type 1 diabetes[75,75,80-82] or type 2 diabetes.[83] When these investigators grouped all mothers with diabetes, they found an overall association between maternal diabetes during pregnancy and offspring obesity. However, Persson et al. reported results separately for the offspring of mothers with GDM and showed no association between GDM and childhood obesity.[82] In one of the first studies to compare childhood obesity rates in offspring of mothers with and without GDM, Whitaker et al. revealed no differences in the prevalence of obesity or in

the mean BMI (adjusted for age and sex) in the offspring of mild, diet-treated GDM.[84] There also was no significant increase in the rate of offspring obesity according to the quartile of maternal screening glucose or oral GTT. A significantly higher obesity rate in children whose mothers or fathers were obese was found, and after controlling for parent obesity, analyses revealed that the risk of obesity was no higher in the offspring of mothers with GDM than in offspring of control mothers.[84]

Vohr et al. found that LGA offspring of mothers with GDM were more likely to be heavier and have a higher BMI from 4 to 7 years of age than average for gestational age (AGA) offspring in this group or normal controls.[85] Multivariable analyses showed that infant BMI and maternal prepregnant BMI predicted 7-year BMI for the GDM group, whereas maternal prepregnancy BMI and weight gain during pregnancy were positive predictors for control subjects. Overall, the data on obesity in the offspring of mothers with GDM are limited and mixed and confounded by parent obesity.

Furthermore, the adverse effects of diabetic metabolic factors during pregnancy may affect the developing brain, and these effects may correlate with the degree of diabetes control. Some studies found that although the rates of major neuropsychological disturbances are not different from national estimates, abnormal maternal metabolism including glucose metabolism was associated with poorer intellectual performance and pyschomotor development according to various tests of child performance.[86-88] By contrast, one study did not find any correlation between maternal pregestational diabetes or GDM with the children's behavioral adjustment.[89]

Overall, the available data include patients with both pregestational diabetes and GDM, so the potential adverse effects on offspring of GDM mothers are limited. No large observational study has followed a group of children with GDM mothers and a comparison

group with non-GDM mothers long enough to demonstrate whether any of these hypotheses are correct. The available evidence has methodologic flaws; these mixed results may be explained by multiple confounders.[79,82,84,85]

Maternal Health Outcomes

The diagnosis of GDM can increase adverse health outcomes for the mother during her pregnancy (Table 4). Fetal macrosomia may lead to maternal trauma by increasing the risk of cesarean delivery[39,49,52,90-92] and the risk of third- and fourth-degree perineal lacerations.[51,93] Limited data of unrecognized or untreated women with GDM since 1980 reveal total cesarean delivery rates of 22%[40] to 30%[35] compared with a rate of about 17% for non-GDM women. Although the overall literature suggests an association, some studies are limited by a lack of adjustment for maternal obesity and by the impact of the diagnosis of GDM on clinical decisionmaking.

Some evidence suggests that physicians are more likely to perform a cesarean delivery for women with GDM, regardless of other indications. For example, Naylor et al. found that cesarean delivery rates were 34% for women with treated GDM, about 30% for an untreated borderline GDM group (health care providers masked to results), and 20% for controls without GDM.[35] The higher rate for the treated GDM group could not be attributed to macrosomia in light of the fact that macrosomia was 10% in both the GDM group and the control group. The increased risk of cesarean delivery among treated patients compared to controls persisted after adjustment for multiple maternal risk factors (adjusted OR, 2.1; 95% CI, 1.3-3.6).

Limited evidence is available on the rate of third- or fourth-degree lacerations in women with GDM (Table 4). The only study that found a substantial percentage of women with GDM

who had such lacerations included only 16 subjects.[34] Another study found equally low rates among women with and women without GDM.[35]

Overall, observational studies are inconclusive as to whether women with GDM have a higher risk of pre-eclampsia than women without GDM;[2,43,94-96] however, several studies have found an increased risk.[42,64,97-100] Jensen et al. found a rate of 20% of maternal hypertension in women treated for GDM versus 11% for controls.[97] A retrospective cohort study of 874 class A_1 diabetics compared to 61,209 controls, found pregnancy induced hypertension (PIH) in 17% of the cases and in 12% of the controls ($P = 0.001$).[64] In a study of 24,290 singleton pregnancies, a statistically significant risk of PIH was found in individuals with gestational impaired glucose intolerance, GDM, or established diabetes mellitus, after adjusting for maternal age, BMI, parity, and ethnic origin.[98] Obesity is also a risk factor for pre-eclampsia and may confound this relationship.[42,101,102] Recent data from untreated women with GDM[35] reveal a rate of pre-eclampsia (about 9%) that is similar to that for treated women and women in the non-GDM group.[103-106] Pre-eclampsia is commonly screened for inpatients receiving prenatal care. No evidence suggests that screening for GDM improves health outcomes related to pre-eclampsia.

The diagnosis of GDM may have long-term implications for mothers. Mothers identified as gestational diabetics have a higher risk of developing type 2 diabetes over the years after delivery.[107] Observational studies have shown that of women with GDM, 2% may develop adult-onset diabetes within 6 months of delivery; 40% of Hispanic-American women will develop diabetes over 6 years, and 20% to 40% of white Europeans will develop it over 20 years.[108-110] Overall, women with GDM have a 17% to 63% risk of nongestational diabetes within 5 to 16 years after delivery.[109,109,111-118] This increased risk most likely arises because

pregnancy serves as a provocative test for uncovering women with subclinical degrees of glucose intolerance, not because pregnancy has an actual etiologic effect.[119]

Studies of the rate of development of type 2 diabetes after gestational diabetes have suffered from low participation rates, retrospective design, short follow-up, and variation in definition of both GDM and new diabetes. Thus, even though nearly all studies show that women who have GDM face some increased risk of developing diabetes, the degree of risk elevation they experience and the degree of glucose abnormality they develop are uncertain.[1] Additionally, no long-term follow-up studies show that postpartum diagnostic glucose testing is beneficial.[1] Further, the added benefit of early detection of diabetes in young women with few cardiovascular risk factors is uncertain.[120]

Accuracy and Reliability of Screening Tests

Reference Diagnostic Test

Before we can determine the sensitivity, specificity, and validity of a screening test (KQ No. 3), we need a reference diagnostic test for comparison. Unfortunately, no universally agreed on reference test for the diagnosis of GDM exists.

O'Sullivan et al. developed standards for whole blood glucose to identify mothers at risk of developing diabetes later in life.[32] In the United States, the diagnostic test most commonly used consists of a 100-gram (100-g) 3-hour (3-h) oral GTT that is performed in the fasting state.[1,121] The NDDG diagnostic criteria for GDM are defined as 2 or more abnormal values during a 3-h GTT using 100-g of glucose.[122] These are based on extrapolations from the O'Sullivan standards because of the change made by most laboratories to measure plasma or

serum glucose instead of whole blood glucose.[123] Sacks et al. stated that the conversion factor used to develop criteria for plasma glucose measurements may have been incorrect.[124] Thus, modified criteria by the Carpenter and Coustan proposal with lower thresholds that may be more sensitive predictors of adverse pregnancy[125] and these are recommended by the Fourth International Workshop-Conference on Gestational Diabetes.[78] Thus, two different national groups have proposed competing cutpoints for this test (left hand panel of Table 5). For making the diagnosis of GDM, the 1979 National Diabetes Data Group (NDDG) criteria[122] require higher levels of glucose (in milligrams per deciliter ([mg/dL]) than the American Diabetes Association (ADA) criteria.[126]

The ongoing controversy over the diagnosis of GDM is fueled by poorly standardized criteria for a positive oral GTT in pregnancy. Outside of North America, the diagnosis of GDM is usually based on World Health Organization (WHO) criteria (Table 5), which uses a 75-g 2-h oral GTT with a cutpoint of 140 mg/dL.[127]

The prevalence of GDM varies depending on which criteria are used. In general, the WHO criteria identify twice as many women with GDM as the NDDG criteria; the ADA criteria give an intermediate prevalence.[128,129] For all criteria, the majority of women (70% or greater)[74,130] diagnosed have lower levels of hyperglycemia and are treated by diet alone; a minority of women have hyperglycemia high enough to require insulin.

Controversy also exists regarding universal versus selective screening based on risk factors. Because no reference standard for the diagnosis of GDM has been established, it is questionable to base the validity of either the method of screening or the various tests used on the diagnosis of GDM by the arbitrary diagnostic thresholds of the oral GTT.

Ideally, a reference diagnostic test would be based on the cutpoint that identified a group at increased risk of developing disease-associated complications.[31] Studies that compare the result of one test with the result of another test in the same patient provide little useful information. Studies that examine the effects of screening and their subsequent impact on perinatal, maternal, or obstetrical outcomes are more indicative of the validity of the various screening tests; this was the literature we reviewed.

Abnormal values on both the 75-g 2-h[131,132] and 100-g 3-h[13,37,133] oral GTTs, using any of proposed criteria discussed above, are predictive of fetal macrosomia and, in some studies, pre-eclampsia as well. These associations are generally continuous, without a clear threshold. They are diminished or eliminated when adjustments are made for such potential confounders as pregravid weight, age, parity, and race. Although cesarean delivery rates are also directly associated with maternal hyperglycemia, the most careful study of this issue suggested that part of this increase in cesarean delivery can be attributed to the impact of the GDM diagnosis on physician decisionmaking rather than an increase in macrosomia.[35]

Observational studies have indicated that a positive 75 g oral GTT is predictive of macrosomia. Pettitt et al., in a cohort of Pima women tested in the third trimester, found a direct relationship between fetal macrosomia and the plasma glucose levels on the 75-g oral GTT.[33] The same study found a similar relationship with the perinatal mortality rate. The results of the GTTs were not used in the management of these patients.

Sacks et al. studied 3,505 unselected pregnant women and also found a direct relationship between the 75-g, 2-h oral GTT and fetal macrosomia, which was independent of several potential confounders.[29] The factors found to be statistically significantly associated with macrosomia were maternal race, parity, prepregnancy BMI, weight gain, gestational age at

testing, fasting plasma glucose level, and the 2-hour post-glucose-load value. However, no clinically meaningful glucose threshold values relative to birth weight or macrosomia were found.

Schafer-Graf et al. studied 325 women with risk factors for GDM who underwent a 75-g oral GTT and were subsequently treated with diet or diet plus insulin therapy if they met the diagnostic criteria of GDM.[134] They found that the rates of LGA infants were 24% for those with GDM and 11% for those with normal oral GTTs ($P < 0.05$).

Roberts et al. screened 953 pregnant women who were identified on the basis of risk factors for GDM, with a 75-g oral GTT.[135] Based on the WHO criteria, 120 showed impaired glucose intolerance. The incidence of any complications did not differ significantly between mothers with normal and impaired glucose tolerance. Labor was induced more frequently ($P < 0.05$) and cesarean delivery was performed more frequently ($P < 0.01$) in the impaired glucose tolerance group, but there was no difference in fetal outcome or neonatal morbidity.

Tallarigo et al. followed up 249 women with normal oral GTT's by NDDG criteria.[136] In women with 2-h results in the range of 120 mg/dL to 165 mg/dL on the 100 g-oral GTT compared with those in less than 100 mg/dL, there was a rise in the risk of fetal macrosomia (27.5% v. 9.9%) and risk of pre-eclampsia and/or cesarean delivery (40.0% v. 19.9%). Berkus et al. followed 764 women with GDM who were stratified by the number of abnormal values on their oral GTTs.[137] This cohort was compared to 636 gravidas with a positive GCT but no abnormal values on the oral GTT. The patients with one or more abnormal oral GTT values had comparable incidences of LGA infants (23% to 27%), which were significantly greater than the group with no abnormal oral GTT values (13%; $P < 0.01$).

Lindsay et al. screened 4,618 pregnant women for GDM at 24 to 28 weeks gestation and 13% had abnormal screening tests.[138] Of those, 139 had one abnormal value on the subsequent 3-hour oral GTT and these women were compared with 725 randomly selected patients with a normal screening test. The incidence of macrosomia (greater than 4000 g) was significantly greater in the study group (18%) versus the control group (6.6%) (OR 2.18; 95% CI, 1.77,5.37). The incidence of pre-eclampsia was also significantly greater in the study group (7.9%) than the control group (3.3%) (OR 2.51; 95% CI, 1.14,5.52). Other studies also suggest that increasing carbohydrate intolerance among patients not meeting current criteria for the diagnosis of GDM leads to increased rates of unfavorable outcomes.[139,140]

These findings were supported by Sermer et al. who examined the results of GCT's and 100 g oral GTT's performed between 26 weeks and 28 weeks gestation on 3,637 pregnant women who did not meet the criteria for GDM.[28] The health care providers were masked to the results of the oral GTT's.

In the study by Sermer et al., univariate analyses found that oral GTT and GCT values show a graded relation to cesarean delivery, macrosomia, and pre-eclampsia rates.[28,141] The risk gradient was strongest for macrosomia with the fasting oral GTT value and the incidence of macrosomia was 14.3% if a 4,000 gram cutoff was used, but dropped to 2.2% if macrosomia was defined as greater than 4,500 grams. The odds of cesarean delivery rose with progressively increasing plasma glucose values on all oral GTT results, as well as with the GCT level. The risk gradient was strongest for cesarean delivery with the 3-h oral GTT value. In addition, a positive GCT (>140 mg/dL) predicted higher cesarean delivery rates even in patients with normal oral GTT results (P=0.017). Any 1 abnormal oral GTT value by the NDDG criteria and

increasing plasma glucose levels on the 2-h value on the oral GTT were both associated with a significant increase in the incidence of cesarean delivery, macrosomia, and pre-eclampsia.

Multivariate analyses controlling for potential confounders such as age, maternal weight, race, and parity, revealed that only the 3-h oral GTT value remained a significant risk factor for cesarean delivery and only the fasting value was an independent predictor of macrosomia. Glucose values no longer predicted pre-eclampsia.[28]

As the proposed criteria for diagnosing GDM based on the 3-h oral GTT values have been lowered in order to diagnose more pregnant women with GDM, it is unclear that health outcomes have improved. Some data suggest that the additional women detected by the ADA criteria compared with the NDDG criteria have the same risk of macrosomia as those meeting the higher criteria.[37,124] Others note that the risk of macrosomia in these additionally classified women is predicted more by the degree of prepregnant obesity than by the level of hyperglycemia;[142] some observers claim that the adoption of the ADA criteria would increase the number of women with GDM by more than 50% while offering little opportunity to reduce the prevalence of fetal macrosomia.[143]

Lu et al. compared the use of the Carpenter and Coustan Criteria for the diagnosis of GDM on the 100 g oral GTT to the NDDG criteria in 3,253 women.[37] Four hundred and seventy-eight women met the NDDG criteria, 319 women would have been reclassified as GDM by the Carpenter and Coustan criteria, and 2,456 women met neither criterion. After controlling for maternal weight, age, race, parity, and smoking status, the adjusted odds ratios and 95% CI for fetal macrosomia, comparing women with GDM with those without GDM, were similar for women diagnosed either by NDDG criteria (OR, 1.4; 95% CI, 1.0-2.0) or by Carpenter and Couston criteria (OR, 1.6; 95% CI, 1.1-2.3). This study concluded that the utilization of the

Carpenter and Coustan criteria would increase the diagnosis of GDM by 40% but identify gravidas at similar risk to those identified by the NDDG criteria.

Schwartz et al. retrospectively reviewed the cases of GDM in the Kaiser Permanente Northwest Division between 1995 and 1996.[143] Of the 8,857 women screened, 284 (3.2%) met the NDDG criteria and 438 (4.9%) met the Carpenter and Coustan criteria. The authors estimated that use of the latter criteria in their population could at best reduce the prevalence of infants weighing greater than 4,000 g from 17.1% to 16.9% and of those weighing greater than 4500 g from 2.95% to 2.91%. At the same time, the number of pregnant women with a diagnosis of GDM would increase by 54%.

Berkus et al. studied 708 normal untreated gravidas who were not considered to have GDM by the ACOG criteria (NDDG criteria of fasting 105, 1-h 190, 2-h 165, 3-h 145), but would have been given the diagnosis once reclassified by the criteria of Coustan (fasting 95, 1-h 180, 2-h 155, and 3-h 140 mg/dL), Sacks (96, 172, 152, and 131 mg/dL), or Langer (at least one abnormal ACOG value).[144] A greater incidence of LGA infants was identified by the Coustan criteria (23.6%) and the Langer criteria (25.3%) compared with the non-GDM group (14%; $p<0.05$). The efficiency of testing is similar for the ACOG, Coustan, and Langer criteria, with the identification of one LGA infant for every four GDM subjects treated. There was no difference between the incidence of LGA between the Sacks and non-GDM groups indicating that the cutoffs used in the Sacks criteria may be too low to efficiently identify subjects at risk for LGA infants.

Another study, by Rust et al., indicates that lowering the oral GTT cutoff for the diagnosis of GDM may result in more diagnoses of GDM without improving perinatal outcome.[142] In this study, the authors retrospectively studied 434 patients with abnormal 50-g

GCTs (≥140 mg/dL) who subsequently underwent a standardized 3-h oral GTT. The results were stratified according to maternal weight and the proposed GDM diagnostic criteria of Sacks or Carpenter and Coustan. The results from the two stratified diagnostic criteria did not differ in any statistically significant way except that the newly diagnosed patients with GDM, due to lowering the diagnostic cutoffs, were both older and weighed more. The stratification of the same patients by prepregnancy weight revealed a greater incidence of cesarean deliveries and a higher cumulative maternal morbidity in the overweight patients. A regression analysis revealed that macrosomia was not predicted by the degree of hyperglycemia but was predicted by prepregnant maternal BMI.

A recent study showed that lowering the cutoff for the WHO criteria for diagnosing GDM minimally alters the prevalence of GDM.[145] Schmidt et al. studied 5,004 consecutive women aged 20 years and older without the diagnosis of diabetes mellitus outside of pregnancy and found that 379 (7.6%) had GDM by the 1998 criteria (fasting glucose ≥ 7.0 mmol/l or 2-h glucose ≥ 7.8 mmol/l) while 378 cases of GDM were found using the 1985 criteria (fasting or 2-h glucose > 7.8 mmol/l). Of these 379 cases diagnosed using the 1998 criteria, 21 (5.5%) had hyperglycemia in the range of diabetes mellitus outside of pregnancy (fasting glucose ≥7.0 mmol/l or 2-h glucose ≥11.1 mmol/l) versus 15 in the 1985 criteria group, while 358 (94.5%) had hyperglycemia in the impaired glucose tolerance range (fasting glucose ≥7.0 mmol/l or 2-h glucose ≥7.8 mmol/l and < 11.1 mmol/l) versus 363 in the 1985 group. This study also shows that the vast majority of cases of GDM have hyperglycemia in the range considered impaired glucose tolerance outside of pregnancy.

The reliability of any oral GTT test is open to question. In one of the few studies of this issue, Harlass et al. found that 23% of 64 unselected pregnant women who had had a positive

screening test for GDM had inconsistent results between two different 100-g oral GTTs performed a week apart.[9] Other studies have also raised concerns about the reproducibility of the oral GTT in nonpregnant groups.[141] All of these factors lead to the lack of a reference standard for the diagnosis of GDM.[146,147]

Screening Tests

The cutpoints for the current reference diagnostic tests do not clearly distinguish women at high risk from women at low risk of adverse maternal or fetal health outcomes. Thus, we can evaluate screening tests only against imperfect standards. Most studies on GDM screening strategies compare the results of one test with the results of another test rather than examining how the test predicts adverse health outcomes. Some studies assess the association of the test with such intermediate outcomes as macrosomia rather than health outcomes such as brachial plexus injury.

Because the diagnostic 100-g 3-h oral GTT is time consuming and expensive, a simpler test is used for screening. In the United States, this is most commonly the 50-g, 1-h GCT (right hand panel of Table 5). The GCT is more simple not only because it requires only 1 hour of time (as opposed to 3 hours for the 100-g 3-h oral GTT), but also because it requires no previous diet and can be done any time of the day, whether the woman is fasting or postprandial. The 100-g 3-h oral GTT must be performed in the morning after an overnight fast and after at least 3 days of an unrestricted diet and physical activity preceding the test.

Two groups have proposed different cutpoint criteria to define a positive screening test. If the 1-h GCT glucose value is above either 130 mg/dL[125] or 140 mg/dL,[122] then the patient is given the 100-g 3-h oral GTT for diagnosis. The 130 mg/dL and 140 mg/dL cutpoints of the 50-

g 1-hour GCT identify subgroups of 20% to 25% and 14% to 18%, respectively, of all pregnant women, depending on the presence of risk factors.[121] The 130 mg/dL GCT cutpoint identifies 90% and the 140 mg/dL cutpoint identifies 80% of all women with a positive 100-g 3-h oral GTT.[121] Sermer et al. prospectively studied the use of higher cutoffs (142 to149 mg/dL) as well as adjustments for time since their last meal in nearly 4,300 pregnant women and found that misclassification of patients based on the initial screening test could be reduced.[148]

However, no single threshold that accurately separates normal from abnormal results on the GCT has been described.[149] In addition, the reproducibility of the GCT is only fair.[150]

In the general population, false-positive results for the GCT are common. Fewer than one in five women with a positive GCT will meet criteria for GDM on a full oral GTT.[148] Like other GTTs, therefore, the reliability of the GCT may be a problem.[29]

In many countries outside North America, clinicians use the WHO screening approach: the 75-g 2-h oral GTT as a single-step screening and diagnostic test. As noted above, this approach classifies at least twice as many women as having GDM as the two-step approach, although the evidence is sparse about whether the one-step test is more or less predictive of adverse health outcomes than the two-step approach.[128,129]

As the sensitivity of this screening test increases with gestational age,[76] both universal and selective screening of high-risk groups for GDM is done, by convention, between the 24th and 28th week of gestation. This timing is not based on any evidence that this is the optimal time to identify the women who would benefit most from treatment. The evidence is clear that those few women identified with GDM during the first trimester have a higher risk of neonatal hypoglycemia, perinatal deaths, and pregnancy-induced hypertension (PIH) than women diagnosed at a later stage of pregnancy.[151] Determining the best time to screen involves

examining the trade-off between the potential benefits of early screening (i.e., finding fewer women at higher risk and treating them for a longer time) and the potential benefits of later screening (i.e., finding a larger number of women at lower risk and treating them for a shorter time).[31] We found no study of this issue.

Because the diagnostic oral GTT is time consuming and expensive, other tests have been examined for their ability to identify at-risk populations. Important questions remain unanswered regarding the optimal screening test for GDM. Because the elevations in plasma glucose are less pronounced than in type 1 or 2 diabetes mellitus, neither serum glycosylated proteins[152 153-156]nor urine glucose[157] are adequately sensitive for detecting GDM. Glucosuria is also common among nondiabetic pregnant women.[14] Random blood glucose has been proposed as a screening test for GDM,[158,159] but its performance has yet to be fully evaluated.

In summary, there are no RCTs comparing the various screening or diagnostic tests for GDM in relation to maternal, obstetrical, or perinatal outcomes. All of the current evidence is indirect and comes from observational studies. The 2-h 75-g and 3-h 100-g oral GTTs both appear to be predictive of fetal macrosomia and possibly cesarean delivery. Lowering the cutoffs of these tests leads to a greater number of gravidas with the diagnosis of GDM, but improvement in outcomes for the additional cases has not been proven. The literature does not lead to conclusions regarding the gold standard test and cutpoint; thus, the optimal screening test and cutpoint remains uncertain.

A future study, which will examine at least short-term neonatal outcomes, is in progress. The Hyperglycemia and Adverse Pregnancy Outcome study (HAPO) is enrolling 25,000 pregnant women in 16 different centers worldwide and will attempt to determine which test is

the best screening method to predict pregnancy outcomes. All of these patients will undertake a standard 75 g oral GTT at 28 weeks gestational age.[160]

Does Treatment for GDM Improve Health Outcomes?

As noted earlier, we searched first for well-conducted RCTs of treatment for women with GDM. Although we examined observational evidence, we also noted the potential biases inherent in these studies. Evidence Table 2 presents selected studies of the impact of treatment of GDM and Table 6 highlights 9 RCTs of particular importance.

Glycemic Control

Three factors are important in considering studies of the impact of tight glycemic control on health outcomes for women with GDM. The first is the degree of hyperglycemia in study participants. As the risk of at least some adverse health events increases with the level of hyperglycemia, the potential absolute risk reduction may be larger with higher glycemic levels. Over 70% of women diagnosed with GDM have a mild degree of hyperglycemia and are usually treated with diet alone.[23,74,130]

The second important factor is the degree of separation of glycemic control between treatment groups. If intensive treatment does not produce a reasonable reduction in glycemic level compared with conventional treatment (or no treatment), the hypothesis of improved glycemic control leading to better health outcomes cannot be tested.

The third factor in considering these studies is assessment of outcomes: which ones to assess and how to assess them. Most of these studies focused on intermediate outcomes, such as fetal macrosomia, or chemical findings, such as fetal hypoglycemia. Intermediate outcomes are

useful only insofar as they predict important health outcomes that people care about.[20] In the case of fetal macrosomia, only a small percentage of these cases lead to maternal or fetal trauma. In the case of chemical findings (e.g., glucose or bilirubin level), few studies reported the percentage of abnormalities that required treatment; none clearly reassured the reader that any differences were not attributable to more intense surveillance of infants born to GDM mothers. Finally, because few of these studies masked the obstetricians,[161,162] interventions or outcomes that are dependent on clinician judgment (e.g., cesarean delivery rates) could be biased by knowledge of GDM status.[35]

Table 6 records data from nine RCTs examining the impact of therapy on a variety of outcomes. The first four RCTs are of women with low glycemic levels and the last five RCTs, of women with high or very high glycemic levels, are in chronological order.

Few studies have examined the effectiveness of intensive compared with less intensive glycemic control among GDM women with lower levels of hyperglycemia. In the Cochrane database, a meta-analysis of 4 randomized clinical trials involving 612 women and examining diet therapy for impaired glucose tolerance in pregnancy revealed no significant reduction in the number of neonates weighing greater than 4,000 g (OR, 0.78; 95% CI, 0.45-1.35) or for cesarean deliveries (OR, 0.97; 95% CI, 0.65-1.44).[163] The trials were small, however.

A RCT by Li et al also examined the effect of dietary therapy on clinical outcomes in GDM. In this study, 158 women diagnosed with GDM by NDDG criteria but not WHO criteria were randomized to diet treatment or no therapy.[161] Although perinatal outcomes did not differ, there were 3 infants (4%) with a birth weight over 4,000 g born to diet-treated mothers as compared to 5 (7%) born to women receiving no therapy.

Three RCTs[36,162,164] have compared intensive with less intensive glycemic control among GDM women who had varying degrees of hyperglycemia, but who had at least a mean entry fasting plasma glucose (FPG) of 95 mg/dL or less or a mean HbA1c of 5.6% or less. All three trials achieved some glycemic separation between groups, from 5 mg/dL to 10.8 mg/dL glucose level[36,164] or 0.2% to 0.7% HbA1c.[162] Two studies found statistically significant improvements in intermediate outcomes (e.g., LGA infants;[164] neonatal hypocalcemia;[36] the third found a nonstatistically significant trend toward fewer neonatal intensive care unit admissions.[162] None of these studies, however, found clear differences in health outcomes between glycemic control groups.

In a pilot study, Garner et al. randomized 300 women with GDM to either treatment with strict glycemic control and tertiary level obstetric care (including diet alone or diet and insulin therapy) or routine obstetrical care with an unrestricted diet.[36] The two groups had similar demographics and mean plasma blood glucose levels after glucose screening tests. By 32 weeks gestational age, the treatment group did achieve significantly lower preprandial and 1-h postprandial glucose levels and a nonsignificant trend in lower birth weight was seen with a mean decrease of 107 g in the treatment group ($P = 0.118$). There were no statistically significant differences in any of the other maternal or neonatal outcomes with the exception of neonatal hypocalcemia, which was higher in the treatment group ($P = 0.048$). The 2 groups were comparable with regards to infants with birth weights greater than or equal to 4,000 g (controls 18.7% and treatment group 16.1%, $P = 0.666$) and birth weights greater than or equal to 4,500 g (controls 4.0% and treatment group 4.0%, $P = 0.991$).

One of the concerns with this study was that because it was a pilot study, it included only 300 patients so there is insufficient statistical power to detect a significant difference in outcomes

such as macrosomia rates, operative delivery rates, or adverse fetal and neonatal outcomes. Bias may have been introduced because control subjects were not masked to either the oral GTT or home glucose level monitoring results, so many may have discussed this with their primary obstetrician and possibly changed their behavior including not following an unrestricted diet once this information was known. The unmasked obstetrical care may also have impacted the operative delivery rates. This study provides fair evidence overall. It shows that intensified treatment for GDM will provide improved glycemic control over routine obstetrical care. However, this improved glycemic control did not translate into improved intermediate outcomes such as less macrosomia or improved maternal or perinatal health outcomes. The lack of power in this study greatly limits any conclusions that can be made.

Buchanan et al. randomized 59 Latina women with GDM who, at 29 weeks to 33 weeks of gestation, had a fetal ultrasound abdominal circumference of greater than or equal to the 75th percentile for gestational age, into 2 groups: diet therapy (n = 29) and diet plus twice daily insulin (n = 30).[165] The diet only group had a higher mean birth weight (3,878 g compared to 3647 g, $P < 0.04$), a higher LGA infant rate (45% compared to 13%, $P < 0.01$), but a lower cesarean delivery rate (14% to 21%, using range for 3 diet groups, compared to 43%, $P < 0.05$). Rates of birth weights greater than 4,000 g or 4,500 g were not provided and there was no significant birth trauma in this study.

This trial provides poor evidence due to concerns that the intervention being examined was not the only factor that differed between the two study groups.[165] The obstetrical management (unmasked providers) was not standardized as the insulin-treated subjects were managed by a "high-risk" obstetrical service while the diet-treated subjects were managed by the "routine" obstetrical service, which may account for some of the disparity in the cesarean

delivery rates. Labor was induced for an ultrasound estimated fetal weight (EFW) greater than or equal to 4,200 g and elective cesarean delivery was done for EFW greater than or equal to 4,500 g; both are strategies that remain controversial. There were also 25 refusals, 5 drop-outs, and 9 births prior to completion of the trial, from the original 98 potential subjects, with little information provided regarding these women. No information was provided as to how the randomization was completed. Concerns regarding external validity are that this study may not be generalizable since this was done on an exclusively Latina population.

Overall, this trial provides poor evidence that insulin and dietary therapy can improve health outcomes when compared to dietary therapy. The addition of insulin therapy in these Latina women with GDM, may reduce the number of LGA infants born, but there is no evidence from this trial that this will improve other important health outcomes. In fact, the cesarean delivery rates are higher for the insulin treated group. The study is limited by a lack of power for many of the important health outcomes, a lack of comparability of the 2 groups, and a large percentage of refusals for which no information is provided.

In the third RCT of this group, Bancroft et al.[162] randomized 68 women with GDM by the WHO criteria to either intensive diabetic monitoring (n = 32) or no diabetic monitoring (n = 36). All women were on dietary therapy. The care of these women was managed by a diabetoligist (unmasked) but the obstetrical care was provided by obstetricians who were masked to the results. The monitored group underwent capillary glucose samples five times per week and monthly glycosylated hemoglobin determinations. Insulin therapy was added if five or more capillary glucose measurements were > 7.0 mmol/L in one week. The unmonitored group only had monthly glycosylated hemoglobin measurements performed, but the results were not made available during the study. Antenatal care included serial ultrasounds for growth, amniotic fluid

and Doppler studies of umbilical artery waveforms. The gestation and mode of delivery were determined by the obstetrician, but took place no later than 40 weeks of gestation.

The two groups were similar demographically at the beginning of the trial including BMI, age, and parity.[162] The two-hour glucose levels were statistically higher in the unmonitored group (8.9 versus 8.5 mmol/L, $P = 0.03$) but the gestational age at entry, HbA1c (%), and fasting glucose measurements were similar. The glycosylated hemoglobin values were similar between the two groups at 28, 36, and 38 weeks of gestation, as well as at term; however, they differed at 32 weeks of gestatation (monitored group, 5.2 versus unmonitored, 5.9).

There were no statistically significant differences in neonatal outcomes such as admission to the neonatal intensive care unit (NICU), hypoglycemia, birth weight, or LGA. Maternal outcomes differed with more capillary specimens performed in the monitored group as well as more insulin use (19% in the monitored group versus 0% in the unmonitored, $P = 0.008$). The rate of vaginal delivery and cesarean delivery did not differ.

This study is limited by the fact that it was a pilot study with a small sample size. In addition, the groups differed in that the unmonitored group had more severely abnormal glucose metabolism at the initiation of the trial.

Four other RCTs have examined tight and less tight glycemic control among women with GDM with higher glycemic levels (the second half of Table 6).[65,104,105,166] Of these trials, one achieved no difference in glycemic control between groups and found no difference in outcomes.[104] Two studies achieved small differences in glycemic control (from 3.2 mg/dL glucose level[65] to 0.3% HbA1c difference[105] and found no differences in fetal macrosomia. Nachum et al found that tight glycemic control led to a small absolute reduction in chemical abnormalities in the fetus; e.g., neonatal hypoglycemia was 5.9% in the group less intensive vs.

0.7% in the more intensive group).[105] Kjos et al. found a reduction in cesarean deliveries in the more intensive group, although this was not explained by fetal size.[65] These RCTs reported found no other health differences between groups.

The randomized trial by Nachum et al.[105] examined perinatal outcomes and glycemic control in both pregnant pregestational diabetic patients and patients with GDM (NDDG criteria) who required insulin therapy and compared insulin given 4 times daily versus twice daily. In the GDM group, 138 patients were randomized to receive insulin 4 times daily while 136 received insulin twice daily. All subjects received treatment prior to 35 weeks gestational age and the 2 groups were similar in the gestational age at diagnosis (mean, 26 weeks) and gestational age at initiation of treatment (mean, 28 weeks) as well as age, gravidity, prepregnancy weight and BMI.

Glycemic control was better with the 4 times daily regimen; cesarean delivery, preterm birth, pregnancy-induced-hypertension, and macrosomia were similar in both dosing groups.[105] There was a statistically significant lower incidence of neonatal hypoglycemia in the 4 times daily group (0.7% compared to 5.9%, $P = 0.02$) and lower incidence of hyperbilirubinemia (11% compared to 21%, $P = 0.02$) when compared to the twice daily group. There were no statistically significant differences with regards to other perinatal outcomes such as birth weight, macrosomia, LGA, small-for-gestational-age (SGA), Apgar scores, respiratory distress syndrome, perinatal mortality, hypocalcemia, polycythemia, major congenital anomalies, or birth trauma (peripheral nerve injuries or bone fracture).

There was a lower overall rate of neonatal morbidity with the 4 times daily regimen (RR, 0.59, 95% CI, 0.38,0.92).[105] However, few conclusions can be made from this statistic. This outcome variable was defined as a combination of arbitrary diagnoses including RDS, hypoglycemia, hypocalcemia, hyperbilirubinemia, and birth trauma. From these diagnoses, 37 of

the 40 cases making up the overall neonatal morbidity for the twice daily group were from the neonates with either the diagnosis of hypoglycemia (n = 8) or hyperbilirubinemia (n = 29). With regards to the 4 times daily insulin group, 16 of the 24 the cases included in the overall neonatal morbidity were from these same 2 diagnoses.[105] If the diagnoses of hypoglycemia and hyperbilirubinemia are excluded, the number of cases included in this variable are actually greater for the 4 times daily group, and each of these outcome variables are not statistically significantly different from each other.

Concerns regarding this trial include that no information is provided on the number or outcomes of the refusals. In addition, the overall rate of neonatal morbidity statistic is a random selection of criteria strongly influenced by two diagnoses and the definitions of those two diagnoses, hypoglycemia and hyperbilirubinemia, were based on laboratory values only, which may be intermediate outcomes. No clinical outcome data such as the number of neonates requiring treatment due to having these diagnoses is provided.

Overall, this study provided fair evidence that a regimen of 4 times daily insulin compared to twice daily may decrease the incidence of neonatal hypoglycemia and hyperbilirubinemia (based on laboratory values only). The study did not show that the increased frequency of insulin dosing provides any other important maternal or perinatal health benefit.

Kjos et al., in a pilot study, randomized 98 women with fasting plasma glucose concentrations of 105-120 mg/dL to either insulin and diet therapy (standard group, n = 48) or insulin added to diet therapy only if the abdominal circumference (AC) on ultrasound (measured monthly) was $\geq 70^{th}$ percentile and/or if any venous FPG measurements (measured every 1-2 weeks) were > 120 mg/dL or the subject failed to perform >50% of the recommended capillary glucose measurements (experimental group, n = 49).[65]

Thirty of 49 women in the experimental group received insulin therapy (21 at the start of the trial).[65] Insulin management differed between the two groups in that the doses of insulin were adjusted to achieve preprandial capillary blood glucose concentrations ≤ 90 mg/dL and 2-h postprandial concentrations ≤ 120 mg/dL, while the experimental group had glycemic targets of ≤ 80 mg/dL before meals and ≤ 110 mg/dL 2-h after meals. All patients underwent a baseline ultrasound and additional fetal AC measurements at 20, 24, 28, 32, and 36 weeks of gestation. Obstetrical management was standardized, including antepartum fetal testing twice weekly beginning at 34 weeks. Elective induction of labor or cesarean delivery was scheduled between 38.5 and 39 weeks of gestation. The obstetricians were not masked.

The baseline characteristics of the two study groups were similar except for the fact that both groups had a mean BMI at entry in the obese range, and the standard group had a higher mean BMI than did the experimental group (33.8 versus 31.2 kg/m^2, $P = 0.03$). Maternal outcomes differed in that the standard group had significantly lower mean venous FPG levels (84.9 versus 88.1 mg/dL, $P = 0.003$) and capillary blood glucose levels (97.0 versus 99.0 mg/dL, $P = 0.049$) than the experimental group. The duration of insulin therapy and incidence of pregnancy induced hypertension did not differ significantly.

The two groups differed in that the experimental group had 9 subjects with prior cesarean deliveries without subsequent vaginal birth compared with 4 in the standard group. The standard group also had twice as many women with a favorable cervix at the time of induction (21 versus 10, $P = 0.03$). The standard group had a significantly lower abdominal delivery rate (14.6 versus 33.3%, $P = 0.03$) but more women in the experimental group were not allowed to labor and more failed induction of labor, while only one subject had arrest of labor in the study. There were also more emergency cesarean deliveries in the experimental group; all for reasons that appeared not

to be related to maternal diabetes. Infant birthweights and neonatal anthropometric measurements did not differ between those who underwent a cesarean delivery and those that did not; nor did they differ based on predelivery maternal weight, maternal venous fasting and capillary blood glucose levels after randomization.

Neonatal outcomes included one stillbirth in the standard group at 36.5 weeks of gestation. There were no statistically significant differences in gestational weeks at delivery, mean birth weight, macrosomia, polycythemia, birth trauma, treatment-requiring hypoglycemia or hyperbilirubinemia. The experimental group had more LGA neonates (8.3% versus 6.3%) but less that were SGA (0 versus 6.3%).[65]

Problems with this study include its lack of power to determine important health outcomes. The obstetricians were not masked and used a policy of elective induction of labor by 39 weeks gestational age. The two groups differed in obstetrical risk factors which played a role in the cesarean delivery rates.

In the Persson et al. RCT, the investigators randomized 202 pregnant women with impaired glucose tolerance to either treatment with diet (n = 105) or diet and insulin (n = 97).[104] All of the women self-monitored their blood glucose (6 times per day) 3 days per week and all received antenatal care every second week. Pregnancies were allowed to continue until 40 weeks gestation. Insulin therapy was started in the diet group (15 of 105) if either fasting and/or 1-h postprandial blood glucose values exceeded 7 or 9 mmol/L, respectively, at least 3 times during a period of 1 week.

The two groups were similar age, prepregnancy weight, obesity, and parity. There was no difference in the rate of pre-eclampsia. The newborns were statistically similar in gestational age at delivery, mean birth weight, LGA, and SGA. There were no perinatal deaths. There were

no statistically significant differences in neonatal complications such as symptomatic hypoglycemia, hypocalcemia, treated hyperbilirubinemia, or polycythemia. This trial is again limited by a lack of power for important health outcomes.

Langer et al. achieved a larger glycemic separation between groups (difference in mean glucose 24 mg/dL); the infants of less intensively treated women had a higher mean birth weight plus higher rates of hypoglycemia and polycythemia.[166] These differences were small and of uncertain clinical importance.

De Veciana et al. compared tight with less tight control among women with very high glycemic levels, some of whom likely had pre-gestational diabetes.[106] They also achieved the largest separation in glycemic control (HbA1c difference of 1.6%); and found some of the largest reductions in fetal macrosomia and neonatal hypoglycemia. Given the study population, however, this trial may have little relevance for the great majority of women detected with GDM.

In the de Veciana et al. RCT, the investigators compared the efficacy of postprandial versus preprandial monitoring in achieving glycemic control in 66 women with insulin-requiring GDM (at $\leq$ 30 weeks of gestation) and the effect on maternal and neonatal outcomes.[106] Other monitoring and diet therapy was standardized for all subjects. This study found a statistically significant lower glycosylated hemoglobin before delivery (6.5% v. 8.1%), less cesarean section for cephalo-pelvic disproportion (CPD) (12% v.36%), lower mean birth weight, fewer number of LGA infants (12% v. 42%), and fewer infants with birth weight greater than 4,000 g (9% v.36%) in the postprandial monitoring group. The postprandial monitoring group used more insulin than the preprandial group. There was a trend towards more neonatal hypoglycemia and shoulder dystocia in the preprandial monitoring group but these differences were not statistically

significant. The two groups did not differ with regards to other important obstetrical or neonatal outcomes.

This RCT provides fair evidence but has several limitations. The authors do not provide the number and demographics of the eligible subjects who refused to participate in the trial. Bias may have been introduced due to the lack of masking of the health care team. An unproven strategy of performing cesarean deliveries for "suspected fetal macrosomia" due to an estimated fetal weight (EFW) on ultrasound of greater than 4,000 g was utilized, and more of these elective cesarean sections were done in the preprandial group. In addition, some of these subjects may have had undiagnosed type 2 diabetes mellitus due to the early diagnosis in this pregnancy. Lastly, it may be difficult to apply this study to many populations in that 56 of the 66 subjects were Latina, which may have an independent influence on the prevalence of GDM and birth weight.

This study indicates that changes of insulin therapy based on postprandial monitoring in insulin-requiring Latina women with GDM may lead to fewer macrosomic infants and fewer cesarean deliveries, but does not change other important health outcomes. The study is limited by several factors, including the small number of subjects, the lack of masking, and the use of an unproven strategy for elective cesarean deliveries.

A major issue in all these trials is that they have too few participants to be able to detect small differences among treatment groups in such uncommon adverse health outcomes as perinatal mortality and brachial plexus injury. They have even less power to determine if the health benefit is different for GDM women with high levels of hyperglycemia compared with lower levels. They provide insufficient evidence to confirm or refute the hypothesis that glycemic control improves health outcomes.

Several observational studies without randomized controls have suggested improved intermediate or health outcomes with more intensive treatment of women with GDM.[35,63,131,140,167-171] The weakness in these studies is that women in the treatment groups differ from women in the control groups in multiple ways (some known and some unknown) other than glycemic control; most of these factors are also associated with health outcomes. Thus, observed improvements in health outcomes may be attributable to factors other than glycemic control.

Antepartum Surveillance

Various approaches to antepartum surveillance might improve health outcomes among women with GDM. This might happen either by detecting pregnancies at risk of stillbirth to allow institution of interventions to preserve the fetus or by allowing better targeting of insulin therapy to decrease fetal macrosomia and birth trauma (see ET 3 for selected studies).

Antepartum testing to detect fetuses at risk of stillbirth includes non-stress testing (NST) and ultrasound biophysical profile (BPP). In addition, all pregnant women are urged to monitor fetal movement. Maternal evaluation of fetal movements is a simple and inexpensive screening technique that has a low false-negative rate (<1%), but the false-positive rate is high and may reach 60% to 80%.[172] Since there is a low antepartum stillbirth rate, there is no specific data with regards to this type of monitoring and fetal outcomes in mothers with GDM.

NST and BPP are usually done in high-risk pregnancies, including women with GDM. For NST or BPP to constitute a rationale for GDM screening, evidence would need to show that the use of these tests reduces stillbirth among women with GDM who otherwise have no

indication for these tests. This would require a large RCT as most women with GDM have a low risk of having a stillbirth.

No completed study of women with GDM has examined health outcomes among groups randomized to receive or not receive NST or BPP. Observational studies have found that using NSTs (with or without amniotic fluid index) or BPPs in women with GDM is associated with either absent or very low rates of stillbirth.[173-176] In GDM women with low levels of hyperglycemia, who constitute the majority, small studies have found no stillbirths when delaying testing until 40 weeks gestation.[176,177]

Kjos et al. studied 1,501 gravidas with diabetes (505 had diet-controlled GDM and 885 GDM patients had fasting plasma glucose level $\geq$ 105 mg/dL, of which 305 were diet-controlled and 580 received insulin).[176] All women were delivered within 4 days of their last antepartum test. The patients were monitored with an NST and amniotic fluid evaluation twice weekly. A BPP was performed if the NST was not reactive. No stillbirths occurred within 4 days of the last antepartum test but the corrected stillbirth rate of the entire tested population was 1.4 per 1000. Approximately 3% to 4% of the patients with GDM had a nonreactive NST with fetal heart rate decelerations and 5% had cesarean delivery of suspected fetal distress.[176] The outcome of the neonates delivered by cesarean delivery for suspected fetal distress is not described.

Landon and Gabbe reviewed the perinatal outcomes of 69 patients with diet-controlled GDM followed with NSTs starting at 40 weeks gestation.[174] They also reviewed 28 women with GDM who required insulin therapy (or if they had chronic hypertension, history of a previous stillbirth, or developed pre-eclampsia) who were monitored with twice weekly NSTs initiated at 32 weeks gestation. More patients in the GDM group also complicated by hypertension and prolonged gestation had abnormal antepartum test results. Only one of the 6 women with GDM

in whom the fetal heart rate testing was abnormal had a true-positive result.[178] Landon and Gabbe also state that, after monitoring over 1,000 patients with GDM who require insulin for treatment (or with a prior stillbirth or hypertension) with twice weekly NSTs starting at 32 weeks gestation, they have observed 2 intrauterine deaths in the last 15 years. This rate is no higher than the general population.[172]

Manning has described their experience with nearly 6,000 diabetics, including 4,657 patients with GDM, in which weekly BPP were performed of most patients.[179] He found a lower perinatal mortality than in the low-risk general obstetric population.[179]

Johnson et al. performed weekly BPP examinations in 188 women with GDM and in 50 women who were insulin-dependent.[173] There were no stillbirths and only 8 of 238 BPPs (3.3%) were abnormal. There was minimal morbidity in the 230 fetuses with normal BPPs, but 3 of the 8 fetuses with abnormal BPPs had clinically important neonatal morbidity.

Girz et al. studied 389 women with GDM and found an intrauterine fetal death rate of 7.7 per 1,000 compared to a rate of 4.8 per 1,000 observed in non-diabetic low-risk patients.[175] This difference was not statistically significant. Only 7% of the fetuses in this study were delivered on the basis of a low score on a BPP.[175] Thus, using this modality to monitor all patients with GDM remains in question.

Without appropriate control groups we do not know whether the low rate of fetal demise can be attributed to the additional procedures.[176] NSTs or BPPs have high false-positive rates, and they may lead to interventions that may, on occasion, be unnecessary.[173,174,176] No data exists which clearly demonstrates how to optimally apply NST or BPP to the management of women with GDM.

Observational studies of ultrasound to predict fetal weight and guide cesarean delivery have been disappointing. Ultrasound lacks the accuracy necessary to assess the need for cesarean delivery.[180] If fetal macrosomia is defined as a birth weight greater than 4,000 g and/or birth weight greater than 90th percentile, the sensitivity of ultrasound for predicting macrosomia in most ultrasound units is 65% and the positive predictive value is 60% to 70%, regardless of the ultrasound growth parameters chosen.[181]

McLaren et al., in a study of 7 different ultrasound programs for estimating fetal weight, found a standard error of plus/minus 700 g.[182] These findings indicate that many fetuses of borderline size are misrepresented by the estimated fetal weight of ultrasound.

This misrepresentation can have an impact on cesarean delivery rates. Levin et al. showed that a false-positive prediction of macrosomia (birth weight greater than 90th percentile) increases the incidence of abdominal delivery by 50% in same-weight babies.[183]

Few clinical trials have been conducted to evaluate the efficacy of ultrasound to determine fetal weight and then select the route of delivery based on this. Conway and Langer retrospectively evaluated a protocol of delivering all babies with an ultrasonographic fetal weight estimation of greater than or equal to 4,250 g by elective cesarean delivery.[132] The cesarean delivery rate increased from 22% to 25% (P <0.04), while the rate of shoulder dystocia decreased from 2.4% to 1.1% (OR = 2.2).[132] In light of the fact that clinical data has suggested that vaginal delivery of infants over 4,500 g is safe[51,90] and that there may be no difference in birth weights of neonates born to women with GDM delivering vaginally compared with those delivering abdominally,[184] the plan of elective cesarean delivery based solely on ultrasound estimated fetal weight remains unproven.

Using obstetrical ultrasound to predict shoulder dystocia may be possible. Cohen et al. revealed that shoulder dystocia occurred in 6 out of 20 cases if the estimated ultrasound abdominal circumference minus the biparietal diameter was greater than 2.6 centimeters. Shoulder dystocia never occurred below this cutoff in this study.[181-183,185]

Antepartum surveillance to allow improved targeting of insulin therapy includes ultrasound assessment of abdominal circumference and amniotic fluid (AF) insulin measurement. Much evidence indicates that maternal glucose level is only one of several factors leading to fetal macrosomia and birth trauma. If one could monitor fetal growth (or growth factors such as insulin), then insulin therapy could be directed more appropriately at the fetus rather than the mother.

Three RCTs have enrolled women with hyperglycemia into insulin therapy triggered by ultrasound abdominal circumference.[65,186,187] One of these studies compared standard insulin with insulin only when the ultrasound abdominal circumference was greater than the 70th percentile among women with GDM who had higher glycemic levels (FPG of 105 mg/dL to 120 mg/dL).[65] In this RCT by Kjos et al. (discussed above), birth weight and health outcomes were similar in both groups. The other two studies examined adding insulin therapy for women with lower levels of GDM when ultrasound abdominal circumference was greater than or equal to the 75th percentile.[164,187] Both studies found a reduction in birth weight in the insulin groups but no differences in health outcomes. All three lacked power to detect health outcomes and in none were the obstetricians masked to the intervention group.

The Buchanan et al. RCT is discussed in detail above. The second RCT by Rossi et al. randomized 141 women with mild GDM to undergo ultrasound assessment of fetal abdominal circumference at both 28 and 32 weeks gestation (n = 73) or at 32 weeks gestation only (n =

68).[187] If the abdominal circumference exceeded the 75th percentile, insulin therapy was initiated in addition to the dietary therapy all of these women had already started. The ultrasonographers were unaware of the hypothesis being tested by this study (ET 3).

Of the 141 women, 29 had fetal abdominal circumferences exceeding the 75th percentile and initiated insulin therapy.[187] A greater percentage of macrosomic infants were born from women who underwent the ultrasound assessment only at 32 weeks gestation (71%), compared with those that had it at 28 weeks and 32 weeks (33%). This difference was statistically significant ($P < 0.05$). In addition, the rate of macrosomic infants was reduced to 11.1% in those cases that had insulin initiated by 28 weeks gestation when compared with those in the first group who had insulin initiated at 32 weeks gestation (66.7%) as well as the second group (71.4%) ($P <0.01$).

There were no statistically significant differences between the two groups with regards to spontaneous vaginal delivery, vacuum use, or cesarean section. There were also no differences between the 2 groups when comparing neonatal hypoglycemia, hypocalcemia, hyperbilirubinemia, or 5 minute Apgar scores.

Indirectly, this trial found that earlier intervention with insulin therapy may reduce macrosomia rates, but the overall effectiveness of insulin therapy in preventing macrosomia in women with a fetal ultrasound abdominal circumference greater than the 75th percentile cannot be assessed because there is no control group that did not receive insulin.[187] Moreover, this study includes a small number of patients, raising concerns over lack of power in relation to many of the maternal and neonatal outcome variables evaluated.

A single open-label RCT at a referral center compared women with GDM whose insulin therapy was determined by maternal glucose or by AF insulin. Hopp et al. randomized 123

women with GDM to either be managed with amniotic fluid insulin concentrations (Group A: n = 61) or mean maternal blood glucose levels (Group B: n = 62).[188] The 2 groups were similar with regards to age, parity, BMI, time of diagnosis, and degree of hyperglycemia before initiating treatment. All patients received counseling, started dietary therapy, and self-monitored capillary whole-blood glucose levels. Group A underwent amniocentesis between 28 weeks and 32 weeks gestation and started insulin therapy if the amniotic fluid insulin concentration was greater than or equal to 10 microU/ml. A second amniocentesis was performed at 2- to 4-week intervals to evaluate the fetal response to maternal insulin therapy. Although the entry glycemic level is not given, about 40% of the maternal glucose group required insulin, indicating a mean maternal glucose level of 100 mg/dL or higher.[188] About 50% of women in the AF insulin group received insulin.

The metabolic control was equal in both groups.[188] There was no difference found when comparing number of patients treated with insulin or mean dosages used, mean maternal blood glucose levels, or mean HbA1c percentages. There also was no difference between the 2 groups with regards to pregnancy complications. The groups had similar rates of miscarriage, stillbirth, neonatal death, severe pre-eclampsia, urinary tract infections, or preterm birth.[188]

The number of LGA infants was greater in Group B (22/62; 35%) when compared to Group A (3/61; 5%); this finding was statistically significant ($P < 0.01$).[188] There were also statistically significant ($P < 0.05$) more cesarean deliveries in Group B (17/62; 27%) when compared to Group A (8/61; 13%). In addition, fewer of the neonates in Group A had hypoglycemia (8/61; 13%) than in Group B (17/62; 27%). This finding was statistically significant ($P < 0.05$). The groups did not differ when comparing rates of neonatal hypocalcemia or hyperbilirubinemia.[188]

One concern regarding this trial is that the healthcare providers performing the obstetrical management of these patients were not masked to the results of the study. This may have led to bias in their management and changed thresholds for performing cesarean sections. The obstetrical management included early inductions of labor for suspected fetal macrosomia, which has unproven benefit and may also subsequently change cesarean section rates. Lastly, the study does not have enough statistical power to determine if a difference exists for many of the outcome variables.

Observational studies are mixed as to whether AF insulin levels in women with GDM predict adverse health outcomes.[189-192] AF insulin level determination (amniocentesis) is an invasive procedure with a small but real rate of complications, although one study found it is generally safe and well accepted.[193]

Fraser and Bruce investigated the use of amniotic fluid insulin as a predictor of neonatal morbidity in the macrosomic newborns of diabetic mothers.[190] The AF insulin level was measured in 41 pregnant diabetic women in whom there was normal fetal growth; this was compared with the amniotic fluid insulin levels in 22 women who had fetuses with accelerated fetal growth. The amniotic fluid insulin level was higher in pregnant women with type 1 and 2 diabetes mellitus than in women with GDM or impaired glucose intolerance. No significant correlation was found between raised amniotic fluid insulin and macrosomia, except in the type 1 diabetic women.[79]

Star et al. conducted a case-control study of 39 women with GDM who had undergone genetic amniocentesis for advance maternal age and were matched with normoglycemic controls.[191] Amniotic fluid insulin concentrations were significantly higher in the cases; 35% of the cases (those with GDM) had amniotic fluid insulin levels at or above the 90th percentile.

There were no significant differences between the amniotic fluid glucose concentrations; 20% of the controls with concentrations at or above the 90th percentile subsequently developed GDM. The authors concluded that amniotic fluid insulin concentration in the second-trimester is a more sensitive predictor of impending glucose intolerance than amniotic fluid glucose, but neither is sensitive enough to be used as a screening test.[191] The same group examined the second-trimester amniotic fluid samples of 296 pregnancies and found that pregnant women in whom GDM was later diagnosed (21 cases) had higher mean amniotic fluid insulin levels than women who did not. In this study, amniotic fluid insulin did not predict macrosomia in either group.[194]

Targeted ultrasound examinations are commonly performed in pregnancies complicated by diabetes; however, for all patients with GDM, the frequency of major congenital malformation (1.6% to 2.2%) has continued to not exceed the background level over the last 2 decades.[195,196] The increased risk of major congenital anomalies in the fetuses of mothers with GDM is limited to infants whose mothers have severe hyperglycemia (initial fasting serum glucose concentrations >120 mg/dL) early in pregnancy.[195,197] Thus, targeted ultrasound examinations to detect fetal anomalies are not warranted unless these thresholds are met or if other indications exist.[188,197]

Respiratory distress syndrome due to surfactant-deficiency is rare in term infants of mothers with GDM.[198-200] Berkowitz et al. studied 501 women treated with GDM compared with 561 nondiabetic women and showed that, in pregnancies with treated GDM (and are dated by reliable criteria), the biochemical maturation of the fetal lung is not significantly delayed compared to the nondiabetic population.[198] No studies are available that compare the rates of delay of biochemical fetal lung maturation in treated GDM gravidas versus those that are untreated.

In summary, minimal data is available regarding fetal surveillance in gravidas with GDM. The Fourth International Workshop-Conference on GDM recommends starting NSTs at 32 weeks gestation in women who require insulin therapy, but awaiting near-term in women with diet-controlled GDM. There is insufficient evidence to prove that fetal surveillance changes perinatal outcome in the fetuses of women with well-controlled diabetes. It is difficult to conclude the magnitude of benefit of fetal monitoring from these studies because some compromised fetuses will be detected simply by chance in the course of frequent routine monitoring with NSTs or BPPs,[181] and large studies would have to performed because of the low incidence of intrauterine fetal death in patients with GDM. In addition, fetal monitoring leads to some unnecessary interventions in pregnant women with GDM. Overall, it is not possible to determine whether any benefit exists to antepartum fetal surveillance in patients with uncomplicated GDM unless large prospective clinical trials are performed which will compare the outcomes of monitored to unmonitored patients.[172,201] There is no clear data that supports performing elective cesarean delivery based on ultrasound estimated fetal weights in patients with GDM. The error of such ultrasound estimates at term is significant and no prospective trials have proven the magnitude of benefit or harm of such a policy. There is no evidence that supports the use of targeted ultrasound examinations to find major congenital malformations because such malformations do not appear to be increased in patients with GDM. Cases that have elevated early fasting plasma glucose levels, which may be consistent with undiagnosed pregestational diabetes, could be considered for targeted ultrasound examination. No direct data exists that shows any difference in outcomes with this test. There is no evidence that amniotic fluid insulin concentrations are sensitive enough to be used as a screening test for GDM. A small amount of data shows that these concentrations may hold promise in guiding therapy for

cases of GDM that require insulin therapy. In patients with well-controlled GDM, the evidence suggests that there is no need for amniocentesis for fetal lung maturity, other than the usual indications for nondiabetic patients. The is no evidence available comparing treated patients with GDM to those not treated with regards to delays of biochemical fetal lung maturation.

What are the Harms of Screening and Treatment?

Screening for GDM may subject many women to the psychological effects of labeling in addition to the inconvenience, costs, and possible risks of follow-up testing, dietary restriction, or insulin management.[14] There are no RCTs that directly address the harms of screening, treatment, or the application of antepartum tests for GDM.

The data are limited and mixed as to whether labeling negatively influences womens' perceptions of their health during pregnancy.[202-205] This is important because, in the general population, greater than 80% of all positive GCT screening tests are false-positive.[202] Limited data do suggest that women diagnosed with GDM may have long-term changes in their perception of their own health.[203,206] The impact of these long-term changes in perception of health is unclear.

In a prospective cohort study, Kerbel et al. found that at 32 weeks gestation, only 20% of the 88 women with false-positive GCT results rated their health as excellent, compared with 38% of the 897 women who either had negative results or were not tested ($P = 0.001$); these results were sustained at 36 weeks gestation.[202]

Additionally, Sjogren et al. retrospectively studied 113 women with previous GDM and compared them to 226 controls. The authors found that women with GDM reported less well being ($P<0.05$), psychic health ($P <0.001$), and vigour ($P <0.001$) during pregnancy. They also

report a less positive experience of pregnancy ($P < 0.001$) than controls and more worry about their health during their pregnancy ($P < 0.001$).[203]

Two studies which both utilized the Profile of Mood States-Bipolar test have shown that the label of GDM may not adversely affect patients during their pregnancy.[204,205] Langer and Langer found no significant differences between women with GDM (either the diet or insulin treated group) compared with nondiabetic women, even after controlling for maternal age, size, and marital status.[204] The authors also found that patients with stringent glycemic control were less distressed and felt more reassured than those having poor control.

Spirito et al. found no difference in psychological profiles between a group of patients with GDM and pregnant nondiabetic controls during the index pregnancy.[205] They also found no difference in the scores between women that received insulin compared with those that were treated with diet only, but the study lacked power for significant differences on the individual subscales.

Labeling a woman with GDM may cause long-term harms. Two studies suggest that the diagnosis and treatment of GDM during pregnancy may influence a woman's perception of her health both during and after the pregnancy. In the same Sjogren et al. study, the GDM group reported more physical health problems ($P < 0.05$) and more worry about health ($P < 0.05$) after pregnancy, but they also adhered to a diet more often (34%) than controls without the label of GDM (13%, $P < 0.001$).[203]

Feig et al. analyzed the mail surveys of 65 women diagnosed with GDM compared with 197 controls without the diagnosis, which were completed 3 years to 5 years after the subjects' diagnosis.[206] The mean general health scores were lower for the women with GDM than the controls (68.9 compared to 73.8, $P = 0.05$), but this difference was no longer statistically

significant after controlling for other factors independently associated with health perception. The women with GDM were more worried about their own health ($P = 0.02$), rated their children as less healthy ($P = 0.005$), and perceived themselves as more likely to have diabetes ($P < 0.0001$). A problem with this study is that the women studied may have been biased due to the fact that they were a part of a larger study that focused on GDM.[141]

Few of the RCTs of various treatment strategies for women with GDM have examined potential harms of treatment or antepartum testing in women with GDM. Identification of GDM may needlessly increase false-positive NSTs or BPPs and rates of cesarean delivery (because of a lowered intervention threshold).[35,201] Because of the lack of evidence, the magnitude of other potential harms of aggressive glycemic-lowering therapy, such as increased maternal starvation ketosis and SGA infants, are difficult to quantify.[30,207]

In summary, there are no RCTs that address the harms of screening, treatment, or the use of antepartum testing in women with GDM. The evidence from observational data is limited and insufficient to make conclusive statements regarding these harms. The data suggests that at least a proportion of the increased cesarean delivery rates associated with the diagnosis of GDM is due to bias of the health provider and their reaction to false-positive antepartum tests. The data is limited and mixed as to whether labeling harms women's perception of their health during their pregnancy. Limited data does suggest that women diagnosed with GDM may have long term changes in their perception of their health.

What are the Costs of Screening? What is the Most Efficient Way to Screen?

As the effectiveness of screening in improving health outcomes is uncertain, so the cost-effectiveness cannot be calculated with any precision. Some studies have examined the direct costs of screening and intensive management; others have investigated approaches to improving efficiency by targeting screening or aggressive management to women at highest risk. No randomized trials have been done to determine if the diagnosis and treatment of GDM would reduce the outcome costs compared to those without GDM[78] or compared to a group with untreated GDM. Without such trials, meaningful cost-effectiveness studies of screening for GDM must at least include data on the costs of the diagnostic tests as well as the costs of providing various treatments for GDM and for treating any complications of the mothers or their babies and compare them to the costs of an untreated group with GDM.[78] No studies currently meet all of these criteria, thus, we do not have good information about the differences in health care costs between screened and nonscreened women.

Obesity is a potential confounder in the literature on health care costs for women with GDM. Being moderately overweight is a risk factor for GDM; moreover, macrosomia and cesarean delivery are increased in obese mothers,[40,101,102,208] as are anesthetic and postoperative complications.[208] Also, the average cost of hospital prenatal and postnatal care is higher for overweight mothers and their infants require more admissions to NICUs than do those of normal weight mothers.[209,210]

Kitzmiller and colleagues, using the perspective of managed care, identified the direct costs of screening and intensive management of GDM,[211] he also reviewed studies examining aspects of the costs of treating women with GDM.[209] More than 50% of these costs involve

surveillance such as NSTs, ultrasounds, and amniocenteses. According to 1996 reimbursement data, if weekly NSTs are started at 36 weeks gestation in diet-controlled GDM patients, the 4 NSTs would cost $652. If serial ultrasonography is started at 28 weeks gestation, 3 sonograms would cost $506.[209] As the use of such tests have unproven benefit in well-controlled, diet-treated women with GDM, and there are no large prospective studies comparing the outcomes of monitored and unmonitored women with GDM,[172] $1,159 could be saved if such patients were not monitored until 40 weeks gestation.[172,206,211]

Despite these analyses, we found no clear, generalizable study from the societal perspective of the additional total costs of screening and treating GDM compared with not screening. Thus, in addition to lacking clear evidence concerning the effectiveness of screening, we also lack clear evidence of the additional cost of a strategy of screening.

Although many of these studies assume that intensive treatment of GDM will reduce cesarean deliveries, other evidence indicates that the reverse may often be true. The knowledge of the diagnosis of GDM by the obstetrician may lower the threshold for cesarean deliveries such that these procedures are actually increased, thus increasing costs.[35,186,211] If aggressive NSTs and BPPs are overly performed without a health benefit for many women with GDM, cost-effectiveness will be less favorable.

One approach to improving the efficiency of screening for GDM is to restrict screening to women at higher risk ("selective screening") rather than screening all women ("universal screening"). Some risk-factor-based screening strategies, however, improve efficiency to a minimal degree, actually eliminating only 10% of pregnant women from being screened.[1,212] For the most detailed study of selective screening strategies, Naylor et al. developed a scoring system

that excluded nearly 35% of women from screening and actually detected more cases of GDM than universal screening.[103]

A second strategy to improve the efficiency of screening is to screen universally but restrict the number of women who receive intensive treatment. Only a minority of women with GDM are at risk of adverse health outcomes. If those women at risk could be identified, intensive treatment could be targeted to those at highest risk.[213] Although theoretically such tests as AF insulin and ultrasound abdominal circumference should help separate high- from low-risk women, research remains uncertain as to whether these tests are sufficiently discriminating to direct intensive treatment safely. The magnitude of benefit of intensive treatment even for these high-risk women is also unclear.[213,214]

Chapter 4. Discussion

Benefits and Harms of Screening and Treatment

Maternal and fetal morbidity increase with increasing levels of maternal glycemia. Screening and intensive treatment for gestational diabetes mellitus (GDM) aim to reduce this morbidity. Various screening strategies can detect women with different levels of hyperglycemia, but the cutpoint at which health outcomes begin to deteriorate to a clinically important degree, given today's obstetric care, is uncertain.

The magnitude of any benefit of intensive treatment at various levels of glycemia associated with GDM is uncertain, but it is likely to be small among the many women with lower glycemic levels. The magnitude of the harms and costs of screening and intensive treatment is also uncertain, but potentially substantial.

We have no direct evidence about the health outcomes of screening compared with no screening. No controlled trial has examined the benefit of either universal or selective screening compared to routine care without screening. In addition, little information is available from well-conducted and analyzed randomized controlled trials (RCTs) that have examined the benefit of universal versus selective screening.

The direct evidence about the health outcomes of intensive treatment of women with GDM at various levels of maternal glycemia is limited by the small number of studies, the small number of participants, the lack of masking of obstetrical care, the lack of control for important confounders, and the lack of emphasis on health outcomes rather than intermediate outcomes.

Observational studies provide some indirect evidence that screening may reduce macrosomia, an intermediate outcome, but the extent to which this provides a further health benefit is unclear.

For women with GDM who have higher levels of glycemia, intensive treatment likely reduces macrosomia. The extent to which this translates into a reduction in birth trauma is uncertain but is substantially less than the reduction in macrosomia. For women with GDM with lower levels of glycemia, the existing evidence does not show that dietary therapy improves important clinical outcomes compared with no diet therapy. About 70% or more of all women with GDM are in this group.

By making various assumptions, we can calculate illustrative values for the number needed to screen (NNS) – i.e., the number of women needed to screen to prevent 1 case of brachial plexus injury (Table 7). If we take Case 1, for example, and assume that 4% of pregnant women have GDM,[1] that 30% of them will have a high enough glycemic level to require insulin,[130] and that, among these women, the macrosomia rate is reduced to 9% (i.e., the degree seen in the most positive study[106]), then the NNS to prevent 1 brachial plexus injury is about 8,900. At least 80% of brachial plexus injuries resolve within the first year of life.[1,58,66,67] If we make more generous assumptions that 6% GDM has a prevalence of 6% (essentially, a high-risk group) and that 50% of women with GDM are treated with insulin (Case 3), then the NNS is about 3600. If, to Case 3, we add the further assumptions that infants less than 4,000 g also benefit – the best-case scenario shown in the footnote to Table 7 – the NNS becomes 3,300.

One potential benefit of detecting women with GDM is the knowledge that they have a higher risk for developing type 2 diabetes. The extent to which this information can lead to a health benefit for the women is uncertain.[120] A recent review of screening for type 2 diabetes found that screening primarily benefits people with increased cardiovascular risk factors.[215]

Thus, women with hypertension might well be screened, but the benefit of detecting diabetes earlier among young women with few cardiovascular risk factors is not clear.

GDM may also have long-term implications for the offspring, such as increased risk of childhood obesity, glucose intolerance, or neuropsychological disturbances. Current data are limited and mixed about these issues. Data are insufficient to show that routine screening will significantly influence these outcomes.

The evidence concerning the harms and costs of screening and intensive treatment is even more limited than the evidence about benefits, but several harms are of concern. Many women may suffer anxiety of uncertain duration because of a false-positive screening test. Labeling women with GDM as having an increased risk of future GDM and type 2 diabetes may have psychological implications. Detection of GDM may increase the probability of cesarean delivery; multiple antenatal tests may increase the probability of a false-positive test leading to unnecessary procedures. Costs may be increased with little health benefit for many women, especially those many women with lower levels of hyperglycemia.

Future Research

It is difficult to see how the issue of screening for GDM versus no screening can be clarified without RCTs that mask obstetrical care and examine health outcomes, not simply intermediate outcomes. Ideally, the RCT would compare screening with no screening among women without pregestational diabetes. Some clinicians might consider such a study unethical, but we think the level of uncertainty in this situation gives adequate justification for at least consideration of such a study, if not directly moving ahead.

If, however, an RCT of screening *per se* cannot be mounted, another approach might be a series of RCTs focused on treatment. First-round RCTs should begin with women diagnosed with GDM who have lower levels of hyperglycemia; they should compare intensive glycemic control and antepartum surveillance with usual non-GDM obstetrical care. If intensive treatment does not demonstrate improved health outcomes among these women, then a second round of RCTs ought to investigate the effects of therapy among women with higher levels of hyperglycemia should be studied. These studies should also monitor and report harms and costs associated with screening and intensive treatment.

In summary, the issue of screening for GDM remains a contentious one. The reason for this controversy is largely a lack of high-quality research addressing the central issues of both screening and therapy. Only good research can end the controversy and tell us how to best serve women and their infants.

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Appendix B

Evidence Tables

Glossary

BMI	Body Mass Index
EFW	Estimated Fetal Weight
FBS	Fasting Blood Sugar
g	Gram
GCT	Glucose Challenge Test
GDM	Gestational Diabetes Mellitus
GTT	Glucose Tolerance Test
h	Hour
l	Liter
LGA	Low for Gestational Age
mmol	Millimol
NDDG	National Diabetes Data Group
NICU	Neonatal Intensive Care Unit
RCT	Randomized Controlled Trial

Evidence Table 1. Efficacy of Screening for Gestational Diabetes Mellitus

Source: Author, Year	Research Design and Randomization	Subjects	Measurements	Intervention
Griffin et al., 2000[21]	Prospective RCT: universal screening versus risk factor screening	Universal screening: n = 1,889 Selective screening: n = 1,853	Universal: 1-h 50-g GCT at 26-28 weeks If plasma glucose >7.8 mmol/l then 3-h 100-g oral GTT Risk factor: 3-h 100-g oral GTT at 32 weeks If a risk factor is present, repeat GCT at 32 weeks if GCT normal or had been abnormal but with normal oral GTT	GDM subjects referred to combined care clinic of obstetrician and endocrinologist Uniform diabetic and obstetrical management

Evidence Table 1. Health Consequences of Gestational Diabetes Mellitus (continued)

Results		
Obstetrical Outcomes	**Neonatal Outcomes**	**Comments**
Total with GDM: Universal: 1.45% (n = 27) Risk factor: 2.7% (n = 35 GDM) Mean gestational age at diagnosis: Universal: 30+2.6 weeks Risk factor: 33+3.7 weeks	Comparison of GDM patients in two groups: Term spontaneous vaginal delivery: Universal: 77% Risk factor: 56% Emergency cesarean delivery: Universal: 11.4% Risk factor: 18.5% Delivery at <37 weeks: Universal: 2.9% Risk factor: 18.5% Birth weight:>4500g: Universal: 0% Risk factor: 11.1% NICU admission: Universal: 2.9% Risk factor: 18.5% Hyperbilirubinemia: Universal: 2.9% Risk factor: 14.8% No fetal losses in either group with GDM	Grade: Poor No data on lost patients (i.e., 32/249 in risk factor group with no oral GTT) or on refusals Testing/intervention done at different gestational ages for the two groups "Control" group a combination of non-GDM subjects from each group No intention-to-screen analysis

Evidence Table 2. Impact of Treatment of Gestational Diabetes Mellitus

Source: Author, Year	Research Design and Randomization	Subjects	Measurements	Intervention
Garner et al., 1997[36]	Prospective RCT (pilot study). Primary objective: Determine if strict maternal glycemic control in treatment of GDM lessens the risk of macrosomia	n = 149 GDM in treatment arm n = 150 GDM controls "Control Failures" (FBS >140 mg/dl, 1-hr post prandial>200): n = 16 in control group (10.6%); n = 13 in treatment group (8.7%) with same values	75-g glucose screening test between 24-28 weeks' gestation with a 1-hr postscreen cutoff level of 144 mg/dL. If positive screen, underwent oral GTT with 75-g glucose load; diagnosed GDM by application of Hatem, et al., 1987	<u>Treatment group:</u> (1) Follow-up in tertiary care setting with obstetrician and endocrinologist (2) Initial dietary counseling, calorie-restricted diet (3) Taught home glucose monitoring; if fasting glucose levels <80 mg/dl and 1 hour postprandial glucose levels <140 mg/dl on > 2 occasions, insulin treatment started (4) Seen biweekly, biophysical profile and ultrasound each visit <u>Controls</u>: (1) Returned to primary obstetrical care provider (2) Not seen by dietician (3) 2 glucose levels checked weekly at home; results telephoned to independent observer (4) No high-risk fetal monitoring unless indicated <u>Failed control group:</u> Transferred to treatment arm and placed on diet, insulin, fetal monitoring

Evidence Table 2. Impact of Treatment of Gestational Diabetes Mellitus (continued)

Results		
Obstetrical Outcomes	**Neonatal Outcomes**	**Comments**
Mean maternal weight gain similar Treatment arm: 24.2% required insulin Treatment group had significantly lower preprandial and 1-hour postprandial glucose levels by 30 to 32 weeks' gestation, which continued until term (36-38 weeks) No difference between groups in mode of delivery (*P* = >0.8)	No difference between groups (*P* >0.1) in mean birth weight, hyperbilirubinemia, or hypoglycemia No stillbirths, neonatal deaths, congenital anomalies or birth trauma in either group Neonatal hypocalcemia: Control: 30%; Treated: 40.9% (*P* = 0.048) No significant difference in other maternal and fetal outcomes	Grade: Fair n = 300 does not reach the statistical power to detect many differences Control women not masked to results of GDM screen and follow-up glucose testing results; may have led to self-education on diet therapy and self-treatment by modification of diet. Primary obstetrical care providers also not masked to results; may play a role in cesarean section rates if diagnosis was known

Evidence Table 2. Impact of Treatment of Gestational Diabetes Mellitus (continued)

Source: Author, Year	Research Design and Randomization	Subjects	Measurements	Intervention
de Veciana et al., 1995[106]	RCT Primary objective: To compare the efficacy of postprandial versus preprandial monitoring in achieving glycemic control in womenwith insulin-requiring GDM	n = 66 women with GDM who required insulin therapy. All pregnant women who had risk factors for GDM screened at initial visit or if negative screen, rescreened at 24-28 weeks No difference between two groups with regard to age, gravidity, race/ethnicity, prepregnancy weight, BMI, weeks of gestation at diagnosis	Goals: Preprandial 60-105 mg/dL Postprandial <140 mg/dL. Initial screening: 1-hour plasma glucose after a 50-g glucoseoral load; if >140 mg/dL and 190 mg/dL, then 3-hour 100-g oral GTT GDM diagnosed if >2 plasma glucose values were abnormal:FBS >105 mg/dL 1-hour >190 mg/dL 2-hour >165 mg/dL 3-hour >145 mg/dL If initial GCT value >190 mg/dL, classified as GDM and monitored with fasting and postprandial glucose values to determine need for insulin therapy	GDM patients treated with diet and monitoring Insulin therapy started if FBS >105 mg/dL or postprandial values >140 mg/dL or if had elevated FBS at 3-hour oral GTT Preprandial monitoring plan: daily monitoring of fasting, preprandial, and bedtime capillary glucose concentration. Postprandial monitoring plan: Daily monitoring of fasting blood glucose concentration and 1 hour after each meal

Evidence Table 2. Impact of Treatment of Gestational Diabetes Mellitus (continued)

Results		
Obstetrical Outcomes	**Neonatal Outcomes**	**Comments**
No significant difference between groups withregards to gestational age at delivery, maternal weight gain, hospitalizations for glycemic control, or pre-eclampsia Glycosylated hemoglobin (%) comparable at initiation of insulin therapy but was lower in postprandial group prior to delivery	Birth weight: Preprandial: 3,848 g Postprandial: 3,469 g Shoulder dystocia: Preprandial: 18% Postprandial: 3% Neonatal hypoglycemia: Preprandial: 21% Postprandial: 3% No difference in small for gestational age, hyperbilirubinemia, apgar score of ≤ 7, or stillbirths	Grade: Fair Unknown number of refusals Clinicians not masked; may impact on obstetrical outcomes Predominantly Hispanic population Because GDM was diagnosed early in pregnancy, some women may have had previously undiagnosed type 2 diabetes Exclusion of women started on insulin therapy after 30 weeks' gestation increased the likelihood that a difference in perinatal outcomes would be found between the two groups

Evidence Table 2. Impact of Treatment of Gestational Diabetes Mellitus (continued)

Source: Author, Year	Research Design and Randomization	Subjects	Measurements	Intervention
Buchanan, et al., 1994[164]	RCT of diet versus diet plus insulin in Latina women with GDM and fetal ultrasound abdominal circumferrence >75th percentile n = 59 randomized to: diet (n = 29); diet plus twice daily insulin (n = 30)	n = 73 randomized n = 59 completed RCT	Nonstress tests twice weekly if fasting glucose levels before diet therapy >105 mg/dL; once at > 34 weeks' gestation All others started non-stress tests at 40 weeks' gestation. Heel capillary blood from infants All infants examined by neonatologist within 24 hours of birth	All subjects met with dietary staff; were taught to monitor capillary glucose levels Weekly outpatient clinic visits Diet only managed by routine obstetrical service; diet plus insulin managed by high-risk service Standard obstetrical guidelines followed for all patients
Nachum et al., 1999[105]	RCT Primary objective: Compare twice daily versus four times daily insulin to treat GDM and pregestational diabetes	n = 138 received insulin four times daily n = 136 received insulin twice daily n = 118 patients with pregestational diabetes Insulin treatment began prior to 35 weeks gestation GDM diagnosed by NDDG criteria	Monthly HbA1c Capillary whole blood glucose 7 times daily until adequate control, then at least twice daily	Four times daily regimen: Three doses of regular insulin before meals; intermediate dose at bedtime Twice daily regimen: Combination of regular and intermediate insulin morning and evening Standardized obstetrical management Standardized neonatal care, close monitoring

Evidence Table 2. Impact of Treatment of Gestational Diabetes Mellitus (continued)

Results		
Obstetrical Outcomes	**Neonatal Outcomes**	**Comments**
Symptomatic hypoglycemic episodes Diet only: 0 Diet plus insulin: 0.3 per patient-week Glycemic control in diet plus insulin (6-9mg/dl) better than in diet only ($P < 0.005$)	Same mean gestational age at delivery Diet only had higher mean birth weight than diet plus insulin No significant birth trauma in either group No differences in mean infant glucose levels or rates of hypoglycemia during first 3 hours of life	Grade: Fair Obstetrical management not standardized Small sample size Question clinical significance of birth weight difference Cesarean delivery rates did not parallel LGA rates or birth weights; may reflect difference in intrapartum management
Glycemic control: Four times daily group had improved glycemic control compared to twice daily group Adequate glycemic control achieved in 17% more women in four times daily group than in twice daily group No statistically significant differences in gestational age at delivery, maternal weight gain, cesarean sections, or pregnancy-induced hypertension	Hypoglycemia: Four times daily: 0.7% Twice daily: 5.9% Hyperbilirubinemia: Four times daily: 21% Twice daily: 11% "Overall neonatal morbidity": Four times daily: 29% Twice daily: 17% No significant difference in mean birth weight, perinatal mortality, major congenital anomalies, small or large for gestational age, macrosomia, Apgar score <7, hyaline membrane disease, polycythemia, or birth trauma (peripheral nerve damage, bone fracture)	Grade: Good Improvement in overall neonatal morbidity statistic comprised almost entirely of decrease in hypoglycemia and hyperbilirubinemia, as other factors not significantly different between the groups No data provided on the treatment required (if any) for those neonates with hypoglycemia or hyperbilirubinemia

Evidence Table 3. Impact of Antepartum Testing and Surveillance

Source: Author, Year	Research Design and Randomization	Subjects	Measurements	Intervention
Hopp, et al., 1996[188]	Prospective RCT Primary objective: Compare the amniotic fluid insulin concentration (AFI) to the mean maternal blood glucose (MBG) for managing GDM.	n = 123 women diagnosed with GDM. Group A: n = 61 Group B: n = 62 (see intervention)	Diurnal and nocturnal measurement of fasting, pre- and postprandial blood glucose levels	Group A: Managed according to the amniotic fluid insulin concentration. Group B: Managed only on the basis of mean blood glucose. All subjects hospitalized initially; provided comprehensive education program; placed on dietary regimen; taught self-monitoring of capillary whole-blood glucose levels; readmitted every 3 weeks for 24-hour blood glucose profile and HbA1c
Rossi et al., 2000[187]	RCT Primary Objective: Investigate the adequate timing for ultrasound assessment of abdominal circumference (AC) early in the 3rd trimester to use as a guide for initiation of insulin	n=141 women with mild GDM n=73 evaluated at both 28 and 32 weeks' gestation n=68 evaluated at 32 weeks' gestation only n=29 with abdominal circumference >75th percentile	Ultrasound measurement of fetal abdominal circumference done by staff unaware of the hypothesis being tested in the study Group A: 28 and 32 weeks' gestation Group B: 32 weeks' gestation Frequent neonatal monitoring	Insulin started for both groups if abdominal circumference >75th percentile Diet and instruction for daily multiple self-monitoring of capillary blood glucose Weekly obstetrical care Labor induced before 42 completed weeks gestation, EFW >4,000 g and other maternal, fetal, or abnormal labor indications

Evidence Table 3. Impact of Antepartum Testing and Surveillance (KQ6) (continued)

Results		
Obstetrical Outcomes	**Neonatal Outcomes**	**Comments**
Glycemic control equal in both groups No difference between the two groups regarding miscarriage, stillbirth, or neonatal death No difference in severe pre-eclampsia, urinary tract infection, preterm labor, premature delivery, or delivery at <37 weeks or >37 weeks	Large for gestational age: Group A: 4.9% Group B: 35.4% Neonatal hypoglycemia: Group A: 13.1% Group B: 27.4% (No difference in hyperbilirubinemia or hypocalcemia)	Grade: Fair Complication rate of amniocentesis (0.5% to 1%) Physicians managing labor not masked
n = 29 (21%) placed on insulin therapy based on fetal abdominal circumference > 75th percentile; no hypoglycemia episodes No statistically significant differences with regard to: gestational age at delivery; spontaneous vaginal delivery; cesarean delivery; vacuum use; 5 minute Apgar <7; neonatal hypoglycemia, hypocalcemia, or hyperbilirubinemia	Macrosomic infants: Group A: 33.3%; Group B: 71.4% ($P < 0.05$.) Macrosomic rate 11.1% in Group A cases where insulin started by 28 weeks	Grade: Fair Error of abdominal circumference measurement on ultrasound 60% of fetuses with abdominal circumference >75th percentile at 32 weeks in Group A (60%) met this threshold at 28 weeks No control group without insulin prophylaxis so the effectiveness of insulin therapy in preventing macrosomia in those with abdominal circumference >75th percentile could not be assessed The effectiveness of insulin therapy in this study is indirect Small number of women in trial

Table 1. Key Prior Recommendations for Screening for Gestational Diabetes Mellitus

Organization	Conclusion and Recommendation
Canadian Task Force on the Periodic Health Examination (1992)[13]	Insufficient evidence for or against screening Evidence for screening is poor
US Preventive Services Task Force (1996)[14]	Insufficient evidence for or against routine screening
The Fourth International Workshop-Conference on Gestational Diabetes Mellitus (1998)[16]	Selective screening based on risk factors
Australian Diabetes in Pregnancy Society(1998)[15]	Selective screening based on risk factors
American Diabetes Association (1999)[17]	Selective screening based on risk factors
American College of Obstetricians and Gynecologists (2001)[1]	No definite recommendation No data to support the benefit of screening Selective screening in some settings; universal in others

Table 2. Inclusion Criteria, Search Strategy, and Results of Searches for Six Key Questions on Screening for Gestational Diabetes Mellitus

Key Question	Inclusion Criteria*	Number of Articles Meeting Criteria
1. Screening efficacy for maternal and fetal health outcomes	RCT Screening for GDM Maternal or infant health outcomes	0
2. Adverse health outcomes of untreated GDM	RCT Screening for GDM Maternal or infant health outcomes	9
3. Accuracy and reliability of screening tests	Screening test for GDM Data available to calculate sensitivity and specificity Criterion standard used	13
4. Treatment for GDM: • Glycemic control	RCT Glycemic control Health outcomes	9
• Antepartum surveillance	RCT Surveillance or antepartum health outcomes	5
5. Harms of screening and harms of treatment	Any research design Any harm associated with either screening or treatment of GDM	9
6. Costs and cost-effectiveness of screening or treatment, efficiency of screening	Any research design Costs, efficiency of screening for GDM	7

* All searches started with exploding “diabetes, gestational.”

Note: GDM indicates gestational diabetes mellitus; RCT,randomized clinical trial.

Table 3. Studies Addressing Complications of Gestational Diabetes Mellitus in Unrecognized and Untreated Groups: Offspring Health Outcomes

Outcome	O'Sullivan et al.[32] N = 308 (1954-1960) * %	Pettitt et al. [33] N = 122-173 (1965-1979) † %	Pettitt et al. [33] N = 17-23 (1965-1979) ‡ %	Beischer, et al.[23] N = 578 (1971-1980) § %
>4000 grams	13.1	NR	NR	NR
>4500 grams	NR	NR	NR	NR
Large for gestational age	NR	38.5	94.1	NR
Hypoglycemia	NR	NR	NR	NR
Hypocalcemia	NR	NR	NR	NR
Hyperbilirubinemia	NR	NR	NR	NR
Stillbirth	2.6	1.2	4.3	1.4
Brachial plexus injury	NR	NR	NR	NR
Clavicular fracture	NR	NR	NR	NR
Preterm Birth (<37 weeks)	7.8	5.7	5.9	NR
Major congenital anomaly	NR	1.8	2.5	NR

GDM, gestational diabetes mellitus; NR, not reported

***** 3-hour 100-gram:
Fasting blood glucose > 110 mg/dL
1-hour ≥ 170 mg/dL
2-hour >120 mg/dL
3-hour >110 mg/dL

† 2-hour 75-gram: 120 - 159 mg/dL

‡ 2-hour 75-gram: 160-199 mg/dL

§ 1-hr plasma glucose ≥ 162 mg/dL but < 180 mg/dL and 2-hour plasma glucose > 126 mg/dL but < 141 mg/dL

‖ Carpenter and Coustan criteria

****** National Diabetes Data Group criteria plus:
75-gram fasting blood glucose <144 mg/dL 2-hour <198 mg/dL

†† National Diabetes Data Group criteria

‡‡ 2-hour 75-gram:
2nd trimester: >135 mg/dL
3rd trimester: >173 mg/dL

§§ Carpenter-Coustan criteria but less than American College of Obstetricians and Gynecologists criteria

Table 3. Studies Addressing Complications of Gestational Diabetes Mellitus in Unrecognized and Untreated Groups: Offspring Health Outcomes, continued

Outcome	Coustan and Imarah[171] N = 146 (1975-1980) ‖ %	Li et al.[38] N = 73 (1985-1986) ** %	Adams et al.[34] N = 16 (1986-1996) †† %
>4000 grams	17.8	7	44
>4500 grams	NR	NR	19
Large for gestational age	21.9	22	44
Hypoglycemia	17.1 (lab diagnosis)	0	0
Hypocalcemia	NR	NR	NR
Hyperbilirubinemia	6.2 (treatment-requiring)	NR	NR
Stillbirth	0.7 (perinatal mortality)	0	0
Brachial plexus injury	NR	0	6
Clavicular fracture	NR	0	13
Preterm birth (<37 weeks)	Nr	NR	NR
Major congenital anomaly	NR	4.1	NR

Table 3. Studies Addressing Complications of Gestational Diabetes Mellitus in Unrecognized and Untreated Groups: Offspring Health Outcomes, continued

Outcome	Naylor et al.[35] N = 115 (1989-1992) ‖ %	Garner et al.[36] N = 150 (1991-1994) ‡‡ %	Lu, et al.[40] N = 319 (1991-1998) §§ %
>4000 grams	28.7	18.7	17.0
>4500 grams	6.1	4	NR
Large for gestational age	NR	NR	28.1
Hypoglycemia	NR	8.7	NR
Hypocalcemia	NR	30	NR
Hyperbilirubinemia	No difference vs. non-GDM	6.6	NR
Stillbirth	NR	0	NR
Brachial plexus injury	No difference vs. non-GDM	NR	NR
Clavicular fracture	No difference vs. non-GDM	NR	NR
Preterm birth (<37 weeks)	NR	NR	NR
Major congenital anomaly	NR	NR	NR

Table 4. Complications of Gestational Diabetes Mellitus in Unrecognized and Untreated Groups: Maternal Health Outcomes

Maternal Health Outcome	O'Sullivan et al.[32] N = 308 (1954-1960) * %	Pettitt et al.[33] N = 122-173 (1965-1979) † %	Pettitt et al.[33] N = 17-23 (1965-1979) ‡ %	Beischer et al.[23] N = 578 (1971-1980) § %
Cesarean delivery, total	NR	5.5	8.7	NR
Cesarean delivery, cephalopelvic disproportion	NR	NR	NR	NR
Third or fourth degree laceration	NR	NR	NR	NR
Pre-eclampsia	NR	19.7	13	NR

NR, not reported.

* 3-hour 100-gram:
Fasting blood glucose > 110 mg/dL
1-hour ≥ 170 mg/dL
2-hour >120 mg/dL
3-hour >110 mg/dL

† 2-hour 75-gram: 120 - 159 mg/dL

‡ 2-hour 75-gram: 160-199 mg/dL

§ 1-hr plasma glucose ≥ 162 mg/dL but < 180 mg/dL and 2-hour plasma glucose > 126 mg/dL but < 141 mg/dL

‖ Carpenter and Coustan criteria

** National Diabetes Data Group criteria plus:
75-gram fasting blood glucose <144 mg/dL
2-hour <198 mg/dL

†† National Diabetes Data Group criteria

‡‡ 2-hour 75-gram: 2nd trimester: >135 mg/dL
3rd trimester: >173 mg/dL

§§ Carpenter and Coustan criteria but less than American College of Obstetricians and Gynecologists criteria.

Table 4. Complications of Gestational Diabetes Mellitus in Unrecognized and Untreated Groups: Maternal Health Outcomes (continued)

Maternal Health Outcome	Coustan, Imarah[171] N = 146 (1975-1980) ‖ %	Li et al.[38] N = 73 (1985-1986) ** %	Adams et al.[34] N = 16 (1986-1996) †† %
Cesarean delivery, total	NR	26	25
Cesarean delivery, cephalopelvic disproportion	NR	NR	19
Third or fourth degree laceration	NR	NR	13
Pre-eclampsia	NR	NR	NR

Table 4. Complications of Gestational Diabetes Mellitus in Unrecognized and Untreated Groups: Maternal Health Outcomes, (continued)

Maternal Health Outcome	Naylor et al.[35] N = 115 (1989-1992) ‖ %	Garner et al.[36] N = 150 (1991-1994) ‡‡ %	Lu et al.[40] N = 319 (1991-1998) §§ %
Cesarean delivery, total	29.6	NR	21.8
Cesarean delivery, cephalopelvic disproportion	16.8	18.6	NR
Third or fourth degree laceration	No difference vs. non-GDM	NR	NR
Pre-eclampsia	8.7	NR	NR

Table 5. Screening and Diagnostic Criteria for Gestational Diabetes Mellitus

	Reference Diagnostic Test – Glucose Tolerance Test: Cutpoints in Milligrams per deciliter (mg/dL)			Screening
Glucose Level	National Diabetes Data Group*[122] 100 g	American Diabetes Association*[126] 100 g/75 g	World Health Organization†[127] 75 g	Glucose Challenge Test 50 g
Fasting	105	95	≥126	--
1 hour	190	180	--	130/140
2 hours	165	155	≥ 140	--
3 hours	145	140	--	--

* Two or more criteria must be met or exceeded for a positive diagnosis.
† One or more criteria must be met or exceeded for a positive diagnosis.
-- Indicates glucose levels not used for the test indicated.

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Table 6. Randomized Controlled Trials of Treatment of Gestational Diabetes Mellitus

Author, Year, Total N Glycemic Level of Participants	Random-ization	GDM Diagnosis Inclusion	Glycemic Separation During Study	% Stillbirth (Stat Sig)	% > 4000 g (Stat Sig)	% Large for Gesta-tional Age (Stat Sig)
Li et al., 1987[161] N =158 Low	A: Controls: no treatment (n = 73) B: Treatment; diet, monitoring (n = 85)	GDM by NDDG[122] criteria and normal or impaired glucose tolerance by WHO[127] criteria	NR	NR	A: 7 B: 4 (NS)	A: 22 B: 18 (NS)
Buchanan et al., 1999{[165] N = 59 Low	A: Diet (n = 29) B: Diet and twice-daily insulin (n = 30)	GDM and fasting blood glucose <105 mg/dL; fetal ultrasound abdominal circumference ≥ 75th percentile	5.4 - 10.8 mg/dL mean glucose difference in mixed-meal tolerance test	NR	NR	A: 45 B: 13 (P < 0.02)
Garner et al. 1997[36] N = 300 Low	A: Routine care (n = 150) B: Strict glycemic control and tertiary care (n = 149)	Hatem and Dennis, 1987[159] criteria; controls treated with insulin if fasting blood glucose >140 mg/dL or 1-hr postprandial value >200 mg/dL (n = 16)	Lower in treated group by 5 - 9 mg/dL 1 hr postprandial	A: 0 B: 0 (NS)	A: 18.7 B: 16.1 (NS)	NR
Bancroft et al. 2000 [162] N = 68 Low	A: Diet and no diabetic monitoring (n = 36) B: Diet and intensive diabetic monitoring (n = 32)	WHO[127] criteria Fasting blood glucose <126 mg/dL; 2-hr 75 g = 140-200 mg/dL	HbA1c: 0.2% - 0.7% difference	A: 0 B: 0 (NS)	NR	A: 7 B: 8 (NS)

GDM, gestational diabetes mellitus; Stat Sig, statistical significance; NR, not reported; NS, not statistically significant; NDDG, National Diabetes Data Group; WHO, World Health Organization, CPD, cephalopelvic disproportion

Table 6. Randomized Controlled Trials of Treatment of Gestational Diabetes Mellitus (continued)

% Brachial Plexus Injury (Stat Sig)	% Clavicular Fracture (Stat Sig)	% Hypoglycemia (Stat Sig)	% Hyperbili-rubinemia (Stat Sig)	% Hypocalcemia (Stat Sig)	% Total Cesarean Delivery (Stat Sig)
A: 0 B: 0 (NS)	A: 0 B: 0 (NS)	No difference	NR	NR	A: 26 B: 27 (NS)
A: 0 B: 0 (NS)	A: 0 B: 0 (NS)	A: 18 B: 14 (NS) (lab diagnosis)	NR	NR	A: 14-21 B: 43 ($P < 0.05$)
A: 0 B: 0 (NS)	A: 0 B: 0 (NS)	A: 8.7 B: 14.1 (NS)	A: 6.6 B: 5.4 (NS)	A: 30 B: 40.9 ($P = 0.048$)	A: 18.6 B: 20.1 (NS)
NR	NR	NR	NR	NR	A; 31 B: 31 (NS)

Table 6. Randomized Controlled Trials of Treatment of Gestational Diabetes Mellitus (continued)

Author, Year, Total N Glycemic Level of Participants	Random-ization	GDM Diagnosis Inclusion	Glycemic Separation During Study	% Stillbirth (Stat Sig)	% > 4000 g (Stat Sig)	% Large for Gesta-tional Age (Stat Sig)
Persson et al. 1985 [104] N = 202 High	A: Diet, add insulin for high glucose (n = 105) B: Diet and insulin (n = 97)	Impaired glucose tolerance	No difference	A: 0 B: 0 (NS)	NR	A: 13 B: 11 (NS)
Langer et al., 1989[166] N = 272 High	A: Controls: No treatment (n = 146) B: Treatment: Diet and/or insulin (n = 126)	National Diabetes Data Group [122] criteria One abnormal value on 3-hr glucose tolerance test B: Goal of glucose ≤ 95 mg/dL	24 mg/dL difference in mean capillary blood glucose	NR	NR	A: 26 B: 6 ($P < 0.05$)
Nachum et al., 1999 [105] N = 274 High	A: Diet and twice daily insulin (n = 136 B: Diet and 4 times daily insulin (n = 138)	National Diabetes Data Group [122] criteria	3.4 mg/dL difference in mean blood glucose; 0.3% in HbA1c	A: 0.7 B: 0 (NS)	A: 19 B: 16 (NS)	A: 30 B: 26 (NS)
Kjos et al., 2001[65] N = 96 High	A: Standard: Insulin (n = 48) B: Experimen-tal Insulin only if fetal AC is ≥ 70 percentile (n = 48)	Fasting plasma glucose > 105 and < 120 mg/dL	Mean fasting plasma glucose: 88.1 (B) 84.9 (A) 3.2 mg/dL difference	No difference (only one reported)	A: 4.2 B: 6.3 (NS)	A: 6.3 B: 8.3
de Veciana et al., 1995[106] N = 66 insulin dependant GDM Very high	A: Preprandial monitoring (n = 33) B: Postprandial monitoring (n = 33)	National Diabetes Data Group [122] criteria Fasting plasma glucose >105 mg/dL or 1-hr >140 mg/dL	1.6% difference in HbA1c	A: 3 B: 0 (NS)	A: 36 B: 9 ($P = 0.01$)	A: 42 B: 12 ($P = 0.01$)

Table 6. Randomized Controlled Trials of Treatment of Gestational Diabetes Mellitus (continued)

% Brachial Plexus Injury (Stat Sig)	% Clavicular Fracture (Stat Sig)	% Hypoglycemia (Stat Sig)	% Hyperbili-rubinemia (Stat Sig)	% Hypocalcemia (Stat Sig)	% Total Cesarean Delivery (Stat Sig)
NR	NR	A: 0 B: 5 (NS)	A: 20 B: 20 (NS)	A: 6.7 B: 12.5 (NS)	NR
NR	NR	A: 13 B: 2 (*P* < 0.02) (lab diagnosis)	A: 14 B: 6 (NS) (lab diagnosis)	NR	A: 11 B: 10 (NS)
A: 2.2 B: 1.4 (NS)	A: 0 B: 0 (NS)	A: 5.9 B: 0.7 (*P* = 0.02) (lab diagnosis)	A: 21 B: 11 (NS)	A: 0 B: 0.7 (NS) (lab diagnosis)	A; 28 B: 28 (NS)
No difference (small number)	No difference (small number)	A: 10.4 B: 10.4 (NS)	A: 2 B: 4 (NS)	NR	A: 14.6 B: 33.3 *P* = 0.03 (Greater % women with previous cesarean delivery in Group B)
A: 0 B: 0 (NS)	A: 3 B: 3 (NS)	A: 21 B: 3 (*P* = 0.05)	A: 12 B: 9 (NS)	NR	A: 39 (CPD: 3) B: 24 (CPD: 12) (*P* 0.04)

Table 7. Number Needed to Screen (NNS) for Gestational Diabetes Mellitus (GDM) to Prevent 1 Case of Brachial Plexus Injury

Case 1: Screen 100,000 pregnant women

Assume:
a. The prevalence of gestational diabetes is 4% (average risk).[1]
b. Of women with gestational diabetes, 30% require insulin (assuming aggressive criteria).[130]
c. Tight control of glucose reduces the development of macrosomia (birth weight >4,000 grams) from 36% to 9% among women treated with insulin.[106]
d. Infants weighing greater than 4,000 grams at birth have a 3.5% rate of brachial plexus injury.[58]
d. There is no benefit from treating women who do not require insulin.[163]

Number detected by screening	20,000
Diagnosis of gestational diabetes	4,000
Number requiring insulin	1,200
Number of macrosomic infants (treatment/no treatment)	108/432
Brachial plexus injuries in macrosomic infants (treatment/no treatment) *	3.8/15.1
Difference: cases avoided	11.3
Number needed to screen †	8,900

Case 2: Same as Case 1, except that we assume the prevalence of gestational diabetes is 6% (high-risk population)[1]

Diagnosis of gestational diabetes	6,000
Number requiring insulin	1,800
Number of macrosomic infants (treatment/no treatment)	162/648
Brachial plexus injuries in macrosomic infants (treatment/no treatment) *	5.7/22.7
Difference: cases avoided	17.0
Number needed to screen †	5,900

Case 3: Same as Case 2, except that we assume that we treat 50% of women with GDM with insulin

Diagnosis of gestational diabetes	6,000
Number requiring insulin	3,000
Number of macrosomic infants (treatment/no treatment)	270/1,080
Brachial plexus injuries in macrosomic infants (treatment/no treatment) *	9.5/37.8
Difference: cases avoided	28.3 ‡
Number needed to screen †	3,600 ‡

* Injuries category rounded to nearest 0.1.
† All NNS calculations are rounded upward to nearest hundred.
‡ Best-case scenario: If we assume a further 10% increase in cases avoided from treatment of women with GDM but without macrosomic infants, then the cases avoided for Case 3 would be 31.1 and the NNS would be about 3,300.