Screening for Gestational Diabetes Mellitus: A Critical Review

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Gestational diabetes mellitus (GDM) occurs in 1% to 3% of pregnant women. Generally, the clinical focus in these cases is on intermediate outcomes such as macrosomia, hypoglycemia, or hypocalcemia. Only macrosomia is consistently associated with gestational diabetes, yet the risks of macrosomia such as shoulder dystocia and birth injury are highly variable.

The screening test and the reference standard, the oral glucose tolerance test, are problematic in that there are no standardized testing procedures or definitive criteria for diagnostic interpretation and poor reproducibility of test results.

There have been no methodologically sound randomized controlled trials of therapy for GDM. Studies that attempted randomization show, however, that therapy reduces the incidence of macrosomia, which is an intermediate outcome.

A critical review of the literature revealed that there is insufficient evidence to justify routine screening for gestational diabetes. A reassessment of the relation between maternal glucose levels in pregnancy and neonatal outcomes is needed to determine if there are correctable adverse outcomes. In the meantime, management should be based on careful assessment of each individual pregnancy.

Key words. Diabetes, gestational; mass screening; pregnancy complications; fetal macrosomia. (*J Fam Pract 1993; 37:277-283*)

Gestational diabetes mellitus (GDM) is defined as "carbohydrate intolerance of variable severity with onset or first recognition during the present pregnancy."[1] In North America, there are two schools of thought as to who should be screened for this condition. One bases the decision to screen on certain obstetrical risk factors and maternal factors such as age and obesity.[2,3] The other suggests that all pregnant women should be screened.[1,4]

Cadman et al[5] suggest seven criteria for assessing the evidence when evaluating a screening program (Table 1). As there have been no randomized trials to evaluate the efficacy of screening, this paper considers the criteria of burden of illness, screening tests, and treatment. If findings for these three areas are inconclusive or unsatisfactory, then the other criteria are not relevant.

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The Burden of Illness

The burden of illness imposed by GDM is assessed in terms of its magnitude and severity. The most quoted prevalence of gestational diabetes is 2% to 3%[2] with a range of 0.31%[6] to 37.4%.[7] One reason for such a large range is the type of population studied. For example, higher rates of GDM are found in hospital-based populations because of problems such as referral-filter bias and expectation bias.[8] (Definitions of types of bias are detailed in Table 2.) In one study based in obstetrician offices, the rate of GDM was 2%.[9] In three community-based studies the prevalences were 0.31%,[6] 1.2%,[10] and 3.1%.[11] Variations in the screening criteria, screening tests, and diagnostic criteria for the oral glucose tolerance test (OGTT) all affect prevalence. This latter point was illustrated in one study[12] in which women who were tested for GDM using the National Diabetes Data Group[13] criteria were reevaluated using a 75-g OGTT and the World Health Organization diagnostic criteria.[14] The prevalence of GDM was almost halved, with only

Table 1. Criteria for the Assessment of a Screening Program

1. Has effectiveness of the screening program been demonstrated in a randomized trial?
2. Does current burden of suffering warrant screening?
3. Is there a good screening test?
4. Are efficacious treatments available?
5. Can the health care system cope with the screening program?
6. Does the program reach those who would benefit from it?
7. Will positive screenees comply with subsequent advice and interventions?

Adapted from Cadman D, Chambers L, Feldman W, Sackett D. Assessing the effectiveness of community screening programs. JAMA 1984; 251:1580–5. ©1984 American Medical Association. Used with permission.

45.4% in whom GDM had been diagnosed testing positive on the second OGTT. The community-based studies suggest that the prevalence is probably low. Given its low frequency, is gestational diabetes of sufficient severity in terms of perinatal mortality rate (PMR) and morbidity to warrant universal screening?

The PMR ascribed to gestational diabetes ranges from 0%[15] to 28.5%,[16] but three major factors affect these ranges. First is the general decline in the prenatal mortality rate to the current overall perinatal mortality rate in Canada of 0.21%.[17] Second, studies often have insufficient power to determine whether the PMR is significantly higher in women with GDM because of inadequate numbers of subjects. Third, a review of the literature demonstrates that studies have failed to control for other prognostic factors. The perinatal mortality rate is closely related to neonatal weight and gestational age,[16,18] and these were often not controlled for in the analyses of studies. Given the variability in PMR attributed to gestational diabetes, only studies that consider the above three factors will allow determination of the actual PMR directly related to gestational diabetes.

Macrosomia is the most common condition cited in perinatal morbidity. The reported rate in infants of women with gestational diabetes varies from 0.7%[19] to 47.4%,[20] depending on the criteria for the diagnosis of macrosomia. A review of many studies[21] revealed a higher incidence of macrosomia in infants of women with gestational diabetes when compared with a control group, regardless of how the control group was derived. In contrast to population data,[22] the mean birthweight of infants of gestational diabetics in the United States was 3466 g, compared with a mean birthweight for normal infants of 3336 g. The clinical significance of this 130-g difference is unknown.

The real question is whether a macrosomic infant is at any increased risk compared with a normal-weight infant. Shoulder dystocia is often quoted as a consequence of macrosomia. However, in three case-control studies that compared macrosomic infants with normal infants, macrosomic infants were 3 times,[23] 9 times,[24] and 19 times[25] more likely to have shoulder dystocia than controls. In another case-control study,[26] there was a statistically significant increase of shoulder dystocia as birthweight increased. Neonates greater than 4000 g were 13.17 times more likely to have shoulder dystocia than those with birthweights of less than 4000 g (relative odds). This wide variation in rates raises questions about the methodology of the studies and the definitions of shoulder dystocia.

Another effect of macrosomia is birth trauma. Studies suggest that birthweight may be related to birth trauma[27,28] but the relation is unclear given the variation in rates between the studies. Rates for fractured clavicles and brachioplexus injuries in macromsomic infants compared with controls were 0.17% vs 0.05%, and 0.1% vs 0.01%, respectively.[28] Birthweight is not the only factor involved. In one study in which there was an overall birth injury rate of 0.26%, two thirds of the neonates injured were less than 4000 g.[29] For the mother, there is an increased cesarean section rate if the infant is macrosomic (24.7% vs 10.9% in controls[25]). Given that current methods for estimating birthweight prior to delivery are imprecise,[30] it is not known whether the increased rate is related to the actual size of the infant or anticipation by the physician of a difficult delivery. Also, the quoted increased risks of postpartum hemorrhage,[25] failure to progress,[31] etc, are all determined using a case-control approach, which tends to overestimate the effect.[8]

Finally, gestational diabetes is not the only cause for

Table 2. Types of Biases in Studies on Gestational Diabetes Mellitus

Term	Definition
Referral filter bias	Concentration of rarer diagnoses increases as a group of subjects is referred from primary to tertiary care
Expectation bias	Systematic erring by observers to conform to prior expectations
Diagnostic suspicion bias	Knowledge of subject's prior history may influence the intensity and outcome of the diagnostic process

Based on data from Sackett et al.[8]

macrosomia. Maternal age, weight, and multiparity are highly correlated to birthweight.[32] For example, in one study using regression analysis, only 4% of birthweight was attributable to maternal glucose tolerance.[33] More recently, Spellacy et al[34] reported that the incidence of macrosomia was 3 per 1000 for women with GDM, compared with 25.8 per 1000 for obese women.

Hypoglycemia is another frequently cited cause of neonatal morbidity in infants of women with GDM. In the literature the incidence ranges from 0%[35] to 20%.[36] There are several problems with the studies reviewed.[21] The study samples are too small to control for confounding variables such as gestational age and birthweight. This may be critical, given that one study[37] reported an incidence of hypoglycemia of 66.7% in infants who were small for gestational age, compared with only 4.2% in infants who were large for gestational age. Populations are occasionally mixed, with some mothers developing GDM and some with preexisting diabetes mellitus.[38] Furthermore, studies do not clearly show whether testing is routine or done only when the neonate is symptomatic. One study[39] illustrates the impact of this diagnostic suspicion bias; the incidence of hypoglycemia was 16% in routine testing vs 9% when only symptomatic infants were tested. In addition, maternal treatment with insulin, which many gestational diabetics receive, may[40] or may not[41] increase the incidence of hypoglycemia.

The short- and long-term effects of hypoglycemia are unclear. The risk for long-term damage appears related to the occurrence of a hypoglycemic seizure[42] or recurrent hypoglycemia.[43] There is little data on the prognosis for patients with mild or asymptomatic hypoglycemia.[44]

Hypocalcemia, postulated to occur secondarily to hypoglycemia,[45] is the next most commonly cited neonatal complication of GDM, with a reported occurrence of 0%[35] to 10%.[46] Generally, as the study quality increases, the rate falls. In one cohort study[47] the rate was 0%. Finally, hyperbilirubinemia of >12 mg/dL in infants of mothers with GDM ranged from 6%[48] to 50.6%,[49] with a similar range for normal infants. This finding suggests that a diagnostic suspicion bias was occurring, or there was variation in the level of bilirubin considered abnormal, or the population was considered to be at high risk for other reasons. Even if there was a high incidence, it may not be important, as pointed out by Dixon,[50] in his review of hyperbilirubinemia, which showed a lack of risk associated with levels of bilirubin below 20 mg/dL.

The literature is unclear about the frequency of lethal or potentially harmful outcomes to the neonate of a gestational diabetic. The result is a focus on intermediate outcomes such as macrosomia or biochemical changes in the fetus. These outcomes are monitored, as they are thought to be predictors of lethal or potentially harmful outcomes. Macrosomia confers an increased risk of birth trauma on the fetus, but the extent of this is unclear. Hypoglycemia, hypocalcemia, and hyperbilirubinemia are not harmful except in very specific circumstances, and the rare occurrence of this harm does not justify the screening of all pregnant women.

The Screening Test

There are two competing strategies: screening all pregnant women or only those at increased risk. Do the risk factors in the Canadian guidelines[2] predict the presence of gestational diabetes? In only one study[51] were the risk factors directly linked to gestational diabetes that had been determined by an OGTT. Calculation gives a positive likelihood ratio of 1.75 and a negative likelihood ratio of 0.28. This means that a person with a positive test is only 1.75 times more likely to have GDM when tested with an OGTT than a person with a negative test. A likelihood ratio for a positive test greater than 6 indicates an acceptable diagnostic test, which means that the presence of risk factors is not a good indicator of the presence of gestational diabetes.[52]

The most common screening test used is the 50-g glucose challenge test (GCT). In Table 3, likelihood ratios suggest that this screening test was only a fair predictor of gestational diabetes in two of the four studies.[53,54] Yet, other results from O'Sullivan's study[54] and another study[55] indicate that it is a poor test. Part of the problem may be that the screening test[56] and the OGTT may not be reproducible.[57]

The OGTT is the reference standard for the diagnosis of gestational diabetes; however, a number of factors have been shown to affect the OGTT.[21] Only three major factors are considered here. First, two studies[58,59] have shown that the intrasubject variation is equal to or greater than the intersubject variation. This means that either the test is not reliable or that glucose tolerance is not a stable measure; therefore, as in the evaluation for hypertension, several readings are necessary to assess the patient's true status. The second factor is blood glucose measurement. The original values from O'Sullivan and Mahan's[60] work were assessed using whole blood and the Nelson Somogyi method. Problems exist with converting whole blood values to venous or capillary values, as well as with comparing blood glucose readings obtained by different analytic methods. Furthermore, the National Diabetes Data Group criteria are an incorrect transformation of the original O'Sullivan and Mahan figures.[61] The third factor is the variation in criteria used for diagnosis of gestational diabetes. For example, the level

Table 3. Ability of 50-g Glucose Tolerance Test (ie, O'Sullivan Test) to Predict Gestational Diabetes Mellitus as Diagnosed by a Subsequent Oral Glucose Tolerance Test

Study	1-Hour Blood Glucose Result Needed for a Positive Test	Likelihood Ratio for a Positive Test	Likelihood Ratio for a Negative Test
O'Sullivan et al[53]*	>130 mg/dL	6.07	0.24
O'Sullivan[54]	>130 mg/dL	3.75	0.625
O'Sullivan[54]	>130 mg/dL	7.0	0.24
Carpenter[55]	>130 mg/dL (and maternal age >25 years)	3.8	0.11

**A positive test is 6 times more likely to occur in patients with gestational diabetes mellitus (GDM) compared with patients without GDM while a negative test is approximately 0.2 times as likely to come from patients with GDM as from patients without GDM. For a good diagnostic test, the likelihood ratio for a positive test should be greater than 6, and for a negative test, less than 0.1.*

of the 2-hour blood glucose on the oral glucose tolerance test ranges from 130 mg/dL[52] to 165 mg/dL.[1]

The final problem is that original values for diagnosis were derived in the 1950s from an atypical population[59] and were based on their ability to predict future non–insulin-dependent diabetes mellitus in the mother. In the early 1970s, these diagnostic criteria for gestational diabetes were endorsed in the belief that they predicted neonatal outcome, a purpose for which they were not originally developed.

Effective Treatment

Finally, are there effective treatments for GDM? According to Sackett et al,[8] the optimal method of assessing therapy is through a randomized controlled trial. Four randomized trials comparing the benefits of therapy with no therapy in gestational diabetes have been conducted (Table 4). However, problems exist with the randomization processes used in all four studies; the processes were incomplete,[62] unclear,[63] or not truly randomized.[12] Therefore, the results reported may have resulted from preexisting differences between groups not accounted for in the randomization process. Also, the use of unique populations[12] and the use of unique criteria for the diagnosis of gestational diabetes[62] further limits the generalizability of the reported results. This means that there are *no* reliable data proving the benefit of diet and insulin therapy in gestational diabetes; a conclusion also reached by the US Preventive Services Task Force.[64]

The only consistent finding in the four studies was a reduction in macrosomia, which is an intermediate outcome. To place this benefit in clinical perspective, effect size,[65] which is a measure of the impact of treatment on outcome, was calculated from two studies.[62,66] Using mean birthweight, the effect size was −0.17[66] to −0.13,[62] comparing the control group with the diet and insulin treatment group in the latter study. Combining the effect sizes for both studies, the overall impact of

Table 4. Randomized Controlled Trials Reporting Therapy for Women with Gestational Diabetes

Study	No. of Study Participants	Intervention	Study Problems	Conclusions
Coustan & Lewis[62]	72	No treatment vs treatment with diet vs treatment with diet and insulin	28% of sample not randomized. Unique criteria for diagnosis of GDM	Less macrosomia in diet and insulin group
O'Sullivan et al[63]	943	No treatment vs treatment with diet vs treatment with diet and insulin	Unclear if random or alternatively allocated. Confusion over control group selection. PMR rate high in control group	Decrease in PMR microsomia in diet and insulin group
O'Sullivan et al[66]	229	Routine care vs insulin	Random allocation. Study stopped early	No significant difference in PMR
Li et al[12]	158	No treatment vs treatment with diet	Assignment alternate. Unique population (24.4% lost to follow-up)	Small decrease in birthweight and gestational age in treated group

GDM denotes gestational diabetes mellitus; PMR, perinatal mortality rate.

treatment is a reduction in birthweight of 87 g. A decrease of this limited magnitude is of questionable clinical significance.

Conclusions

In summary: (1) there is uncertainty about the burden of illness of GDM, (2) major problems exist with the screening test and reference standard, and (3) there are no methodologically sound trials of therapy. As there are no answers to questions raised by criteria 1, 2, and 3 (Table 1), there is no rationale for pursuing criteria 4, 5, and 6. Therefore, based on the evidence available, routine screening for gestational diabetes cannot be supported.

The same conclusion was reached by the Canadian Task Force on the Periodic Health Examination. They state, "Universal screening with the 50-g GCT has not been demonstrated to be superior, yet it can carry considerable costs."[32, p 422]

These costs were examined by Santini and Ales,[67] who state that to prevent one case of macrosomia, 3716 women would need to be screened. As part of the follow-up of those screened, 58 women would have 15 or more antenatal visits. All total, an extra 250 women would have had supplemental tests such as ultrasonography, and 134 more women would have had a primary cesarean section than in an unscreened population.

As well, there are psychological costs. One study,[68] using a qualitative research design, showed that women diagnosed with GDM experience considerable guilt and anticipatory anxiety about future problems with the fetus. There is life disruption from frequent health care visits and changes in food preparation and eating.

Given that the only proven experimental benefit of screening for GDM is a decrease in the incidence of macrosomia, and that there is the potential for harm, the key issue is whether the benefit of a universal screening program is of sufficient magnitude and clinical value to justify routine screening of all pregnant women.[64, p 99]

The conclusion that there is insufficient evidence to support universal screening for GDM differs from consensus-based recommendations from organizations such as the Society of Obstetricians and Gynecologists of Canada,[2] the American College of Obstetricians and Gynecologists,[3] and the American Diabetic Association.[4,69] The principal reason for the difference in conclusions is that specific rules for assessing the quality of evidence were applied to reach the above recommendation, a process that differs from that usually used in consensus conferences.

This does not mean that gestational diabetes has no impact on the neonate. Rather, it implies a need to move from a position of advocating universal screening to one that emphasizes use of basic clinical guidelines to avoid the use of unproven screening in the majority of women. One author,[70] commenting on the Canadian Periodic Health Task Force recommendations, states that the benefit of evidence-based reports is that both positions are reasonable: to screen or not to screen. However, these two approaches to GDM already exist. Gabbe and Landon,[71] in a survey of subspecialists, showed that 10% do not screen all patients for GDM.

Given an unscreened population and a lack of good evidence of harm occurring from GDM, it would be both feasible and ethical to conduct further studies to determine what the relation is between the subdiabetic elevations of maternal glucose seen in GDM and neonatal outcomes. Until such evidence is available, a selective screening approach emphasizing assessment of individual risk factors and monitoring of the mother and fetus as each pregnancy evolves should guide physicians in the management of this condition.

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