Point: Universal Screening for Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is one of the most common medical disorders found in pregnancy. Rates can range from 2 to >10%, and sometimes much higher, depending on the population being tested and the diagnostic criteria being used (1). The prevalence of GDM ultimately reflects the background rate of type 2 diabetes. There has also been an increase in the rate of GDM over the last generation, possibly related to community lifestyle factors as well as better case ascertainment (2,3).

Significance of GDM

GDM is associated with a trilogy of risks. Significant pregnancy complications including increased perinatal morbidity and possibly mortality can occur (4,5). A diagnosis of GDM also identifies a mother at high risk for the future development of type 2 diabetes (1). The effects of maternal hyperglycemia (of any kind) are associated with the development of metabolic problems including type 2 diabetes in the offspring (6). It is, perhaps, for this effect of intrauterine programming that the disorder is most worthy of detection.

It has now been demonstrated that the treatment of GDM improves pregnancy outcomes. In the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS), the incidence of serious perinatal complications (a composite of death, shoulder dystocia, nerve palsy, and fracture) was 4% among women randomized to routine care compared with 1% among the intervention group (5). The number of GDM cases that needed to be treated to prevent one serious perinatal complication was 34. This indicates that excess serious perinatal complications will occur in 3% of cases of untreated or unrecognized GDM. This is a most compelling immediate argument for the screening of GDM given that the failure to identify a woman with GDM denies her the opportunity to have treatment for potentially preventable serious fetal complications.

Why conduct selective screening for GDM?

Therefore, if we accept that GDM is a diagnosis worthy of consideration, then as many women as possible should be tested for this problem. This can only be achieved through universal screening. However, it is well-known that women with GDM have certain definable risk factors, and currently both the American Diabetes Association (7) and the American College of Obstetricians and Gynecologists (8) recommend using such risk factors to selectively screen for GDM. Is it possible to use selective screening based on risk factor identification that would identify the overwhelming majority of cases, be easy to implement, be cost effective, and would not lead to any harm?

The main and ongoing concern with selective screening based on historical and clinical risk factors is that most studies have found that if such a system were used, a significant proportion of GDM cases would be missed. An early study, which did not include age as a risk factor, found that risk factor screening would have missed 53% of GDM cases (9). In another study, using age >30 years as a risk factor would have resulted in 22% of missed cases of GDM (10). Reducing the age threshold to 25 years decreased the number of subjects who would be missed to 7%; however, the number of subjects who would need to be screened increased from 58 to 78%. More recent studies examining broader criteria for risk factor screening found that only 3–9% of GDM cases would be missed but 80–90% of subjects would need to be screened (11–13).

In the well-designed Toronto Tri-Hospital Gestational Diabetes Project, 3,131 pregnant women aged >24 years underwent a 50-g glucose challenge test (GCT) followed by a 100-g oral glucose tolerance test (GTT) (14). Subjects were randomly divided into a derivation group and a validation group. A clinical scoring system based on age, BMI, and race was used to divide subjects into those at low, intermediate, and high risk of GDM. The exclusion of low-risk subjects from biochemical screening would allow 35% of women to avoid the GCT. Applying this to the validation group, screening algorithms using the clinical score, and varying the glucose threshold on the GCT to select patients for the GTT enabled a detection rate of up to 83% and a false-positive rate (from the GCT) of 13–16%.

Although the results of the Toronto Tri-Hospital Gestational Diabetes Project have been used to champion the argument for selective screening, we believe that knowingly failing to detect any woman, let alone a number such as 17% of women with GDM, can never be sanctioned. As illustrated above, reducing the threshold or increasing the number of criteria for selective screening improves the sensitivity; however, this also decreases the specificity. Ultimately, this defeats the main purpose of selective screening, which is to reduce the number of tests needed to be performed.

Naylor et al. (14) have also indicated that the screening strategy of the Toronto Tri-Hospital Gestational Diabetes Project detects more cases of GDM among overweight older women and misses more cases among leaner younger women. They have asserted that this shift in detection pattern is unlikely to be harmful, on the presumption that the missed case subjects are at lower risk. However, this has been refuted by a study that demonstrated that GDM pregnancies among lean young Caucasian women were similar to other women with GDM, in terms of insulin use, emergency cesarean section, and the proportion of large- and small-for-gestational-age babies (11). In this study, exclusion of this low-risk group from screening would have resulted in nearly 10% of missed cases of GDM; however, some 80% would have still required testing.

There are additional data demonstrating that women without risk factors are no less prone to the complications of GDM. Weeks et al. (15) have found that rates of macrosomia, cesarean section, and shoulder dystocia are similar to those in women with GDM who have risk factors. There is also a randomized controlled trial that compared pregnancy outcomes in women with risk factors who

were directly tested with a GTT with those in women covered by universal screening with a 50-g GCT (16). The incidence of GDM diagnosed in the universal screening group was almost double that in the risk factor group (2.7 vs. 1.45%, $P < 0.03$). Macrosomia (large for gestational age), admission to neonatal intensive care, preterm delivery, and hyperbilirubinemia were also more common in the risk factor group. We know that selective screening will miss some cases of GDM in women who do not have risk factors. These data indicate that we cannot afford to do so.

In practice, the application of risk factor screening is challenging. Furthermore, potential additional complexity has recently been added to the selective screening paradigm by the finding that the other established risk factors are less relevant for the prediction of GDM among women without a family history of diabetes (17). The investigators have suggested that a different set of risk factors might need to be applied for selective screening in women without a family history of diabetes. In an editorial to the Tri-Hospital study, Greene has stated that "despite its scientific merits, busy obstetricians are unlikely to wend their way through this complex diagnostic schema" (18).

In support of this view, a survey conducted in New Zealand has shown that even well-trained midwives have difficulty recalling the recognized risk factors for GDM (19). Seventy-nine percent performed risk factor screening, but only a median of three risk factors could be nominated by the respondents, with family history (89%), glycosuria (63%), and obesity (55%) most commonly mentioned. Only 26% included age as a risk factor. Although this may be more easily overcome in large protocol-driven institutions, GDM screening is often performed by private obstetricians, general practitioners, and community midwives. GDM is but one issue they need to be aware of; the simpler the process, the less likely there will be mistakes.

Although our interest is primarily the well-being of a mother and a child, in today's environment, the medical-legal consequences of a missed diagnosis must surely be an additional concern. If there was a suggestion of undiagnosed GDM, could a serious complication from the pregnancy, a failure to detect a woman at risk of type 2 diabetes who has developed some complications by the time of diagnosis, or an adult with type 2 diabetes concerned that this may have in part developed because of adverse intrauterine programming be defended? Surely, the way to overcome this concern is to test all women in all pregnancies.

Universal screening with a GCT or universal testing with a GTT?

If universal testing is preferred, for the variety of very practical reasons outlined above, then there is another dimension to consider. The gold standard for the diagnosis of GDM is a GTT—irrespective of how it is performed and with all its known imperfections. In a similar vein to our determination that selective testing for case identification is unsatisfactory, should we also critically look at the GCT?

The GCT has a significant false-negative rate (20) and is more likely to be positive in the afternoon (21), and the results can vary depending on the time since the last meal (22). Women who have a positive GCT need to return on a second occasion, which is inconvenient and must inevitably result in a delay to the initiation of treatment. Does this delay result in any compromise of the pregnancy outcomes? To our knowledge, this question has not specifically been addressed; however, Langer et al. (23) reported on poorer outcomes for women who are diagnosed late and effectively have inadequate treatment.

It has also been shown that up to 23% of women who screen positive on a GCT fail to attend their diagnostic GTT (24). Even in the Toronto Tri-Hospital Gestational Diabetes Project, where subjects were recruited with the explicit understanding that they would have a GTT after a GCT, 10% did not proceed with the GTT (22). Data on the subject of how many women fail to attend the diagnostic GTT or who have it late are inadequate, but clearly there will be women with possible GDM who are disadvantaged by this two-stage procedure.

The diagnosis of GDM based on selective testing will require a large percentage of pregnant women to be tested and will definitely miss some cases. Further imprecision is guaranteed by using a two-stage procedure to arrive at the diagnosis. However, all of these pitfalls can easily be avoided by the implementation of universal testing with a diagnostic GTT. In resource-poor areas and/or where there is a known low rate of GDM, some alternative to universal testing could be considered. Otherwise, our responsibilities to our patients and their offspring demand that all women should be offered a test with a single-step definitive GTT in every pregnancy.

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