Gestational diabetes is defined as ‘carbohydrate intolerance of variable severity with onset or first recognition during pregnancy’ (1). While there is great controversy surrounding the clinical significance of gestational diabetes (2), it is clear that a number of morbidities occur with increased frequency in offspring of gestational diabetic mothers. The most commonly reported effect on the newborn is called either macrosomia, usually defined as birth weight above either 4 kg or 4.5 kg, or large for gestational age, birth weight above the 90th, 95th, or 97th centile for gestational age. These centiles are often corrected for gender and birth order. Other problems include maternal hypertensive disorders, neonatal hypoglycemia, jaundice, operative delivery and birth trauma including shoulder dystocia. Available evidence indicates an association between maternal hyperglycemia during pregnancy and childhood and adult obesity (3), with elevated amniotic fluid insulin levels in those fetuses destined to become obese in their pre-teen years (4). Similarly, maternal hyperglycemia in response to a glucose challenge during pregnancy has been associated with diabetes during young adulthood in the offspring, as well as gestational diabetes in female offspring who become pregnant (5).

Diagnostic criteria for gestational diabetes vary throughout the world. Recommended glucose challenges include 50 g, 75 g, 100 g, and 1 g/kg body weight. The 100 g, 3-h oral glucose tolerance test (OGTT) criteria of O’Sullivan and Mahan (6), modified in various ways (7, 8), are in common use. However, they were not based on pregnancy outcome, but rather were validated by their predictive value for subsequent diabetes. The World Health Organization (WHO) recommends diagnostic criteria that do not take into account the metabolic changes occurring during pregnancy, but rather are the same criteria that are applied in the non-pregnant state. Since carbohydrate metabolism changes significantly during pregnancy, the only way the WHO recommendation will turn out to be valid for pregnancy is by coincidence. In the search for outcome-based diagnostic criteria, investigators have demonstrated increased macrosomia and other morbidities in subgroups of individuals whose glucose tolerance test results do not quite reach diagnostic thresholds (9), or who manifest only one abnormal glucose tolerance test value rather than two (10).

In this issue of the European Journal of Endocrinology Mello and colleagues report that untreated gravidas with 50 g, 1-h glucose screening test results ≥7.5 mmol/l, but normal 3-h 100 g oral glucose tolerance tests, are significantly more likely to have macrosomic babies than are control subjects with normal screening tests, and are also more likely to have macrosomic babies than women with gestational diabetes who are treated so as to improve glucose control. These data suggest that the relationship between carbohydrate intolerance in pregnant women and macrosomia in their babies is not ‘all-or-none’, but rather is some type of continuum. If this is the case, then it follows that there can be no absolute diagnostic criteria above which all babies are macrosomic and below which none are affected. Support for this concept comes from a number of recent studies. Sacks (11) reported a significant continuous relationship between maternal glucose values and birth weight; it was not possible to delineate a clear threshold. The Toronto Tri-Hospital project (12) included OGTTs on over 3500 gravidas without gestational diabetes, with care givers blinded to the results. Carbohydrate intolerance was an independent predictor of adverse outcomes such as macrosomia and cesarean section, but again the relationship was continuous. For every mmol increase in the 3-h GTT value there was a 10% increase in the likelihood of cesarean section and for every mmol increase in the fasting plasma glucose there was a doubling of the likelihood of birth weight over 4000 g.

In order to select the most appropriate criteria for diagnosing gestational diabetes, a number of attributes should be explored. Because not all individuals diagnosed with gestational diabetes will have adverse outcomes, one can envision the diagnosis as really being a sort of screening test. As in a screening test, the diagnostic threshold should identify a clinically meaningful proportion of the population likely to suffer consequences, but not a high proportion of the normal population. In addition, the relationship between carbohydrate intolerance and adverse outcomes should lend itself to an effective intervention. Mello’s study suggests that the latter is true. Those patients with diagnosed gestational diabetes, all of whom were treated in some manner, manifested a lower likelihood of neonatal macrosomia than did individuals with milder degrees of glucose intolerance who were not treated. Similar data came
from the larger Toronto Tri-Hospital study (13) in which care givers were made aware of the diagnosis of gestational diabetes when one set of thresholds (7) was met, but were blinded to the results when lower thresholds (8) were fulfilled. Patients who were diagnosed and treated manifested a macrosomia rate similar to the normal control population. Those with undiagnosed gestational diabetes, despite milder carbohydrate intolerance, had more than double the macrosomia rate of both the normal control group and those with diagnosed and treated gestational diabetes. Unfortunately, cesarean sections rates were similarly high in both the diagnosed and undiagnosed gestational diabetes groups, presumably because the care givers for women with diagnosed gestational diabetes expected macrosomia even though treatment effectively prevented it. Nevertheless, the Toronto study supported previous reports which suggested that a number of different interventions, including prophylactic insulin, diet, and self glucose monitoring (with insulin prescribed for even mild degrees of daily hyperglycemia) could be effective in reducing the rate of macrosomia.

The controversy surrounding gestational diabetes will not be easily solved. The lack of data relating varying degrees of carbohydrate intolerance to adverse pregnancy outcome in the absence of intervention limits our ability to select meaningful and mutually agreed-upon diagnostic thresholds. The fact that interventions for gestational diabetes became widely accepted by the clinical community at a time when clinical epidemiology was not nearly so sophisticated as it is today has made it difficult to perform the population-based, non-interventional studies that are so highly desirable. The use of varying glucose challenges, and differing diagnostic thresholds even with the same glucose challenge, has made the diagnosis a 'Tower of Babel'. General agreement has been difficult to achieve, at least in part because clinicians in one part of the world are hesitant to change diagnostic criteria to values which were developed in another. The solution lies in collaboration among centers in various countries around the world to carry out investigations that have wide application. A single glucose challenge dose should be used. In order to avoid confounding by various interventions, care givers should be blinded to the glucose tolerance test results, except when the abnormality is so marked as to put the pregnancy at demonstrably increased risk for perinatal mortality. With data from such a study available to demonstrate the relationship between glucose tolerance abnormality and perinatal morbidity, interventions can then be tested in a randomized fashion. Diagnostic thresholds can then be agreed-upon which identify a group of individuals whose gestational diabetes puts their pregnancy at significant risk, and for whom there are effective interventions.

References


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