

EDITORIALS



Gestational Diabetes Mellitus — Time to Treat

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Gestational diabetes mellitus, broadly defined as carbohydrate intolerance beginning or first recognized during pregnancy,^{1,2} was originally described decades ago and has since been the subject of extensive research. Yet the most recent guidelines of the U.S. Preventive Services Task Force, noting the absence of data to establish a clear link between screening and improved outcomes of affected pregnancies, concluded that “the evidence is insufficient to recommend for or against routine screening for gestational diabetes.”³ The American College of Obstetricians and Gynecologists officially recommends screening for and treatment of gestational diabetes but acknowledges that these recommendations are based on “limited or inconsistent scientific evidence.”¹

Unresolved questions include whether gestational diabetes — diagnosed in 3 to 7 percent of all pregnant women in the United States — poses serious risks to the offspring, and if it does, whether treatment reduces those risks. There are well-recognized associations between gestational diabetes and increased risks of fetal macrosomia, birth trauma, and cesarean delivery,⁴ but these associations are confounded to some degree by the presence of maternal obesity. Although greater fetal size at birth is associated with increased risks of shoulder dystocia and birth injury, only a fraction of deliveries complicated by shoulder dystocia result in birth trauma, and in most cases, such trauma (clavicular and humeral fractures and brachial-plexus injuries) does not result in permanent injury. No clear association has been documented between gestational diabetes and perinatal mortality.⁴

Moreover, efforts to demonstrate that interventions to reduce glycemia in pregnancy reduce the

risks of such complications as macrosomia and cesarean delivery have yielded inconsistent results. Evidence is largely observational. For example, a recent report described substantially lower rates of macrosomia among the infants of treated women with gestational diabetes than among the infants of untreated women,⁵ but other differences between the groups may have influenced the results. A randomized trial involving 300 women (a pilot for an ongoing, larger study), in contrast, showed no significant differences in mean birth weight or rates of macrosomia or birth trauma between the infants of women randomly assigned to tight glycemic control and the infants of women assigned to receive routine care.⁶ A possible explanation is that awareness of the glucose levels in the women in the routine care group may have led to behavioral changes that minimized differences between the groups.⁷ There are no long-term data to evaluate whether treatment reduces other risks reportedly associated with gestational diabetes, including obesity and type 2 diabetes in the offspring.

There are several plausible reasons why screening for and treating gestational diabetes have not consistently reduced fetal growth rates. One is that fetal size at birth is influenced by multiple factors in addition to maternal glucose levels, including maternal body-mass index, weight gain during pregnancy, and parity. In addition, the dichotomy between “normal” and “diabetic” glucose levels is somewhat arbitrary. For example, women with a single abnormal value during a three-hour oral glucose-tolerance test (a result that is not diagnostic of diabetes) have a significantly higher incidence of infants who are large for gestational age than do women with normal values at all time points.⁸ Blood

glucose levels during normal pregnancies appear to be controlled within a very narrow range.⁹ Therapeutic goals for normoglycemia may not have been set appropriately, and euglycemia is difficult to achieve in practice.

Regardless of the effects of treatment itself on fetal birth weight, it has been argued that diagnosing gestational diabetes could reduce the incidence of birth trauma by alerting obstetricians to the increased risk. However, Rouse and colleagues estimated that approximately 450 mothers with diabetes would need to undergo cesarean delivery to prevent permanent brachial-plexus injury in one infant¹⁰; this large number needed to treat is explained by the poor predictive value of methods used to estimate fetal weight and the low risk of permanent fetal injury, even among large fetuses. Furthermore, if a diagnosis of gestational diabetes routinely lowers the threshold for cesarean delivery, as has been suggested,¹¹ the resulting morbidity and costs may outweigh any benefits.

In this issue of the *Journal*, Crowther et al. report the results of a large, randomized, multicenter trial of treatment for gestational diabetes.¹² Pregnant women underwent a 75-g oral glucose-tolerance test between 24 and 34 weeks' gestation; those with values below 140 mg per deciliter (7.8 mmol per liter) after an overnight fast and between 140 and 198 mg per deciliter (11.0 mmol per liter) at two hours were eligible for randomization. The 490 women assigned to the intervention group were taught to monitor their blood glucose levels, provided with individualized dietary counseling, and given insulin as needed to maintain fasting and premeal glucose levels below 99 mg per deciliter (5.5 mmol per liter) and levels two hours postprandially that did not exceed 126 mg per deciliter (7.0 mmol per liter); this approach is consistent with a management approach in which screening and treatment for gestational diabetes are routine. The 510 women assigned to the control group received routine care that was consistent with the care provided in facilities in which screening for gestational diabetes is not standard. Neither group of women was informed of their glucose levels on diagnostic testing.

The offspring of women in the intervention group, as compared with the offspring of women in the routine-care group, had a significantly reduced risk of a composite primary outcome mea-

sure that included perinatal death, shoulder dystocia, bone fracture, and nerve palsy (1 percent vs. 4 percent; adjusted relative risk, 0.33; 95 percent confidence interval, 0.14 to 0.75). There were five deaths (three stillbirths and two neonatal deaths) among the offspring of mothers in the routine-care group, as compared with none in the intervention group. Macrosomia (defined as a birth weight of 4 kg or greater) was significantly more common among the infants of mothers in the routine-care group than among the infants of mothers in the intervention group (21 percent vs. 10 percent, $P < 0.001$). The rates of cesarean delivery were similar in the intervention and routine-care groups (31 percent and 32 percent, respectively), although the rates of induction of labor and admission of infants to the neonatal intensive care unit were significantly higher among women in the intervention group. (Physicians' awareness of the diagnosis of gestational diabetes was likely to have prompted these interventions.) Postpartum assessment of mood and the quality of life, performed in a subgroup of the women, indicated improved health status in the intervention group, suggesting that being aware of the diagnosis or the need for frequent monitoring had no negative effect on their quality of life.

This study provides critical evidence that identifying and treating gestational diabetes can substantially reduce the risk of adverse perinatal outcomes without, at least in this trial, increasing the rate of cesarean delivery. However, this report also raises some questions. One is ethical: Was it reasonable to randomly assign pregnant women with elevated blood glucose levels to no treatment? Given the preceding lack of rigorous evidence that attempts to improve glucose control improve pregnancy outcomes and that diagnosis and treatment carry small but real potential risks for the patient (including discomfort, inconvenience, anxiety, and potentially unnecessary interventions), we believe the answer is yes. Past experience — as with postmenopausal hormone therapy — has made it clear that interventions cannot be assumed to be beneficial on the basis of extrapolation from physiological or observational data.

Another unresolved question is the level of blood glucose at which intervention is routinely warranted. The glucose levels used to determine eligibility in the present study were different from those cur-

rently recommended by U.S. organizations to identify gestational diabetes (for example, an accepted criterion for diagnosis in the United States is two or more values on a 100-g oral glucose tolerance test at or above the following: fasting, 95 mg per deciliter; one hour, 180 mg per deciliter; two hours, 155 mg per deciliter; and three hours, 140 mg per deciliter^{1,2}). However, target glucose levels during treatment were similar.

Data from two ongoing studies may help guide thresholds for intervention. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study¹³ is assessing the relationship between glycemia and perinatal outcomes. Another treatment trial⁷ is assessing the benefits of tight glycemic control in pregnant women who receive a diagnosis of gestational diabetes on the basis of findings of elevated glucose levels at two points in time after a 100-g oral glucose load but normal fasting glucose levels.

Recent evidence indicates a worrisome rise in the prevalence of gestational diabetes¹⁴ that is largely explained by the increase in maternal obesity. Efforts to reverse this trend are critical. At the same time, the current report by Crowther et al. provides some long-awaited evidence to support the use of screening and treatment for women at risk.

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Bortezomib for Myeloma — Much Ado about Something

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Multiple myeloma is a neoplastic plasma-cell dyscrasia that will cause more than 11,000 deaths in 2005 in the United States alone.¹ The usefulness of the many therapies for multiple myeloma is limited, and virtually all patients eventually die from the disease. When thalidomide was shown to be effective against relapsed myeloma in 1999,² more than 30 years had elapsed since a clinical response to any single agent had been reported in at least 25 percent of treated patients.³⁻⁵ By the early 2000s, it had become clear that another two agents — lenalidomide⁶ and bortezomib⁷ — had activity against malignant plasma cells.

Bortezomib is the first of a new class of drugs, proteasome inhibitors, that have been shown to be cytotoxic to several tumor types.⁸ Because of the benefit observed in patients with relapsed or refractory myeloma in phase 1 and 2 trials,^{7,9} the drug was fast-tracked by the Food and Drug Administration (FDA), making it available to patients with this kind of advanced myeloma in May 2003. The Assessment of Proteasome Inhibition for Extending Remissions (APEX) trial, which is reported by Richardson et al. in this issue of the *Journal*,¹⁰ supports the FDA's decision.

The APEX trial randomly assigned 669 patients