Effects of Gestational Diabetes on Perinatal Morbidity Reassessed

Report of the International Workshop on Adverse Perinatal Outcomes of Gestational Diabetes Mellitus, December 3–4, 1992

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More than a century ago, physicians recognized gestational diabetes mellitus (GDM), a condition of glucose intolerance that occurs in pregnancy and disappears after delivery, as one of many possible constitutional problems associated with pregnancy. It was not until 1979, however, in the National Diabetes Data Group (NDDG) report entitled "Classification and Diagnosis of Diabetes Mellitus and Other Categories of Glucose Intolerance" that GDM was formally recognized as a subgroup of diabetes mellitus.

In the U.S., GDM occurs in ~3–5% of pregnant women annually. Unlike other types of diabetes, GDM has a limited duration, usually disappearing after delivery. However, women who have GDM are at a high risk of having non-insulin-dependent diabetes mellitus (NIDDM) later in life.

GDM has been linked to obstetric problems at the time of delivery and to subsequent perinatal morbidity. A potential birth complication associated with the disease is macrosomia, commonly defined as a birth weight of >4 kg. The macrosomic infant of a mother with GDM typically has excessive adipose tissue, which accounts for the increased weight, and is not symmetrically large. The macrosomia may result in birth trauma or necessitate operative delivery.

CONFERENCE OBJECTIVES — In an effort to clarify current knowledge of the disease, as well as to identify appropriate areas of future investigation, a group of scientists and clinicians who study or treat GDM met in Bethesda, Maryland, in December 1992, at an international National Institutes of Health conference. Cosponsored by the National Institute of Child Health and Human Development (NICHD) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), "Adverse Perinatal Outcomes of Gestational Diabetes Mellitus" addressed obstetric complications of GDM that may result in perinatal morbidity, testing, and the feasibility of a nationwide screening program for the disease.

Organizers of the conference were Gilman Grave, MD, Chief of the NICHD's Endocrinology, Nutrition and Growth Branch, Maureen Harris, PhD, MPH, Chief of NIDDK's NDDG, and Boyd E. Metzger, MD, Acting Chief in the Division of Endocrinology, Metabolism and Nutrition at Northwestern University Medical School, Chicago, Illinois, who also served as conference chair.

The need to clarify the relationship between GDM and perinatal morbidity is especially critical now for several reasons, noted Dr. Metzger. First, the prevalence of diabetes mellitus is increasing worldwide, and evidence indicates that there are more cases of GDM as well. Second, developing countries, in particular, are ill-equipped to cope with this increase and desperately need programs for diagnosing and treating diabetes. Third, the impact of lifestyle changes on the prevalence of diabetes remains unclear and needs to be determined. Finally, there is a pressing need to identify groups at high risk of developing GDM to intervene with proper treatment and to facilitate the appropriate distribution of finite health care resources. "We have identified the risk of certain adverse outcomes, but we have not specifically related them to the degree of glucose intolerance," Dr. Metzger said. "The data suggest that the more severe the state of glucose intolerance during pregnancy, the higher the risk of later diabetes in the mother."

DISCUSSION OF PERINATAL OUTCOMES — Scientists have identified certain factors that

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GDM, gestational diabetes mellitus; NDDG, National Diabetes Data Group; NIDDM, non-insulin-dependent diabetes mellitus; NICHD, National Institute of Child Health and Human Development; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases.

may help to determine which groups of women are more likely to develop GDM. These include maternal obesity, maternal age >25 years, a family history of diabetes, African-American or Hispanic ethnicity among women in the U.S., previous birth complicated by macrosomia, previous stillbirth, having had a child with a birth defect, and excessive amniotic fluid (polyhydramnios). The benefit of identifying these factors lies in the possibility of developing appropriate interventions to prevent NIDDM in high-risk women, noted Donald Coustan, MD, Professor and Chairman in the Department of Obstetrics and Gynecology at Women & Infants Hospital of Rhode Island, Providence, RI.

Growth of the fetus is stimulated when the extra glucose in the blood of women with GDM causes the fetus to release more insulin to cope with the excess glucose. The extra glucose is then converted to fat, which results in a macrosomic, large-for-gestational-age infant. Additionally, the increased insulin levels may retard maturation of the fetal lungs, which may be associated with respiratory distress in the newborn or may lead to neonatal hypoglycemia necessitating intravenous administration of glucose after delivery. Although not all infants born to women with GDM have macrosomia, the condition occurs twice as frequently in pregnancies complicated by GDM as in uncomplicated pregnancies. "I look at this as a child who is genetically predisposed to developing diabetes," explained David Pettitt, MD, Assistant Chief of the NIDDK's Diabetes and Arthritis Epidemiology Section. "He is just being overfed throughout the later part of pregnancy. By the time the child is born, he's already set up to become obese."

Macrosomia, if severe enough, may mean that the infant is too large for vaginal birth, necessitating operative intervention, such as caesarean delivery or assistance with forceps. Another serious complication of macrosomia is shoulder dystocia, a condition in which the infant's shoulders become impacted during delivery, either because they are too large, or because they are in the wrong position. "I don't think there's any doubt that the bigger the baby is, the more likely it is to get into trouble when it's born," said David Hunter, MD, Chairman of the Department of Obstetrics and Gynecology at Norwalk Hospital in Connecticut.

The risk of perinatal mortality does not appear to be higher in infants born to women with GDM. However, obesity in the offspring of women with GDM is often a lifelong problem, which may be life-threatening. As an example, Dr. Pettitt cited a study of Pima Indians who live in the southern Arizona desert. In this study, investigators found that the children of diabetic women were much heavier at birth than the children of nondiabetic women. And at each of three subsequent reevaluations, done in childhood, adolescence, and the later teenage years, this group of children weighed more than the children of nondiabetic women. Because obesity itself is a risk factor for developing both NIDDM and GDM, the children of women with GDM are beginning life already at risk of future diabetes. "Diabetes in pregnancy is a vicious cycle," Dr. Pettitt said. "Not only does the mother have problems in pregnancy, but the infants have problems at birth and are much more likely to go on to be obese and to develop diabetes; they may already have diabetes by childbearing age."

One question facing clinicians is: How can these problems be prevented? One method is through diet and exercise. Women who fall into one or more of the high-risk groups may want to practice weight control and increase their level of exercise, both of which have been linked to a reduction in risk of GDM. Screening is also extremely important because GDM is usually asymptomatic and the earlier GDM is diagnosed, the earlier diet modification and insulin treatment, if necessary, can be initiated. Appropriate treatment begun in a timely manner has been shown to reduce perinatal morbidity, especially macrosomia. The criteria that were established by O'Sullivan and Mahan (*Diabetes* 13:278–285, 1964) for the diagnosis of GDM were chosen to identify women at high risk for progression to overt diabetes mellitus in the future. Many investigators have provided evidence suggesting that the use of these criteria (as extrapolated for measurements of plasma rather than whole blood glucose concentrations by the NDDG) fails to identify many cases among subjects who have a positive 50-g glucose challenge screening test and who are at risk for macrosomia and perinatal morbidities. Others have raised questions about the specificity of the associations between macrosomia or perinatal morbidities in GDM and the presence of glucose intolerance. This is because women with GDM tend to be older and more obese and have other maternal complications, such as hypertension, more often than expected in the general obstetric population. It is postulated that it is these factors rather than mild glucose intolerance that account for the macrosomia and perinatal morbidities.

Another problem with conventional screening and diagnostic methods that use the standard glucose tolerance test is that the results are not very reproducible. Thus, there may be false-positive readings, as well as false-negative ones. A large percentage of positive screening tests will be negative upon retesting. Also, screening tests generally involve one-time sampling, while glucose tolerance may change throughout the course of pregnancy. The most effective screening would involve a continuum of sampling throughout pregnancy, Dr. Hunter suggested. However, this approach would be expensive relative to the yield.

It has also been argued that a nationwide screening program for GDM would at best have a relatively small impact on the overall incidence of macrosomia. If screening were 100% effective in identifying women with GDM, and if insulin treatment were 100% effective in ameliorating macrosomia, the combined approach would result in only 50 fewer

macrosomic babies per every 10,000 deliveries, Dr. Hunter explained.

Shoulder dystocia may cause birth trauma, such as brachial plexus injury and fractured clavicle. However, long-term benefits of screening women for GDM to prevent birth trauma caused by shoulder dystocia would be minimal. Although 15–30% of infants with shoulder dystocia suffer injury to the nerves in the brachial plexus, most heal in 1 year; only 0.2–2% of them will suffer permanent nerve injury. One study found that most fractures related to shoulder dystocia are clavicular fractures, which heal without long-term complications.

Of the 50 additional infants identified as macrosomic by a screening program, only 6 of 10,000 would experience shoulder dystocia; only 1 of these 6 would have shoulder girdle injury, which is usually of no long-term significance. Such calculations challenge the idea that a screening program would have any significant long-term effect on perinatal morbidity associated with GDM, according to Dr. Hunter and others.

SUMMARY AND RECOMMENDATIONS— It was concluded that these questions about the sensitivity, specificity, and cost-effectiveness of efforts to diagnose and treat GDM to prevent adverse perinatal effects cannot be resolved without additional carefully designed studies. Accordingly, a group of investigators is currently devising a plan for a new multicenter, multiethnic, and multinational longitudinal study to measure adverse outcomes over time. These investigators plan to screen a large population of patients, to conceal their glucose tolerance test results from the women's care givers with the exception of test results of patients with diabetes (overt or asymptomatic), and to assess perinatal complications. This protocol will enable the investigators to correlate various degrees of glucose intolerance with perinatal morbidity, without the confounding variables of obstetric and medical intervention, which may change according to the care givers' knowledge of their patients' laboratory values of blood glucose.

"What I see as the bottom line is that in this country and some other parts of the world, we've established a standard of care and widespread screening based on imperfect data," said Dr. Coustan, who is involved in planning the new protocol. "Rather than continue as we are, I think it's appropriate to stop and obtain more data."

For more information on GDM, contact the NICHD for a free brochure called "Understanding Gestational Diabetes: A Practical Guide to a Healthy Pregnancy." To order, call (301) 496-5133.

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