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What we have learned about treating mild gestational diabetes mellitus

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ABSTRACT

Gestational diabetes mellitus (GDM) is associated with adverse perinatal outcomes, with risks not only associated with more severe forms of GDM, but milder forms of GDM as well. Treatment of mild GDM with dietary intervention and insulin when necessary has proven to be effective in reducing the risks of several, but not all, adverse perinatal outcomes. Less is known about the long-term benefits of mild GDM treatment. This article will review the benefits of mild GDM treatment, and related risk factors, on short-term and long-term maternal and neonatal/child outcomes, with an emphasis on research conducted by *the Eunice Kennedy Shriver National* Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network.

In 1964, O'Sullivan and Mahan[1] developed glucose tolerance test criteria for the diagnosis of gestational diabetes mellitus (GDM), based on thresholds associated with an increased maternal risk in the future development of diabetes. Currently, the criterion most often used in the United States to diagnose GDM is a two-step approach endorsed by the American College of Obstetricians and Gynecologists—a 1-h screening test with a 50-g glucose load followed by a 3-h 100-g oral glucose tolerance test (OGTT) for those found to be abnormal on the screen.[2] The American Diabetes Association, however, endorses the International Association of Diabetes and Pregnancy Study Group's one-step 2-h 75-g OGTT approach that is commonly used outside the United States.[3] Over the past 2 decades, the frequency of GDM has risen dramatically, and the CDC estimates that approximately 5.6% of pregnant women aged 15–44 years delivering in the United States hospitals had GDM in 2009.[4] A recent estimate of 6.1% was observed in an obstetrical cohort of 115,502 women who delivered between 2008 and 2011 at clinical centers of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Maternal–Fetal Medicine Units (MFMU) Network.[5]

GDM is associated with adverse pregnancy outcomes, such as fetal macrosomia, birth trauma, neonatal hypoglycemia, and hyperbilirubinemia.[6] Furthermore, adverse pregnancy outcomes do not appear to be limited to more severe forms of GDM, but also occur in milder forms of GDM.[7,8] Investigators of the multicenter observational Hyperglycemia and

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Adverse Pregnancy Outcome (HAPO) study of 23,316 women with maternal glucose intolerance less severe than that in overt diabetes mellitus observed strong, continuous associations between maternal glucose levels and increased birthweight, increased cord-blood serum C-peptide levels, shoulder dystocia or birth injury, and pre-eclampsia, with no obvious threshold at which risks increased.[9]

Observational data suggest that the frequency of adverse pregnancy outcomes, such as fetal macrosomia, is higher if treatment is not provided.[10,11] Data from randomized controlled trials concur. The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) trial recruited 1000 women with GDM, the majority of whom had a mild form of GDM, who were randomly assigned to receive dietary advice, blood glucose monitoring, and insulin therapy as needed or routine care.[12] They observed a significant decreased risk of the composite adverse perinatal outcome (stillbirth, neonatal death, shoulder dystocia, bone fracture, and nerve palsy) in the treated group.[12] Because some of the women in the ACHOIS trial had glucose levels consistent with more significant hyperglycemia, it was still not clear if treatment of even milder forms of GDM would reduce the risk of perinatal outcomes. To answer this question, the MFMU Network conducted a multicenter randomized controlled trial in mild GDM.[13]

From October 2002 through mid-November 2007, the MFMU Network invited women to participate in the mild GDM trial if between 24 weeks 0 days and 30 weeks 6 days of gestation and had an abnormal blood glucose concentration (135–200 mg/dl) 1 h after a 50-g glucose loading screen.[13] Women were excluded if they had pre-existing diabetes, an abnormal result on a glucose screening test before 24 weeks of gestation, prior GDM, a history of stillbirth, multifetal gestation, asthma, or chronic hypertension; if they were taking corticosteroids; if there was a known fetal anomaly; or if imminent or preterm delivery was likely because of maternal disease or fetal conditions. After an overnight fast, eligible women completed a blinded 3-h 100 g OGTT, and those with a fasting glucose <95 mg/dl remained eligible. Women with an abnormal OGTT consistent with mild GDM (2 or 3 OGTT timed measurements that exceeded established thresholds as follows: 1 h, 180 mg/dl; 2 h, 155 mg/dl; and 3 h, 140 mg/dl) and who provided informed consent were randomly assigned to treatment with formal nutritional counseling and diet therapy, self-monitoring of blood glucose, and insulin if required, or usual prenatal care. Women with a fasting glucose <95 mg/dl and a normal OGTT who provided informed consent were enrolled and received usual prenatal care. By including this observational cohort of women with lesser degrees of glucose intolerance, the patients, their caregivers, and the study staff were unaware of whether women in the control group met the criteria for the diagnosis of mild GDM. Ultrasonography was performed in all subjects before the OGTT to confirm gestational age. A total of 1889 women were enrolled—485 women with mild GDM assigned to the study treatment; 473 women with mild GDM assigned to usual prenatal care; and 931 women with lesser degrees of glucose intolerance that received usual prenatal care.

The MFMU Network mild GDM trial found that although treatment of mild GDM did not reduce the risk of the composite primary perinatal outcome of hypoglycemia, hyperbilirubinemia, elevated cord-blood C-peptide level, stillbirth, neonatal death, or birth trauma, it did reduce the risk of fetal overgrowth (higher birthweight, higher neonatal fat mass, large for gestational age, and macrosomia), shoulder dystocia, cesarean delivery, and hypertensive disorders of pregnancy.[13] One explanation for the lack of treatment benefit in reducing metabolic abnormalities of the newborn was that the women all had mild GDM, and metabolic-related benefits may only apply to more severe GDM.[13] For example, results from the HAPO study suggest that an increased risk of clinical neonatal hypoglycemia may not be apparent until fasting maternal glucose levels exceed 100 mg/dl.[9]

Secondary analyses of the MFMU Network mild GDM trial provided further insights into treatment effects of mild GDM. Interestingly, the effect of treatment on perinatal outcomes, including a composite of neonatal hypoglycemia, hyperbilirubinemia, hyperinsulinemia, and birth trauma, did not vary by the gestational age of initiation of mild GDM treatment, which ranged from 24 to 31 weeks of gestation.[14] This finding, however, may not be generalizable to women with more severe forms of GDM.[14] The treatment effect on fetal overgrowth did vary according to neonatal sex, with a significant treatment reduction in birthweight percentile and neonatal fat mass observed in the males, but not in the females.[15] One explanation hypothesized for these findings was that there may be gender differences in susceptibility to oxidative stress or in the response to a treatment that might mitigate oxidative stress; however, markers of oxidative stress were not measured to evaluate this hypothesis.[15] Results from another secondary analysis found that the treatment effect on fetal overgrowth varied by maternal body mass index (BMI), with treatment reductions in large for gestational age and neonatal fat mass observed in women with a BMI between 25 and 39.9 kg/m^2, but no benefit at the lowest and highest BMI extremes.[16] In the lowest BMI group, the frequency of fetal overgrowth was already low (approximately 2% in the untreated group), and the lack of a treatment benefit in the morbidly obese group may indicate a limit to improvements achievable through a GDM intervention directed toward maternal glucose levels alone.[16]

We have learned much more about varying degrees of maternal glucose intolerance from analysis of the MFMU Network mild GDM trial and observational cohort. In an analysis that included women with untreated mild GDM or lesser degrees of glucose intolerance, increasing maternal glycemia was associated with increasing risk of the composite primary perinatal outcome, large for gestational age, elevated cord C-peptide, shoulder dystocia, and pregnancy-related hypertension.[17] Like the HAPO study,[9] there was no observable threshold at which risks increase, providing additional data and uncertainty regarding the most appropriate threshold for the diagnosis and treatment of GDM.[17]

Analyses of the MFMU Network mild GDM trial and observational cohort data have also demonstrated the significant impact of obesity. Among the women with untreated mild GDM, pre-pregnancy BMI was associated with increased gestational hypertension, birthweight, and neonatal fat mass, independent of OGTT values.[18] These findings are consistent