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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- 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 criteria most often used in the U.S. to diagnose GDM is a two-step approach endorsed by the American College of Obstetricians and Gynecologists: a one-hour screening test with a 50-gram glucose load followed by a three-hour 100-gram 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 Groups one-step two-hour 75-g OGTT approach that is commonly used outside the U.S.[3] Over the past two 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 U.S. 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

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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 milder forms of GDM.[7,8] Investigators of the multicenter observational Hyperglycemia and 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 birth weight, increased cord-blood serum C-peptide levels, shoulder dystocia or birth injury, and preeclampsia, with no obvious threshold at which risks increased.[9]

Observational data suggest that the frequency of adverse pregnancy outcomes, such as fetal macrosomia, are 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 which 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) one hour after a 50-gram glucose loading screen.[13] Women were excluded if they had preexisting 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 three-hour 100 gram OGTT, and those with a fasting glucose <95 mg/dl remained eligible. Women with an abnormal OGTT consistent with mild GDM (two or three OGTT timed measurements that exceeded established thresholds: one hour, 180 mg/dl; two hour, 155 mg/dl; and three hour, 140 mg/dl) 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 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 and neonatal fat mass observed in women with a BMI between 25–39.9 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 with findings from the HAPO study that observed an increased frequency of several adverse perinatal outcomes with high maternal BMI, independent of maternal glycemia.[19] A related issue is the impact of gestational weight loss or gain. Among women who are obese, the Institute of Medicine recommends a gestational weight gain of 5–9 kg, to at least meet the minimum physiologic changes of pregnancy.[20] To evaluate this recommendation, the MFMU Network evaluated weight gain in overweight and obese women with mild GDM or lesser degrees of glucose intolerance, and observed inadequate gestational weight gain (weight loss or gain ≤5 kg) was associated with a significantly lower lean body mass, fat mass, length and head circumference.[21] These results support the Institute of Medicine recommendations[20] and suggest that a far safer alternative to gestational weight loss would be a postpartum diet and exercise lifestyle approach for all overweight or obese women.[21]

The MFMU Network trial, along with the ACHOIS trial, both large-scale multicenter randomized treatment trials, provide evidence that treatment of GDM, including mild GDM, with dietary intervention and insulin when necessary, is effective in reducing the risks of adverse perinatal outcomes.[12,13] These combined results led the U.S. Preventive Services Task Force to acknowledge for the first time that treatment of GDM is beneficial.[22] However, the question remained, what are the longer term maternal and child benefits of treating mild GDM?

GDM is associated with future maternal metabolic disease, in particular type 2 diabetes,[23–25] with its associated cardiovascular complications.[26,27] Indeed, the American Heart Association now includes history of GDM in their classification of cardiovascular risk factors in women.[28] Whether GDM, independent of maternal BMI, is associated with future metabolic disease and obesity in the offspring remains controversial, as much of the earlier results did not control for maternal BMI.[29] Also unknown is if such an association does exist, at what age it becomes apparent. In an analysis of the offspring of the HAPO study, no association was observed between maternal glucose levels and child BMI Z-score at age 2 years[30] or at 5–7 years.[31] Even less clear is whether treating GDM has long-term benefits in the future health of the offspring. In a follow-up study of 89 children evaluated at a mean age of 9 years, no significant differences were observed in fasting glucose, insulin or BMI of the children born to mothers treated with tight glycemic control compared with minimal treatment.[32] Investigators of the ACHOIS trial linked trial data to height and weight data obtained from the South Australia's Children, Youth and Women's Health Service on 199 offspring aged 4–5 years.[33] They observed no difference in BMI between the 4–5 year old children of treated and untreated women.[33] Due to very limited knowledge about the long-term benefits of GDM treatment in the women or their offspring, the MFMU Network conducted a follow-up study to its multicenter mild GDM study that included the randomized controlled trial and the observational cohort in women with lesser degrees of glucose intolerance.[34]

The women who participated in the MFMU Network mild GDM trial and observational cohort study were contacted between February 2012 and September 2013 (5–10 years after the index pregnancy).[34] When contacted, the women and their index children were invited to

participate in the follow-up visit. Maternal eligibility included that the patient had participated in the original GDM study, she was enrolled at a center still participating in the MFMU Network at the time of the follow-up study, and her index child participated in the follow-up study. All index children from a center still participating in the MFMU Network were eligible. Following informed consent, and child assent when appropriate, participating women and their index children underwent anthropometric and blood pressure measurements. The mothers completed a research staff-administered questionnaire about their and their child's medication use, physical activity, and diet. Following a minimum 6-hour fast, participants had their blood drawn. Collection, processing and storage of specimens were conducted per a standardized approach prior to being shipped on dry ice to the Northwest Lipid Metabolism and Diabetes Research Laboratories for lipid panel and glucose laboratory measurements. A total of 982 children and 950 women were enrolled in the follow-up study; approximately half of each were from the mild GDM trial and half from the observational cohort of lesser degrees of glucose intolerance.

The MFMU Network mild GDM follow-up study found that treatment during pregnancy of women identified with mild GDM had no impact on the subsequent risk of maternal diabetes, metabolic syndrome, BMI, or adiposity 5–10 years later.[35] Similarly, no reduction in obesity or metabolic dysfunction in the 5–10 year old offspring of treated women compared with untreated women was observed.[34] However, a difference was observed between the male and female offspring with significantly decreased frequency of impaired fasting glucose, lower fasting glucose and lower log HOMA-IR in the female offspring of treated women, but not in male offspring.[34] Explanations for the null results in the children overall include: only mild GDM was evaluated and more-pronounced hyperglycemia during pregnancy might have demonstrated a long-term treatment effect on obesity in the offspring; although treated women met conventional glucose targets for control, these maternal glucose levels may actually exceed those required to affect later outcomes in the children; or the emergence of both obesity and metabolic dysfunction in the offspring of women with GDM may not occur until adolescence or early adulthood.[34] With regard to sex differences, the MFMU Network results suggest that males may be more immediately sensitive to maternal glycemia as it relates to the development of neonatal adiposity, whereas the females may be more likely to exhibit the effects of in utero exposure to maternal GDM later in childhood.[34]

Secondary analyses of the MFMU Network mild GDM follow-up study have provided insights into the association between varying levels of glucose intolerance during pregnancy, maternal obesity, pregnancy-associated hypertension, and long-term maternal and child health. When evaluating risk factors in the women who had lesser degrees of glucose intolerance during pregnancy, maternal pregnancy OGTT values were not associated with subsequent maternal metabolic syndrome.[36] However smoking and BMI during pregnancy were strongly and significantly associated. In fact, 40% of the women with BMI ≥35 kg/m^2 during pregnancy developed metabolic syndrome.[36] In an analysis of the offspring of women with untreated mild GDM or lesser degrees of glucose intolerance, maternal OGTT values during pregnancy were associated with childhood sum of skinfolds and subscapular-to-tricep skinfold ratio, but not with childhood BMI Z-score, waist circumference, fasting glucose, or HOMA-IR.[37] Hispanic ethnicity and maternal pregnancy BMI were the characteristics most consistently related to childhood outcomes.[37] The MFMU Network

mild GDM follow-up study also revealed other populations at risk, namely women who experienced pregnancy-associated hypertension and their offspring. In the women who had mild GDM or lesser degrees of glucose intolerance during pregnancy, pregnancy-associated hypertension in women who then delivered preterm was associated with a higher frequency of subsequent maternal hypertension, high triglycerides, and metabolic syndrome.[38] In the children, systolic blood pressure and BMI z-score were significantly higher in the children who were born to mothers with pregnancy-associated hypertension and were delivered at term.[39] These associations remained after adjusting for maternal BMI, study group (mild GDM or lesser degrees of glucose intolerance) and race/ethnicity; elevated childhood blood pressure even remained significant after adjusting for childhood BMI.

These results of the MFMU Network mild GDM follow-up study underscore the impact of obesity and hypertension during pregnancy on the long-term health of the mothers and their offspring and suggest that treating glucose intolerance during pregnancy is not adequate, that lifestyle interventions targeting weight reduction and hypertension prevention pre-pregnancy and postpartum are required. Indeed, the Diabetes Prevention Trial has demonstrated the beneficial effects of an intensive and ongoing lifestyle modification in preventing or delaying metabolic disease in at-risk individuals.[40]

In conclusion, treating mild GDM with dietary intervention and insulin when necessary is effective in reducing the risks of fetal overgrowth; however treatment may not reduce metabolic abnormalities of the newborn in milder cases of GDM. Increasing maternal glycemia is associated with increasing risk of adverse perinatal outcomes, with no obvious threshold at which risks increase, making it difficult to determine the optimal threshold for screening and treating mild GDM. Whether treatment of mild GDM is associated with future metabolic disease and obesity in the mother and her offspring remains unknown, with the data at present suggesting no such association at least in the first decade since delivery. However there may be sex differences in the in utero exposure to maternal mild GDM, with treatment effects more apparent in male neonates and treatment effects more apparent in females later in childhood. Because maternal BMI and pregnancy-associated hypertension appear to have a stronger impact on the future health of the women and their offspring than maternal glycemia, postpartum lifestyle interventions aimed not only at glycemia, but also weight and blood pressure appears imperative.

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