Infants Born to Mothers with Gestational Diabetes Mellitus: Mild Neonatal Effects, a Long-term Threat to Global Health

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The incidence of gestational diabetes mellitus (GDM) is increasing in the context of the pandemic in obesity and type 2 diabetes (T2D) in both high-income and emerging countries.[1] More than 1 billion people will develop T2D during the next decade throughout the world.[2] Much of the currently available knowledge on the consequences of maternal diabetes on the offspring is from studies on type 1 diabetes (T1D). The risks related to GDM, which is much more frequent than T1D, need to be clarified to improve and adapt neonatal management. Moreover, converging clinical and experimental data suggest that the offspring of diabetic mothers are at an increased risk of developing diabetes as well as other chronic, noncommunicable diseases at adulthood, with potential transgenerational effects involved in the pandemic. Pediatricians and neonatologists are on the front-line of managing the transgenerational effects of T2D. This review addresses the currently available knowledge on short-term and long-term effects of diabetes in pregnancy on the offspring.

Methods

We performed a bibliographic search using the MEDLINE database. Studies published during the past 12 years (January 2000 to December 2012) were prioritized. The articles were classified by level of evidence according to the Grading of Recommendations Assessment, Development and Evaluation system.[3] Animal experiments and pathophysiological pathways of fetal programming were not the included in this research because of recent exhaustive reports on the subjects.[4,5]

Setting the Scene: The Current Context of GDM

GDM is defined as carbohydrate intolerance of variable severity first recognized during pregnancy. However, GDM encompasses 2 different entities: (1) glucose tolerance defect that generally occurs in the second one-half of pregnancy and disappears at least temporarily postpartum and (2) prepregnancy diabetes (overt diabetes), mainly T2D, discovered during pregnancy or triggered by pregnancy, that persists after delivery.

In population-based studies, the prevalence of GDM ranges from 2% to 6%, with much higher occurrences (10%-22%) in specific populations (India, the Middle East, and Sardinia).[6] In many high-income countries, more than one-half of pregnant diabetic women may have T2D.[7] The estimate of the prevalence of diabetes in the world population in 2030 is 10%, with 90% having T2D.[8]

In 2008, the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study showed continuous graded relationships between increasing maternal plasma glucose and increasing frequency of adverse perinatal outcomes.[9] Following this study, the International Association of Diabetes and Pregnancy Study Group proposed new guidelines for the screening and diagnosis of diabetes in pregnancy.[10] If these recommendations from the association are adopted, the expected incidence of GDM is approximately 16%-18% of pregnancies.[10]

Fetal and Neonatal Consequences of GDM

Numerous studies have reported that high maternal blood glucose is associated with fetal morbidity, macrosomia, and subsequent complications in the neonatal period. For GDM, the level of scientific evidence for a given risk varies widely according to the complication studied. Furthermore, maternal conditions influence the incidence of most of the complications.

Effect of Hyperglycemia on Fetal Growth. The Pedersen hypothesis, formulated >50 years ago, suggested that fetal overgrowth was related to increased transplacental transfer of maternal glucose, stimulating the release of insulin by the fetal beta cells and subsequent macrosomia. The HAPO study demonstrated a continuous association between increasing maternal glycemia and fetal hyperinsulinism with birth weight >90th percentile.[9] There was also a linear and continuous relationship among percentage body fat in newborns, maternal glycemia, and fetal insulin levels.[11] Therefore, maternal glycemia values, not only in overt maternal diabetes but also across the normal population, are associated with excessive fetal growth, particularly in relation to adipose tissue.

Recent robust clinical data demonstrate that the treatment of women with GDM limits fetal overgrowth and reduces the risk of macrosomia.[12,13] However, despite tight glycemic

BMI	Body mass index
GDM	Gestational diabetes mellitus
HAPO	Hyperglycemia and Adverse Pregnancy Outcome
RCT	Randomized controlled trial
T1D	Type 1 diabetes
T2D	Type 2 diabetes

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control, macrosomia persists in some cases of GDM, suggesting that mechanisms other than those evoked by Pedersen contribute to fetal overgrowth. Evidence has recently emerged on the involvement of the maternal metabolic environment and of placental modifications on fetal overgrowth. In GDM, the maternal metabolic environment is characterized by insulin resistance and inflammation.[8] Both conditions influence fetal growth. Insulin resistance facilitates maternal hypertriglyceridemia that enhances substrates availability to the fetus. Furthermore, the placental transcriptome is a target of the altered environment of diabetic pregnancy. For example, genes for lipids transport are upregulated in the placenta of women with GDM, as are genes for inflammatory pathways.[14,15] In total, such alterations directly or indirectly change the availability of the substrates to the fetus, either by increasing their source or by modifying the maternofetal interface. Additionally, placental epigenetic changes were recently reported at gene loci involved in energy metabolism regulation such as the adipokines.[16] These epigenetic adaptations to a detrimental in utero environment may have impacts on the short- and long-term metabolic regulations of the newborn.

Hence, maternal diabetes during pregnancy, regardless of the type, is a risk factor for macrosomia.

The Consequence of Macrosomia on Neonatal Complications. The delivery of infants with macrosomia is associated with a higher risk for adverse neonatal morbidity such as birth injury, respiratory distress, and hypoglycaemia. Macrosomia (birth weight >4500 g), regardless of the cause, is also a risk factor for asphyxia and perinatal death.[17]

Shoulder Dystocia and Brachial Plexus Injuries. Macrosomia increases the risk of shoulder dystocia, regardless of the cause. In the study by Zhang et al, the risk of birth injury was the highest for infants with a birth weight of 4500-4999 g and >5000 g (OR 2.4 [95% CI 2.2-2.5] and 3.5 [3.0-4.2], respectively).[17] A meta-analysis of the 2 randomized controlled trials (RCTs) comparing specific treatment with routine care[18,19] found a non–statistically significant decrease in birth injuries in the treatment group (OR 0.39 [95% CI 0.13-1.15], $P = .088$).[12] Incidence of brachial plexus palsy in newborns of diabetic mothers is low, between 0.2% and 3%. As a consequence, the risk could not be accurately measured.[20,21]

Neonatal Respiratory Distress. The risk of respiratory distress in cases of GDM cannot be accurately established, due to insufficient data. In the Australian Carbohydrate Intolerance in Pregnant Women study, the risk of respiratory distress, defined by the need for supplemental oxygen beyond 4 hours after birth, did not increase in the absence of treatment for GDM.[18] With GDM, there is a particularly high risk of respiratory distress in newborns with a birth weight >4000 g, compared with those with a birth weight of <4000 g (OR 3.1 [95% CI 1.11-8.65]).[21] In another study, the risk of respiratory complications increased with increasing birth weight beyond 4000 g, regardless of maternal diabetic status.[22]

Hypoglycemia. There is a correlation between increased cord C-peptide levels, macrosomia, and hypoglycemia.[23] Recently, the HAPO study, which included mothers who do not have overt diabetes, confirmed this relationship. Biochemical and clinical hypoglycemia were weakly related to maternal oral glucose tolerance test glucose measurements but were strongly associated with elevated cord serum C-peptide levels. Infants with excessive size at birth were more likely to develop hypoglycemia and hyperinsulinemia.[24] The incidence of hypoglycemia in cases of GDM is difficult to assess due to the variable definitions used for neonatal hypoglycemia in the different studies. Comparisons with the risk in healthy newborns are also difficult, because in most of the studies the monitoring of blood glucose at birth was different depending on the history of maternal diabetes. The 2 RCTs that evaluated the effect of specific treatment for GDM vs routine care found a comparable rate of intravenously treated hypoglycemia (7% vs 5%, $P = .16$[18] and 5.3% vs 6.8%, $P = .32$[19]). The risk of hypoglycemia is higher if the infant is macrosomic,[21] and hypoglycemia increases with increasing birth weight, independent of the maternal diabetic status.[22]

The Impact of Preexisting T2D on Fetal and Neonatal Malformations and Mortality. The risk of fetal malformations and perinatal death with GDM increase with undiagnosed prepregnancy T2D. Poor maternal glycemic control in the periconceptual period increases the risk of malformations, particularly with preexisting diabetes. According to population-based registry and database studies, the risk for congenital malformations in preexisting diabetes is 1.9- to 10-fold higher than that in the total population.[25] In most of the studies, the risk is slightly increased with GDM compared with the general population, with ORs between 1.1 and 1.3.[26,27] The malformations described are similar to those reported for pregestational diabetes, especially cardiovascular defects and anomalies involving the musculoskeletal and central nervous systems.[27,28] The risk of malformations increases as maternal fasting blood glucose levels increase.[28,29] This risk also increases with maternal body mass index (BMI)[30,31] and when GDM is diagnosed during early pregnancy.[31] These observations suggest that the increased risk reported in some studies is likely related to the inclusion of women with undiagnosed T2D in the GDM groups.[25]

Unlike in pregestational diabetes, an increased rate of fetal deaths in the second and third trimesters of pregnancy is debatable for GDM.[32,33] In a cohort study, where mothers diagnosed with T2D after delivery were excluded from the GDM group, perinatal mortality was 8.9/1000 in the GDM group, which was similar to rates in the general population and the T1D group (12.5/1000). Mortality was the highest in the group with T2D diagnosed before and after pregnancy (39.1/1000 and 56.2/1000, respectively).[34] The increased risk of perinatal death in case of GDM, reported in some studies, seems to be attributable to undiagnosed T2D. A meta-analysis including RCTs of specific treatments for GDM compared with usual care revealed no significant difference between the 2 groups for neonatal or perinatal mortality.[12]