DRUGS, PREGNANCY, AND LACTATION

Toxicity of Diabetes in Pregnancy

Diabetes is the most common medical complication of pregnancy, occurring in up to 7%-8% of all pregnancies. Gestational diabetes mellitus (GDM), in which the onset or recognition of glucose intolerance occurs in pregnancy, accounts for approximately 90% of diabetes cases. Although most represent true GDM (type 3), a significant number of cases are newly diagnosed type 2 diabetes. Distinguishing the two types is important because uncontrolled pregestational diabetes can cause all aspects of developmental toxicity (growth alteration, structural anomalies, functional/neurobehavioral deficits, and death), whereas true GDM does not cause structural anomalies because its onset is usually after organogenesis. However, both types have the potential to cause major toxicity in the mother and her offspring.

BY GERALD G. BRIGGS, B.PHARM., FCCP

Suboptimal treatment of diabetes is indicated by the biomarker HbA_{1c}, a measure of the mean blood glucose concentration over the preceding 6-8 weeks. HbA_{1c} results when glucose and hemoglobin A react (glycosylation) to form an irreversible compound. Values above normal (greater than 6%, mean blood glucose level greater than 126 mg/dL) are associated with significant maternal, embryonic, fetal, neonatal, and adolescent morbidity and mortality.

Other than serial blood glucose levels, an elevated HbA_{1c} level is the most useful biomarker for predicting diabetes-induced developmental toxicity. Normal levels of HbA_{1c} in nondiabetic patients indicate that even euglycemia and/or brief periods of hyperglycemia cause glycosylation of hemoglobin A and result in accumulation over time. In pregnancy, fetal risk increases directly with increasing HbA_{1c} levels, but it has been thought that the risk does not exceed that in nondiabetic pregnancies until HbA_{1c} concentrations exceed 7% (mean blood glucose level greater than 154 mg/dL).

Recent data challenge this belief. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study examined the effects of hyperglycemia less severe than that in diabetes in 23,316 women. Inclusion requirements were a fasting plasma glucose level of 105 mg/dL or less; after a standard 75-g oral glucose test given between 24 and 32 weeks, a 2-hour plasma glucose level of 200 mg/dL or less; and glucose levels below the predefined threshold at 34-37 weeks (N. Engl. J. Med. 2008;358:1991-2002).

The primary outcomes were a birth weight above the 90th percentile, a primary cesarean section, neonatal hypoglycemia, and fetal hyperinsulinemia; secondary outcomes were preterm birth, shoulder dystocia or a birth injury, the need for intensive neonatal care, hyperbilirubinemia, and preeclampsia.

For most primary outcomes, there was a clear dose-response relationship between increasing glucose levels and increasing frequency of the outcomes. The strongest associations were increased birth weight and increased fetal hyperinsulinemia. There were also significant positive associations with secondary outcomes, especially preeclampsia.

In a 2009 study, the records of 14,693 women, who had been screened and treated for GDM between 1988 and 2001 using only the National Diabetes Data Group (NDDG) criteria, were evaluated on the basis of Carpenter-Coustan (CC) criteria. For both criteria, two of the four threshold values following a 100-g, 3-hour glucose tolerance test need to be exceeded for a diagnosis of GDM. The thresholds for the CC and NDDG, respectively, were a fasting blood glucose of 95 mg/dL and 105 mg/dL, a 1-hour blood glucose of 180 mg/dL and 190 mg/dL, a 2-hour level of 155 mg/dL and 165 mg/dL, and a 3-hour level of 140 mg/dL and 145 mg/dL. The CC and NDDG criteria would have diagnosed GDM in 5.1% and 3.3%.

Compared with controls (women without GDM by either criterion), the 273 women with GDM based on CC, but not NDDG criteria, had significantly higher odds of cesarean delivery, operative vaginal delivery, macrosomia (above 4,500 g), and shoulder dystocia. The authors recommended using the CC method because of its increased sensitivity (Obstet. Gynecol. 2009;114:326-32).

Maternal morbidity associated with poorly controlled pregestational diabetes can worsen underlying metabolic disturbances. Retinopathy and nephropathy may worsen during pregnancy. Ketoacidosis, preeclampsia, infection, and preterm birth also are more common when glucose control is suboptimal. The severity of these complications may be increased if there is underlying vascular disease. Moreover, maternal vascular disease can result in fetal growth restriction. For patients with GDM, poor third-trimester glucose control is associated with increased risks for preeclampsia, traumatic birth, and cesarean section.

A significant risk of major structural anomalies is a concern with uncontrolled types 1 and 2 diabetes early in gestation. An HbA_{1c} of 8.1% has been reported as the threshold at which the rate of birth defects begins to exceed the background incidence. The defects result from hyperglycemia occurring before the 7th week of gestation. They are caudal regression syndrome (including defects of the sacrum and lumbar vertebrae, distal spinal cord disruption with neurologic impairment, and lack of growth in the caudal region); spina bifida, hydrocephalus, and other CNS defects such as anencephalus; cardiac anomalies (ventricular and atrial septal defects and transposition of great vessels); anal/rectal atresia; renal malformations (agenesis, cystic kidney, and ureter duplex); situs inversus (transposition of viscera); and femoral hypoplasia–unusual facies syndrome. Ventricular septal defects are the most common anomaly, and the caudal regression syndrome is the most characteristic.

An HbA_{1c} level near 10% is associated with a birth defect rate of 20%-25%, according to an ACOG Practice Bulletin published in 2005 (Obstet. Gynecol. 2005;105:675-85). This is evidence that the dose-response relationship required to establish a causal association exists between plasma glucose and structural anomalies. Other toxicities include embryo-fetal death (spontaneous abortions before 20 weeks, stillbirths in the third trimester); intrauterine bone resorption; and macrosomia (resulting from fetal hyperinsulinemia). If the fetus is macrosomic, birth trauma including asphyxia is an additional risk.

Hyperglycemia in the latter portion of pregnancy is associated with major neonatal toxicity: neonatal hypoglycemia (from hyperinsulinemia), hyperbilirubinemia, hypocalcemia, polycythemia (may involve thrombosis in the neonate), and respiratory distress syndrome (from inhibition of pulmonary maturation by fetal hyperinsulinemia). Exposure to hyperglycemia during pregnancy also is associated with significantly increased risks of diseases in the adolescent, including morbid obesity, chronic hypertension, and diabetes.

Taken in sum, poorly controlled diabetes in pregnancy extracts a heavy toll on the mother and her offspring. ■

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Most Antibacterial Drugs Not Associated With Birth Defects

BY MARY ANN MOON

Most commonly used antibacterial drugs were not associated with birth defects in a large surveillance study.

The study was performed because even though some antibiotics have been used relatively safely during pregnancy for decades, until now "there have been no large-scale studies addressing safety or risk [of birth defects] for many classes of antibacterial drugs," said Krista S. Crider, Ph.D., and her associates in the National Birth Defects Prevention Study. She reported no financial conflicts.

Their findings lend "support to the established safety profiles for certain classes of antibacterial [drugs] such as penicillins, erythromycins, and cephalosporins." The investigators also found it "encouraging" that the use of antibacterial drugs suspected of being teratogenic—such as aminoglycosides, chloramphenicol, and tetracyclines—was "extremely low to none at all" among women just before conception and in early pregnancy (Arch. Ped. Adolesc. Med. 2009;163:978-85). However, the use of other classes of antibacterial drugs, notably sulfonamides and nitrofurantoins, appeared to be associated with a higher risk for several birth defects, said Dr. Crider of the Centers for Disease Control and Prevention and her colleagues.

The researchers assessed prenatal exposure to antimicrobial drugs in 13,155 mothers of infants with birth defects (cases) born in 1997-2003 and 4,941 mothers of infants without major birth defects (controls) born in the same geographical locations during the same interval.

The case infants had at least 1 of more than 30 categories of major birth defects identified by surveillance systems in 10 states across the country. The cases included live births, stillbirths, and induced abortions. Infants with either isolated or multiple defects were included, although those with suspected chromosomal abnormalities or single-gene conditions were excluded. The mothers reported their use of antimicrobial drugs from the month prior to the estimated date of conception through the end of the first trimester via telephone interviews conducted 6 weeks to 2 years following delivery. Exposure to antibacterial drugs was common among both case (29.4%) and control (29.7%) mothers.

Penicillins, the most frequently used agents, were associated with an increased odds ratio for only one defect (intercalary limb deficiency). Erythromycins, the next most frequently used antibacterial drugs, were associated only with anencephaly and transverse limb deficiency. Similarly, cephalosporins showed only one significantly increased odds ratio, and that was for atrial septal defects.

Nitrofurantoins were associated with anophthalmia or microphthalmos, hypoplastic left heart syndrome, atrial septal defects, and cleft lip with cleft palate. Tetracyclines were associated with a variety of heart defects plus left ventricular outflow obstruction defects, septal heart defects, and oral clefts. Exposure to sulfonamides was associated with the most defects, including anencephaly, hypoplastic left heart syndrome, coarctation of the aorta, choanal atresia, and transverse limb deficiency. ■