Maternal Hyperglycemia Tied to High Fetal Insulin

BY MARY ANN MOON
Contributing Writer

Maternal glucose levels that were high but below the diagnostic threshold for gestational diabetes were strongly associated with high fetal insulin levels and birth weights in an international study of 23,316 pregnant women.

There were also weaker—but still significant—associations between maternal hyperglycemia that fell short of overt gestational diabetes and a host of neonatal problems: hypoglycemia in the neonate, the need for cesarean delivery, premature delivery, shoulder dystocia or birth injury, the need for intensive neonatal care, hyperbilirubinemia, and preeclampsia, investigators reported in the New England Journal of Medicine.

These findings "indicate the need to reconsider current criteria for diagnosing and treating hyperglycemia during pregnancy," reported Dr. Boyd E. Metzger of Northwestern University, Chicago, and his associates in the Hyperglycemia and Adverse Pregnancy Outcome study (N. Engl. J. Med. 2008;358:1991-2002).

The researchers assessed the 23,316 gravid women "to clarify the risk of adverse outcomes associated with degrees of maternal glucose intolerance less severe than overt diabetes mellitus." The study subjects underwent standard oral glucose tolerance testing at 24-32 weeks' gestation at 15 medical centers in nine countries.

Cord blood specimens were obtained at delivery to assess serum C-peptide levels, an indicator of fetal β-cell function.

High levels of fasting, 1-hour, and 2-hour plasma glucose were strongly correlated with birth weight above the 90th percentile and C-peptide levels above the 90th percentile, and the rates of these problems increased as plasma glucose levels increased.

There were weaker but significant correlations between maternal hyperglycemia and two other primary outcomes of this study (cesarean delivery and clinical neonatal hyperglycemia), as well as five secondary outcomes. A similar dose-response relationship was seen between increasing maternal glucose level and rising rates of these problems, Dr. Metzger and his associates said.

In a separate study of gestational diabetes published in the same issue, Dr. Janet A. Rowan of Auckland City (New Zealand) Hospital and her associates in the Metformin in Gestational Diabetes trial found that metformin was "noninferior" to insulin in safety and efficacy, and was preferred by patients with overt disease.

In that open-label study, Dr. Rowan and her associates compared oral metformin with insulin therapy in 733 women who had overt gestational diabetes and were followed at 10 New Zealand and Australian obstetric hospitals.

The composite outcome of numerous neonatal complications, including hypoglycemia in the infant, was no different between the metformin group and the insulin group, at 32% in both. There also were no differences between the two groups in neonatal anthropometric measures or in umbilical cord serum insulin concentrations.

The women preferred metformin to insulin. However, 46% of those who took metformin eventually required supplemental insulin as well, Dr. Rowan and her associates said (N. Engl. J. Med. 2008; 358:2003-15).

Further follow-up data on the offspring are needed to determine the long-term safety of metformin use in pregnancy, they noted. ■

Expert: Itching in Pregnancy May Be Intrahepatic Cholestasis

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — Check serum bile acid levels to determine if severe itching during pregnancy is the result of intrahepatic cholestasis of pregnancy, advises a dermatologic pathologist.

"Intrahepatic cholestasis of pregnancy is about the only dermatosis of pregnancy that has poor outcomes for the unborn," Dr. Senait W. Dyson said at a meeting sponsored by Skin Disease Education Foundation.

An uncommon problem in the United States, intrahepatic cholestasis of pregnancy (also called prurigo gravidarum or obstetric cholestasis) is a reversible form of cholestasis that presents in late pregnancy and persists until delivery.

The disease increases the risk of intrauterine fetal distress and leads to a three- to fourfold increase in the risk of stillbirth.

It typically presents during the third trimester and resolves within days after delivery. Clinically, the problem is characterized by generalized, severe pruritus without primary skin lesions, said Dr. Dyson, director of dermatopathology at the University of California, Irvine. Involvement of the palms and soles is common. You'll seldom see jaundice with intrahepatic cholestasis of pregnancy.

The main diagnostic finding is increased serum bile acids in all cases, resulting from impaired bile flow. Elevated serum bile acid levels greater than 4.07 mcg/mL (10 micromol/L) in these patients can reach as high as 16 mcg/mL (40 micromol/L), she said.

Some patients will have abnormal liver function tests. Histology is nonspecific, and immunofluorescence tests will be negative.

Prolonged disease causes vitamin K deficiency and increases the risk for bleeding in the mother. It is not clear whether the bleeding risk increases in the infant. Check prothrombin times in women with intrahepatic cholestasis of pregnancy, Dr. Dyson advised. Women with increased prothrombin times should get vitamin K injections.

"Treatments that I use for other cholestasis diseases are not helpful in this condition," she noted.

Antihistamines will help control the pruritus. Ursodeoxycholic acid (UDCA), the only approved medication to treat primary biliary cirrhosis, also helps improve pruritus in patients with intrahepatic cholestasis of pregnancy. Dr. Dyson said that most medical centers, including her institution, dose UDCA at 14 mg/kg per day t.i.d. to treat intrahepatic cholestasis of pregnancy from the time of diagnosis until delivery. Some clinicians suggest that dosages as high as 20-25 mg/kg per day t.i.d. might be better.

Delivery by 38 weeks' gestation is advisable, and some physicians suggest elective delivery by 37 weeks to decrease the risk of stillbirth, but it's not clear whether the potential benefits of delivering at 37 weeks outweigh the risks from preterm delivery, Dr. Dyson said.

"It's definitely agreed that patients should have frequent nonstress tests" and biophysical profiles to assess for fetal stress starting at 34 weeks' gestation, she said.

The incidence of intrahepatic cholestasis of pregnancy worldwide ranges from 10 to 760 cases per 10,000 pregnancies, with a higher incidence seen in Latin America (especially in Chile and Bolivia) and low rates in the United States and Europe.

Dr. Dyson reported having no conflicts of interest.

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Consider Using FFP Earlier in Cases of Massive Transfusion

BY CAROLYN SACHS
Contributing Writer

WAIKOLOA, HAWAII — Early administration of fresh-frozen plasma to address coagulopathy can potentially reduce mortality, according to a study of 97 patients who received massive transfusions.

Although hemorrhage is still a major cause of early mortality in trauma patients, it is commonly believed that patients are not coagulopathic when they arrive in the emergency department, and that coagulopathy develops over time, said Dr. Swaminatha Mahadevan, who is associate chief of emergency medicine at Stanford (Calif.) University.

A published study of 97 severely injured patients at the University of Texas, Houston, indicated there is a need for earlier administration of fresh-frozen plasma.

However, recent studies suggest that patients are coagulopathic when they "hit the ED door," Dr. Mahadevan said at a symposium on emergency medicine sponsored by Stanford University.

"Most massive-transfusion protocols don't address this," he added.

In Stanford's massive-transfusion protocol, and in many such guidelines throughout the United States, fresh-frozen plasma (FFP) is not given until the patient has received 4-6 U of blood, Dr. Mahadevan said.

In his presentation, Dr. Mahadevan referred to findings from a published study done at the University of Texas, Houston, which pointed to the need for earlier administration of FFP (J. Trauma 2007; 62:112-9).

The University of Texas investigators reviewed data on 97 severely injured patients who required a massive transfusion of at least 10 U of packed red blood cells during their first 24 hours in the university hospital. "These patients were sick enough that they eventually had to go to the operating room, or to interventional radiology, to stop the bleeding," Dr. Mahadevan said.

All of the patients studied were found to have had severe coagulopathy on arrival at the ED, with international normalized ratios (INRs) of 1.8, plus or minus 0.2.

Nevertheless, Dr. Mahadevan noted, because of the way the massive-transfusion guidelines have been set up, none of the patients received FFP until after they received 6 U of packed red cells.

Upon arrival in the ICU following initial resuscitation in the ED, the patients' INRs were still high (1.6, plus or minus 0.1).

Finally, they would start receiving packed red cells and FFP in a 1:1 ratio, Dr. Mahadevan said.

The patients were still moderately coagulopathic 8 hours later, he noted, with a mean INR of 1.4, plus or minus 0.03.

The University of Texas study found that the severity of coagulopathy on ICU admission correlated with an increase in mortality, Dr. Mahadevan observed.

"If your INR was greater than 2, you had a 50% mortality, which, obviously, is significant," he commented.

Learning from this study, Dr. Mahadevan stressed that "we should be assuming that these patients are coagulopathic, and [we should be] giving FFP right out of the gates," with an initial transfusion in a 1:1 ratio with packed red blood cells.

Based on the study's findings, the University of Texas investigators influenced the hospital to revise its massive-transfusion protocol for severe bleeding, Dr. Mahadevan noted. ■