

# Monitor for and Treat Mild Hypothyroidism in Pregnancy

BY MARY ELLEN SCHNEIDER  
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PHILADELPHIA — Physicians should test pregnant women for subclinical hypothyroidism and treat the condition to prevent possible fetal death and developmental abnormalities, according to Dr. Stephanie L. Lee, director of the Endocrine Clinics at Boston Medical Center.

For the first 15 weeks of development, the fetus is dependent on the mother's thyroid hormone. "So if Mom is hypothyroid, then baby is hypothyroid during that critical development period," Dr. Lee said at Endocrinology in the News sponsored by Boston University, INTERNAL MEDICINE NEWS, and FAMILY PRACTICE NEWS.

The risks of fetal loss and impaired development have been borne out in recent studies, she said. For example, a study that looked at the consequences of mild hypothyroidism among pregnant women found that the fetal death rate was four times greater in women with elevated levels of thyroid-stimulating hormone (TSH).

The researchers measured TSH in serum samples taken from women during their second trimester as part of their routine prenatal care. Of 9,403 women with singleton pregnancies, 2.2% (209 women) had TSH levels of 6 mU/L or greater. The rate of fetal death was 3.8% among the women with elevated TSH, compared with 0.9% in women with TSH levels less than 6 mU/L (*J. Med. Screen.* 2000;7:127-30).

In another study by the same group of researchers, the results of IQ testing in

children born to women who had untreated hypothyroidism during pregnancy were compared with those of children of women who had normal serum thyrotropin levels during pregnancy. Among the children of 48 women with untreated thyroid deficiency during pregnancy, the IQ scores were on average 7 points lower than those of the children of 124 women with normal thyroid levels. In addition, among children of mothers with untreated thyroid deficiency, 19% had IQ scores of 85 or less, compared with 5% of the other children (*N. Engl. J. Med.* 1999;341:549-55).

These are two bits of information that suggest that maternal hypothyroidism is a very serious condition and needs to be treated and monitored, said Dr. Lee, who had no commercial support to disclose.

Dr. Lee recommends TSH testing as soon as pregnancy is confirmed in women with a strong family history of hypothyroidism, who have a goiter on exam, or who were taking thyroid hormone prior to conception. She advises continuing to monitor these patients every 4-5 weeks through the first 20 weeks of gestation. After 20 weeks, the increased demand from the fetus seems to slow or stop, Dr. Lee said.

"Because these pregnant women do not see their [obstetricians] until week 12 or 13, it really is up to the internist to make sure that they know that they have to get the thyroid levels checked," Dr. Lee said.

The Endocrine Society made similar recommendations in clinical practice guidelines released in 2007. The society advises physicians to measure TSH in women at high risk for thyroid disease. ■

# Maternal Hyperglycemia Tied to High Fetal Insulin, Birth Weight

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 a large international study.

There were also weaker—but still significant—associations between maternal hyperglycemia that fell short of overt gestational diabetes, as well as a host of neonatal problems that included hypoglycemia in the neonate, the need for cesarean delivery, premature delivery, shoulder dystocia or birth injury, the need for intensive neonatal care, hyperbilirubinaemia, and preeclampsia.

These findings "indicate the need to reconsider current criteria for diagnosing and treating hyperglycemia during pregnancy," said Dr. Boyd E. Metzger of Northwestern University, Chicago, and his associates in the Hyperglycemia and Adverse Pregnancy Outcome study.

The investigators assessed 23,316 pregnant women in an effort "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  $\beta$ -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 were found to increase as the plasma glucose levels increased, the investigators reported (*N. Engl. J. Med.* 2008;358:1991-2002).

There were weaker but significant correlations between maternal hyperglycemia and two other primary outcomes of this study (the need for 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. ■

## DRUGS, PREGNANCY, AND LACTATION

### Droperidol and the Black Box Warning

In December 2001, the Food and Drug Administration placed a black box warning on droperidol (Inapsine) because of concerns over QT prolongation and torsades de pointes.

This action took the medical and pharmacy communities by surprise and created tremendous controversy. Although the labeling information always had contained warnings of serious and even life-threatening arrhythmias, droperidol had a 30-year history of safe and effective use in a range of patients.

Since its release in 1970, droperidol had been one of the preferred antiemetics for the prevention and treatment of postoperative nausea and vomiting (PONV) and the treatment of hyperemesis gravidarum (HG). But the agency's action resulted in a marked decrease in its use for both indications.

In the early 1990s, manufacturing problems curtailed the availability of parenteral prochlorperazine, the other preferred antiemetic for these indications. With no other viable alternatives, there was an increase in the use of ondansetron (Zofran), which was expensive, but is now available as a generic.

What remains unresolved is the use of droperidol in clinical situations, in which it is the preferred agent for PONV, including after cesarean section, and for HG.

Several small studies that compared droperidol and ondansetron for PONV found no differences between the two in terms of efficacy and toxicity. However, a large study with more than 2,000 subjects concluded that droperidol (1.25 mg IV) was superior to ondansetron (4 mg IV) for both vomiting and nausea (*Anesth. Analg.* 1998;86:731-8).

A review of 76 trials of 5,351 patients receiving 24 different droperidol regimens found no serious adverse events (*Can. J. Anaesth.* 2000;47:537-51). Other studies from California and Montreal reported that droperidol infusions were highly effective in the treatment of HG (*Am. J. Obstet. Gynecol.* 1996;174:1801-6; *J. Soc. Obstet. Gynaecol. Can* 2001; 23:133-9). None of these studies found evidence that droperidol was related to torsades de pointes.

A 2005 study of droperidol (0.625-1.25 mg) for antiemetic prophylaxis during general anesthesia in outpatient surgery observed no significant increase in the corrected QT (QTc) interval, compared with saline (*Anesthesiology* 2005;102:1101-5). A 2007 Mayo Clinic study reported no documented cases of torsades de pointes in the 16,791 patients exposed to droperidol over the 3-year period preceding the black box warning, and the authors concluded the FDA warning for low-dose droperidol was excessive and unnecessary

(*Anesthesiology* 2007;107:531-6).

An editorial voiced the same opinion (*N. Engl. J. Med.* 2004;350:2511-2). In a small study, 49 women with hyperemesis gravidarum received droperidol 1 mg/hr for 37 hours. The pretreatment QTc interval was 404 milliseconds, compared with 412 milliseconds at 37 hours, a clinically insignificant increase. A 2007 report analyzed data received under the Freedom of Information Act used by the FDA to support their black box warning.

After excluding duplicate reports, there were 65 cases of cardiac toxicity possibly caused by droperidol.

Some of these reports appeared to have occurred more than 30 years ago, not merely over the past 4 years as suggested by the FDA. Only two of the cases involved doses commonly used in the United States, one of which was a patient with preexisting cardiovascular disease. In addition, the

FDA used European data that involved doses 50-100 times higher than those used in the United States. The authors concluded that it did not appear that drugs such as ondansetron were safer than droperidol with regard to QT interval prolongation (*Am. J. Health-Syst. Pharm.* 2007;64:1174-86).

For 23 years, my colleagues and I have successfully used droperidol infusions for HG. Before receiving droperidol, patients must have normal concentrations of potassium and magnesium; they are excluded if they have a history of QT prolongation (slow heart rate), congestive heart failure, cardiac arrhythmias, or are taking other drugs known to increase the QT interval.

Because there is a genetic component for QT prolongation, women also are excluded if there is a history of an immediate blood relative (mother, father, or sibling) with QT prolongation or sudden cardiac death secondary to cardiac arrhythmia. Not a single patient has had to be excluded because of personal or family histories, or because of the use of other medications. Nor have we observed any serious adverse effects in the six to seven patients with hyperemesis gravidarum we treat each month.

Considering the strong evidence of safety and efficacy, it is time for the FDA to remove the antiemetic doses of droperidol from the black box warning.

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