

# Graves' Disease in Pregnancy: Choosing the Tx

BY CHRISTINE KILGORE

WASHINGTON — Given growing concerns about propylthiouracil-related liver toxicity, “it may be that we should be weighing the relative risks” of this drug and methimazole for the treatment of Graves’ disease during pregnancy, Dr. Susan J. Mandel said.

Propylthiouracil (PTU) has been the preferred therapy for Graves’ disease during pregnancy, especially during first-trimester organogenesis, because methimazole (MMI) and carbimazole have been associated with aplasia cutis and rare embryopathy including choanal atresia, esophageal atresia, tracheoesophageal fistula, and athelia.

None of these congenital anomalies has been reported with the use of PTU, Dr. Mandel said at an American Thyroid Association–sponsored meeting. Dr. Mandel is associate chief of the division of endocrinology, diabetes, and metabolism at the University of Pennsylvania, Philadelphia.

Last month, the Food and Drug Administration issued a warning about the risk of severe liver injury associated with the use of PTU with the treatment of

Graves’ disease. “After analyzing adverse event reports, the FDA has identified an increased risk of liver injury with propylthiouracil, compared with an alternative treatment for Graves’ disease, methimazole,” Dr. Amy Egan, deputy director for safety, division of metabolism and endocrinology products, FDA Center for Drug Evaluation and Research, said in a statement.

“Health care professionals should carefully consider which drug to initiate in a patient recently diagnosed with Graves’ disease. If PTU therapy is chosen, the patient should be closely monitored for symptoms and signs of liver injury, especially during the first 6 months after initiating therapy.”

The FDA is advising health care professionals to reserve PTU for patients in their first trimester of pregnancy or those who are intolerant of or allergic to methimazole.

The FDA statement, posted on the agency’s MedWatch Web site, said that 32 cases of serious liver injury were reported to the FDA from 1969, when the agency’s adverse event reporting program was established, through October 2008. Of these cases, 22 were in adults,

and included 12 fatalities and 5 liver transplants. Among the 10 pediatric cases, there were 6 reports of liver transplants and 1 fatality, according to the statement.

On the basis of an analysis of these reports, the FDA has determined that the risk of hepatotoxicity is greater with PTU than with MMI. The FDA received only five reports of serious liver injury associated with MMI, which was approved in 1950.

The FDA announced plans to change the prescribing information for PTU to reflect the hepatotoxicity warning

Concerns about PTU’s hepatotoxicity have come largely from the pediatric community. Last year, the National Institute of Child Health and Human Development (NICHD) held a conference on “hepatic toxicity following treatment for pediatric Graves’ disease.” And most recently, Dr. Scott A. Rivkees of Yale University, New Haven, Conn., and Dr. Donald R. Mattison of NICHD called for an end to the use of PTU in children.

In a letter to the editor published in the April 9 issue of the *New England Journal of Medicine* (2009;360:1574-5), Dr.

Rivkees and Dr. Mattison said that PTU-induced liver failure may occur in 1 in 2,000 to 1 in 4,000 treated children, with nearly 10 times that range developing reversible PTU-induced liver injury.

In the context of Graves’ disease in pregnancy, Dr. Mandel said, “it may be that we should be rethinking, what are the relative risks of hepatotoxicity with PTU versus the very rare embryopathy reported with methimazole [and carbimazole].”

Because the changes apparently caused by MMI “all occur by 8-10 weeks’ gestation, and some even earlier, there may be a rationale” to using PTU into early pregnancy and then switching to methimazole afterwards,” added Dr. Mandel, also professor of medicine and radiology at the University of Pennsylvania.

The original recommendations to use PTU in pregnancy—before the teratogenic effects of MMI were reported—came from studies suggesting that PTU was less likely to cross the placenta. More recent data acquired through the use of newer measurement techniques have challenged this, demonstrating a similar degree of transplacental passage with both drugs, she noted. ■

## Thyroid Surgery During Pregnancy Has Risks

BY MARY ANN MOON

Women who undergo thyroid or parathyroid surgery during pregnancy have more operative complications and require longer hospitalizations than do nonpregnant women who have such surgery, as well as relatively high rates of maternal and fetal complications.

These findings, from “the first population-based study to examine predictors of clinical and economic outcomes” in this patient group, suggest that thyroid and parathyroid surgery are not the low-risk procedures in pregnant women that they are in the general population, said Dr.

SreyRam Kuy of Yale University, New Haven, Conn., and associates.

The investigators assessed thyroid and parathyroid procedures in pregnancy because the subject had not been well studied before now, even though most disorders that necessitate such surgery occur in women of childbearing age. In addition, recent attention has focused on developing practice guidelines for pregnant women with endocrine disorders, and there was a glaring lack of evidence on this issue in the literature.

Dr. Kuy and colleagues performed a retrospective cross-sectional analysis of hospital discharge data using “the largest all-payer inpatient database in the United States, with records from approximately 8 million hospital stays each year.” They compared outcomes of 201 pregnant women and 31,155 age-matched nonpregnant women who underwent the surgery for benign thyroid disease, malignant thyroid disease, and hyperparathyroidism between 1999 and 2005.

Pregnant patients had significantly higher rates of surgical complications (24%) than did nonpregnant women (10%), including double the rate of endocrine complications (16% vs. 8%). Pregnant women also had significantly longer median hospital stays (2 days vs. 1 day) and inpatient costs (\$6,873 vs. \$5,963).

In the subset of women who underwent thyroidecto-

my, those who were pregnant had a higher rate of surgical complications for both benign disease (27% vs. 14%) and malignant disease (21% vs. 8%), the investigators said (*Arch. Surg.* 2009;144:399-406).

Although these procedures are considered low risk in the general population, women who underwent thyroid or parathyroid surgery while they were pregnant had a relatively high rate of pregnancy complications. The maternal complication rate was 4.5%, and the fetal complication rate was 5.5%.

Pregnant patients of surgeons who performed a high volume of thyroid and parathyroid procedures showed significantly lower rates of both maternal and fetal complications than did those of less-experienced surgeons. In contrast, hospital volume exerted no effect on complication rates.

“It appears to be essential that pregnant patients who require thyroidectomy or parathyroidectomy be directed to high-volume surgeons to optimize their outcomes,” the researchers said.

Given these findings, the risks and benefits of thyroid and parathyroid surgery must be weighed carefully in pregnant women.

“Thyroidectomy is rarely indicated on an urgent basis unless there is significant concern about the well-being of the mother. For example, airway obstruction from large goiters in symptomatic pregnant women with already compromised breathing from uterine expansion, advanced differentiated thyroid cancer, and poorly differentiated cancers could justify proceeding to thyroidectomy prior to delivery,” the researchers advised.

Similarly, parathyroidectomy during pregnancy is indicated to protect the fetus and prevent neonatal hypoparathyroidism and tetany, they said.

This study was supported by the Robert Wood Johnson Foundation and the U.S. Department of Veterans Affairs. The investigators reported that they had no financial conflicts of interest. ■

**Pregnant patients had significantly higher rates of surgical complications (24%) than did nonpregnant women (10%), including double the endocrine complications.**

## Labor Pain Intensity At Epidural Doesn't Affect Delivery Mode

WASHINGTON — The intensity of women’s labor pain at the time of neuraxial anesthesia placement didn’t influence the mode of delivery, based on data from a study of 555 nulliparous women.

No previous study has addressed whether timing of neuraxial anesthesia with regard to the degree of the patient’s pain has an impact on the mode of delivery, Dr. Yaakov Beilin said in a poster at the annual meeting of the Society for Obstetric Anesthesia and Perinatology.

In this study, Dr. Beilin and Diana H. Mungall, both of Mount Sinai Hospital in New York, reviewed data from term, nulliparous women who presented to the labor floor of a single hospital between July 2005 and September 2008. Pain scores at the time of neuraxial analgesia placement were determined using a scale of 0-10 and divided into three groups: low (0-3), moderate (4-6), and high (7-10).

The cesarean section rate was 41%, 36%, and 34%, in the low-, moderate-, and high-pain groups, respectively; the differences were not significant.

Similarly, the operative delivery rate (which included cesarean plus instrumental assisted vaginal delivery) was 49%, 45%, and 45% in the low-, moderate-, and high-pain groups, respectively; these values were not significantly different. And the vaginal delivery rate of 51%, 55%, and 55% for the low-, moderate-, and high-pain groups, respectively, were not significantly different.

The results were limited by the retrospective nature of the study, but the data suggest that neuraxial analgesia can be safely placed in women with varying degrees of labor pain, Dr. Beilin said.

The researchers had no financial conflicts to disclose.

—Heidi Splete