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Exposure to Methimazole during the First Trimester of Pregnancy Increases the Risk of Congenital Anomalies

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SUMMARY

Background

Several reports have suggested that propylthiouracil (PTU) may be safer than methimazole (MMI) for treating thyrotoxicosis during pregnancy because congenital malformations have been associated with the use of MMI during pregnancy. The authors investigated whether infants exposed in utero to antithyroid drugs had a higher rate of major malformations than infants born to a control group of pregnant women.

Methods

The authors reviewed the records of 6941 women with Graves' disease who became pregnant between January 1, 1999, and December 31, 2010; the pregnancy outcome of 6744 (97%) women was known. The diagnosis of Graves' disease was based on the clinical examination and laboratory data. There were 5967 live births, 30 perinatal losses, 657 miscarriages, and 90 abortions. All of the deliveries were attended by obstetricians. During each mother's first visit after delivery, a physician interviewed her about the congenital malformations diagnosed by the obstetricians. If a malformation was reported, the doctor corresponded with the gynecologist to determine whether there were any life-threatening anomalies in the fetus. The authors classified mothers and infants into three groups according to whether the mothers received treatment with MMI only, PTU only , or no medication (control group) in the first trimester of pregnancy (0 to 12 weeks' gestation). FT_4 was evaluated during the first trimester of pregnancy.

Results

During the first trimester of pregnancy, 1426 women were treated with MMI alone and 1578 with PTU alone; 2065 women received no medication and served as the control group. The remaining 1675 women had been treated with potassium iodide (394 women), levothyroxine (838), or more than one drug during the first trimester (443). Of the 2065 women in the control group, 1695 were in remission after treatment with antithyroid drugs for Graves' disease before their pregnancy, and the rest had received radioiodine ablation therapy. The mean (±SD) dose of MMI was 5.0±8.1 mg/day and PTU 100±113 mg/day. The overall rate of congenital malformation was 2.5% (152 of 5997 infants). The rate of malformed infants born to the women in the MMI group was 4.1% (50 of 1231 infants) as compared with 1.9% (26 of 1399) in the PTU group and 2.1% (40 of 1906 infants) in the control group. The overall rate of major malformations in the MMI group was significantly higher than in the control group (P = 0.002, Fisher's exact test), but there was no increase in the overall rate of major anomalies in the PTU group as compared with the control group (P = 0.709). The dosage of the antithyroid drug did not differ significantly according to whether or not the mothers delivered a child with a congenital malformation. With multivariate logistic-regression analysis, the mothers treated with MMI during pregnancy had higher odds of giving birth to an infant with a congenital malformation (odds ratio [OR], 2.28; 95% confidence interval [CI], 1.54 to 3.33; P = 0.0002) than mothers who did not receive any medication for the treatment of Graves' disease. On the other hand, no increased risk of giving birth to an infant with a congenital malformation was found among the mothers treated with PTU (OR, 0.66; 95% CI, 0.41 to 1.03; P = 0.079). Aplasia cutis congenita, omphalocele, or omphalomesenteric duct anomaly were reported in

continued on next page

20/1231 babies from mothers being treated with MMI and in none from mothers treated with PTU or in those from the control group. Two mothers whose infants were born with an omphalocele took MMI up to 7 weeks' gestation, one mother switched to PTU and the other to potassium iodide. One mother who switched to PTU at 9 weeks' gestation delivered a baby with aplasia cutis congenita and omphalomesenteric anomaly. Multivariate analysis, which included maternal treatment during the first trimester of pregnancy, maternal thyroid status, and maternal age, showed that maternal thyroid status had no effect on the rate of giving birth to an infant with a congenital malformation (OR, 0.86; 95% CI, 0.63 to 1.1; P = 0.28).

Conclusions

Exposure to MMI during the first trimesterof pregnancy increased the risk of congenital anomalies, including the risk of the rare anomalies aplasia cutis congenita, omphalocele, and a symptomatic omphalomesenteric duct anomaly. It seems preferable to treat Graves' disease with PTU because it appears to be safer to use during the childbearing years; however, the reported risk of hepatotoxicity in both the mother and the child is a concern.

ANALYSIS AND COMMENTARY

For many years and without good scientific evidence, PTU was considered to be the drug of choice in the management of hyperthyroidism in pregnancy. Risk of a rare skin lesion, aplasia cutis congenita (1), and less maternal transplacental passage to the fetus favored PTU over MMI. However, studies comparing the two drugs showed an equal therapeutic response (2, 3). The overall incidence of congenital malformations due to MMI is very low, and some authors even suggested that poorly treated maternal hyperthyroidism could be the culprit for these abnormalities (4). Nevertheless, a specific methimazole embryopathy has been described, and reports with a few cases are published regularly. Recently, severe liver toxicity due to PTU administration, including hepatic coma, death, and the need for liver transplantation, has been revisited (5). The ATA (6) has strongly recommended limiting the use of PTU to special circumstances, such as thyroid storm, allergy to MMI, and the first trimester of pregnancy. Some physicians are reluctant to switch from MMI to PTU during early pregnancy and then back to MMI because of the potential difficulty of maintaining maternal euthyroidism, in view of the uncertainty of the equivalence in potency between PTU and MMI. Yoshihara et al. reported from Japan the largest series of pregnant women with hyperthyroidism who were exposed to either PTU or MMI in the first trimester of pregnancy and compared the rate of congenital malformations with a control group of euthyroid women with Graves' disease who were receiving no antithyroid drug therapy. This is an important study because in a 10-year period almost 6000 pregnant women from one institution were studied, and the investigators were able to obtain information on drug exposure and congenital anomalies in the offspring. Their results confirmed the reported specific anomalies in infants exposed to MMI in the first trimester of pregnancy; the reported high incidence of aplasia cutis congenita is of interest because some studies showed an incidence similar to that in the general population (7). The low incidence of choanal atresia and esophageal atresia (one infant) in their population is explained by the authors as the result of a low frequency of these anomalies in Japan. Another interesting observation is the lack of correlation between thyroid status in the first trimester of pregnancy and congenital abnormalities; this obser-

continued on next page

vation is pertinent because of a recent publication of neonatal dysplasia of the hip in infants born from mothers with hyperthyroidism, irrespective of the cause (8). In summary, Yoshihara et al. present strong evidence for using PTU as the antithyroid drug of choice in the first trimester of pregnancy.

— Jorge H. Mestman, MD

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