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Should the Approach to Management of Graves' Hyperthyroidism in Women of Child-Bearing Age Be Revised?

Jorge H. Mestman

Andersen L, Wu CS, Laurberg P. Birth defects after early pregnancy use of antithyroid drugs: a Danish nationwide study. J Clin Endocrinol Metab 2013;98:4373-81. Epub October 22, 2013.

SUMMARY

Background

Maternal and fetal complications occur in poorly controlled Graves' hyperthyroidism. Pregnancy outcome is successful in the majority of cases when antithyroid drugs have been used for over five decades and when the woman is carefully monitored. However, in the past few years, several reports have confirmed the results of early studies of congenital malformations when antithyroid drugs are used in the first trimester of pregnancy.

The authors' objective was to determine to what degree the use of methimazole/carbimazole (MMI/CMZ) and propylthiouracil (PTU) in early pregnancy is associated with an increased prevalence of birth defects.

Methods

This Danish Nationwide Register–based cohort study included 817,093 children born from 1996 to 2008. Exposure groups were assigned according to maternal antithyroid drug use in early pregnancy: PTU (564); MMI/CMZ (1097); MMI/CMZ and PTU (shifted in early pregnancy [159]); no antithyroid drug (antithyroid drug use, but not during pregnancy [3543]); and nonexposed (never used antithyroid drugs [811,730]). Multivariate logistic regression was used to estimate adjusted odds ratios (OR) with 95% confidence intervals (CI) for diagnosis of a birth defect before 2 years of age in exposed versus nonexposed children.

Results

The prevalence of birth defects was high in children exposed to antithyroid drugs in early pregnancy (PTU, 8.0%; MMI/CMZ, 9.1%; MMI/CMZ and PTU, 10.1%; no antithyroid drugs, 5.4%; nonexposed, 5.7%; P<0.001). Both maternal use of MMI/CMZ (adjusted OR, 1.66) and PTU (adjusted OR, 1.41) and maternal shift between MMI/CMZ and PTU in early pregnancy (adjusted OR, 1.82) were associated with an increased OR of birth defects. MMI/CMZ and PTU were associated with urinary system malformation and PTU with malformations in the face and neck region. Congenital malformations in children from mothers exposed to MMI/CMZ early in pregnancy (choanal atresia, esophageal atresia, omphalocele, omphalomesenteric duct anomalies, and aplasia cutis) were common (OR, 21.8 [95% CI, 13.4 to 35.4]).

Conclusions

Both MMI/CMZ and PTU were associated with birth defects, but the spectrum of malformations differed. The authors concluded that more studies are needed to corroborate results with regard to early pregnancy shifts from MMI/CMZ to PTU.

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ANALYSIS AND COMMENTARY

Diagnosis and management of hyperthyroidism in pregnancy is a challenge for the medical team. The most common cause of hyperthyroidism early in pregnancy is gestational thyrotoxicosis (1), a self-limited disorder that requires no specific antithyroid therapy and does not affect the outcome of pregnancy. Graves' hyperthyroidism affects about 0.5% of pregnant women, with different clinical presentations: (a) first diagnosed in pregnancy, (b) women on antithyroid drug therapy from before conception and either euthyroid or hyperthyroid at the time of conception, (c) recurrence of hyperthyroidism soon after conception in women in remission from previous antithyroid drug therapy, and (d) postablation therapy. Obstetrical and maternal complications are significant in women whose disease is poorly managed (2). Furthermore, the dosage of antithyroid drugs needs to be monitored frequently throughout gestation to avoid fetal thyroid dysfunction. The natural course of hyperthyroidism during gestation is characterized by an aggravation of symptoms in the first trimester, with amelioration in the second half of pregnancy, and, interestingly, antithyroid drug therapy may be discontinued in the last 6 to 8 weeks of pregnancy in about 30% of patients without recurrence of hyperthyroidism. Rebound of hyperthyroid symptoms is common in the first 3 months postpartum. Both MMI/CMZ and PTU have been used in pregnancy; PTU was the preferred drug for many years, supported by an early report of a congenital complication, aplasia cutis, in infants of two mothers treated with methimazole (3). Clementi et al. (4) described the syndrome of methimazole embryopathy, which includes choanal atresia, esophageal atresia, omphalocele, omphalomesenteric-duct anomalies, and aplasia cutis. Barbero et al. (5) described characteristic facial features in children whose mothers were treated with MMI in the first trimester. These complications are rare in the general population; however, in the past few years, several articles with large numbers of women exposed to antithyroid drugs consistently showed an association of specific malformations not only to MMI but also to PTU (6-8). Reports of liver failure in children and some adults undergoing PTU therapy prompted the ATA and the Food and Drug Administration to recommend the use of MMI in the management of thyrotoxicosis, with three exceptions: patients allergic to MMI, patients in their first trimester of pregnancy, and patients in hyperthyroid crisis (9). The recommendation suggested by the ATA and Endocrine Society is to prescribe PTU in the first trimester of pregnancy and MMI afterward, or to shift from MMI to PTU as soon as pregnancy is confirmed. In the present Danish Nationwide Register–based cohort study, 817,093 children born from 1996 to 2008 were included. Four groups were analyzed: (a) those with PTU exposure in the first trimester, (b) those with MMI exposure, and (c) those who took MMI and then switched to PTU at some time during the first trimester. These groups were compared with children of mothers with hyperthyroidism who were not exposed to antithyroid drugs during pregnancy and control infants. In addition to confirming a significant increase in congenital malformations in infants exposed to MMI and PTU in the first trimester, they made the interesting observation of congenital malformations in 16 (2 with choanal atresia) of 149 children whose mothers shifted from MMI to PTU at a median time of 44 days (range, 3 to 70) after conception.

In view of these findings, physicians should discuss with their patients with hyperthyroidism who are of child-bearing age several important aspects of future pregnancies: (a) the first, obvious, one is to avoid pregnancy until a proper diagnosis and therapeutic plan is in place (oral contraceptives are the most effective method when taken properly), (b) the potential risk of congenital malformations resulting from antithyroid drug exposure in the first trimester,

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(c) the potential risk of fetal dysfunction due to inappropriate antithyroid drug dosage in the second half of pregnancy, and the limited technical tools available to detect fetal thyroid dysfunction, (d) the risk of fetal hyperthyroidism in mothers with high titers of TSH receptor antibodies (although the incidence is low), (e) the possibility of a marked and persistent increase in TRAb titers after ^{131}I thyroid ablation (10), and (f) the importance of maintaining euthyroidism throughout pregnancy, regardless of the therapy chosen, with frequent contacts with the medical and obstetrical team. For women undergoing antithyroid drug therapy and accepting the potential risk of congenital malformations, it would be prudent to select PTU before conception and consider switching to MMI after the first trimester.

In summary, there is clear evidence from most studies published in the past few years, that both MMI/CMZ and PTU given in the first trimester of pregnancy present an unacceptable risk for congenital malformations. Thyroid ablation before pregnancy is an attractive therapeutic choice; surgery should be strongly considered in women with a relatively high serum TRAb titer. Recently, an allergic reaction to PTU at 7 weeks of gestation developed in one of my patients with recurrent hyperthyroidism who was in her second pregnancy; MMI was started a few days after the 10th week of gestation. The infant was born with a mild congenital defect in both ears. Therefore, the possibility of an allergic reaction to PTU should also be considered and discussed with the patient.

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