Hyperthyroidism during pregnancy

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ABSTRACT

QUESTION I have a 33-year-old patient with hyperthyroidism who is 6 weeks pregnant. Her thyroid function is well controlled with a 5-mg dose of methimazole 3 times daily. She was initially treated with propylthiouracil but was switched to methimazole owing to urticaria. I have heard about birth defects in infants whose mothers used methimazole during pregnancy. How safe is it?

ANSWER In North America, propylthiouracil has been the drug of choice for hyperthyroidism during pregnancy. Methimazole is widely used in Europe, South America, and Asia, and is an alternative for patients who cannot tolerate propylthiouracil. Some case reports raised concern about fetal toxicity from methimazole, which is reportedly characterized by aplasia cutis, esophageal atresia, choanal atresia, facial abnormalities, and mental retardation. However, causality is unclear and the overall risk of congenital abnormalities in infants exposed to methimazole in utero was not higher than in those exposed to nonteratogenic drugs in cohort studies. It is important for a pregnant woman to continue methimazole, if necessary, because uncontrolled hyperthyroidism increases the risk of complications such as preterm labour and low birth weight.

RÉSUMÉ

QUESTION Une de mes patientes de 33 ans atteinte d'hyperthyroïdie est enceinte de 6 semaines. Sa fonction thyroïdienne est bien contrôlée grâce à une dose de 5 mg de méthimazole 3 fois par jour. Initialement, elle était traitée avec du propylthiouracil, mais a dû changer son traitement pour cause d'urticaire. J'ai entendu parler d'anomalies à la naissance chez des nourrissons dont la mère prenait du méthimazole durant la grossesse. Dans quelle mesure ce médicament est-il sécuritaire?

RÉPONSE En Amérique du Nord, le propylthiouracil se révèle le médicament de première intention pour traiter l'hyperthyroïdie durant la grossesse. Le méthimazole est largement utilisé en Europe, en Amérique du Sud et en Asie, et c'est une option de rechange pour les patients qui ne tolèrent pas le propylthiouracil. Selon certains rapports de cas, il y aurait des inquiétudes entourant la toxicité fœtale causée par le méthimazole, qui prendrait la forme d'aplasie cutanée congénitale, d'atrésie œsophagienne, d'atrésie des choanes, d'anomalies faciales et de retard intellectuel. Par ailleurs, il n'y a pas de causalité certaine, et le risque global d'anomalies congénitales chez les nourrissons exposés au méthimazole dans l'utérus n'était pas plus élevé que celui des enfants exposés à des médicaments non tératogènes dans les études de cohortes. Il est important pour une femme enceinte de continuer à prendre du méthimazole si c'est nécessaire parce qu'une hyperthyroïdie non contrôlée accroît le risque de complications comme le travail prématuré et un faible poids à la naissance.

Hyperthyroidism occurs in 1 to 2 of every 1000 pregnant women.[1] The most common cause of hyperthyroidism (80% to 85%) is Graves disease. Other causes include functioning adenoma, thyroiditis, and excessive thyroid hormone intake. Clinical practice guidelines for the management of hyperthyroidism during pregnancy have been developed by academic societies, including the Endocrine Society, American Association of Clinical Endocrinologists, and American College of Obstetricians and Gynecologists.[2-4]

Hyperthyroidism caused by Graves disease tends to get worse during the first trimester, improve later in pregnancy, and get worse again after delivery. Placental human chorionic gonadotropin is structurally similar to thyroid-stimulating hormone (TSH), and the increase in human chorionic gonadotropin in the first trimester has been suggested to be the cause of thyroid stimulation. As pregnancy progresses, patients usually require lower doses of antithyroid drugs. Close monitoring of thyroid function needs to be continued after delivery in anticipation of postpartum exacerbation until the patient reaches a stable euthyroid state.

Fetal thyroid function

The fetus is dependent on the small supply of thyroxine (T_4) from the mother until 10 to 12 weeks of gestation, when the fetal thyroid gland starts secreting thyroid hormones. By 20 weeks of gestation, the fetal thyroid

gland becomes responsive to TSH from its own pituitary gland, but the function of the thyroid gland remains relatively low. While transfer of maternal T_4 across the placenta is limited and the serum T_4 level in a fetus is about one-third of the maternal level, maternal TSH-receptor antibodies in Graves disease are immunoglobulin G antibodies and readily cross the placenta. As a result, maternal TSH-receptor antibodies can cause fetal hyperthyroidism after 20 weeks of gestation. Antithyroid drugs, such as methimazole and propylthiouracil, also cross the placenta and therefore serve as treatment for both maternal and fetal hyperthyroidism.

Complications

Uncontrolled hyperthyroidism is associated with serious maternal, fetal, and neonatal morbidity, and mortality. Maternal complications include miscarriage, pregnancy-induced hypertension, preterm labour, placental abruption, heart failure, and thyroid storm. Fetal and neonatal complications include stillbirth, low birth weight, goiter, hyperthyroidism, and hypothyroidism.[5-7] These risks can be decreased with the appropriate treatment of maternal hyperthyroidism.[5]

Management

Hyperthyroidism during pregnancy should be treated with an antithyroid drug. The goal of treatment is to maintain maternal free T_4 in the upper normal range, using the lowest possible dose of the antithyroid drug. This approach aims at minimizing the risk of fetal hypothyroidism.[8] Thyroid hormones are critical for fetal brain development, and caution against overtreatment is warranted. Mild hyperthyroidism is usually monitored closely without therapy as long as both the mother and the fetus are not symptomatic. If thyroidectomy is indicated for treatment failure with a high-dose antithyroid drug or adverse effects from an antithyroid drug, it is optimally performed during the second trimester of pregnancy. Radioactive iodine is contraindicated during pregnancy, as it readily crosses the placenta and is taken up in the fetal thyroid gland. For pregnant women with past or current Graves disease, Doppler examination of the fetal thyroid gland is useful in detecting goiter, which is associated with fetal hyperthyroidism or hypothyroidism.[9]

Antithyroid drugs during pregnancy

Propylthiouracil is the drug of choice for hyperthyroidism during pregnancy in North America owing to the suspected association of methimazole with congenital abnormalities (sometimes referred to as *methimazole embryopathy*), characterized by aplasia cutis, esophageal atresia, choanal atresia, facial abnormalities, and developmental delay. Since the association of methimazole with aplasia cutis was first suggested by an epidemiological study,[10] cases of aplasia cutis or other associated abnormalities in infants exposed to methimazole in utero have been reported in the literature.[11-13] However, in a prospective cohort study in which 241 women used methimazole and 1089 women used nonteratogenic drugs, the overall risk of serious congenital abnormalities in infants in the methimazole group was not higher than in those in the nonteratogenic drug group.[14] In addition, 2 retrospective studies did not find an increase in congenital abnormalities in infants exposed to methimazole in utero.[15,16] Another reason for the preference of propylthiouracil over methimazole is that a small study reported limited transplacental passage of propylthiouracil compared with methimazole.[17] This finding was refuted by a later study.[18] The risk of fetal hypothyroidism was not different between women with Graves disease taking propylthiouracil and those taking methimazole.[19] Methimazole has been widely used in Europe, South America, and Asia and is an alternative to propylthiouracil in North America for patients with hyperthyroidism who cannot tolerate propylthiouracil.

Antithyroid drugs during lactation

Propylthiouracil is often recommended as the antithyroid drug of choice during lactation because the transfer of propylthiouracil to a nursing infant via breast milk seems to be less than the transfer of methimazole. However, neither propylthiouracil nor methimazole seem to pose a serious risk to nursing infants. A study that included 139 lactating mothers taking methimazole and their nursing infants showed no adverse effects on thyroid function or neurodevelopment of the infants.[20] Methimazole doses of up to 20 mg/d did not cause hypothyroidism in nursing infants.[21] Until more studies are available, thyroid function of nursing infants should be monitored if the mother receives a high dose of methimazole during lactation.

Conclusion

Propylthiouracil is the drug of choice for hyperthyroidism during pregnancy; however, methimazole is an alternative for patients who cannot tolerate propylthiouracil. Although there are case reports of fetal toxicity from methimazole, the overall risk of congenital abnormalities in infants exposed to methimazole in utero does not seem to be higher than those exposed to nonteratogenic drugs or propylthiouracil. It is important for a pregnant woman to continue methimazole, if necessary, because uncontrolled hyperthyroidism increases the risk of complications such as preterm labour and low birth weight.

Competing interests
None declared

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MOTHERISK

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