Pregnancy and the Antithyroid Drug Conundrum

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Abstract

Treating pregnant women with anti-thyroid drugs that have known teratogenic effects continues to present clinicians with multiple concerns.

Keywords

Graves' disease, hyperthyroid, methimazole, propylthiouracil, pregnancy

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The purpose of life is to reproduce. One purpose of physicians is to make sure this happens safely. In the developed world this has been pretty successful. And so we do not want to spoil things: we just want the results to continue improving and to involve more countries in such success. We certainly do not want an old-fashioned thing like thyroid disease to interfere. And so it should not.

Women with thyroid failure can be treated easily with thyroxine replacement therapy and as long as the mother takes sufficient thyroxine during pregnancy the baby will be normal. If she does not take her tablets she will most likely have a dull child or worse.[1,2] Not a good outcome but entirely preventable. The physician needs to verify that the thyroid is being replaced appropriately and must not just trust the mother. Trust and verify. But what about an overactive thyroid? Now that is more of a problem and usually needs an endocrinologist to be involved with the obstetrician. Hyperthyroid Graves' disease is most common in the reproductive age group and although fertility is said to be reduced by hyperthyroidism, the data supporting this assumption for mild disease are relatively weak. Clearly, overt hyperthyroidism will disrupt ovulation but the more common mild degree of hyperthyroidism is much less likely to do so and it has been estimated that the incidence of hyperthyroidism in pregnancy is about one in 20, which seems much too high.[3] Nevertheless, plenty of women with mild disease do become pregnant and need treatment. They need treatment because their risk for complications is increased. Hyperthyroidism in pregnancy is associated with increased pre-eclampsia, preterm birth, and need for induction as well as more rare outcomes,[4] and the neonates more often require intensive care.[5] These increased risks appear not to be just the influence of excess thyroid hormone on the mother but also by the direct effects of thyroid hormone on the fetus. This has been shown elegantly in mothers with thyroid hormone resistance but a normal fetus[6] where growth was restricted and there was an increased risk for pregnancy loss. In addition, in early pregnancy there may be an exaggeration of the hyperthyroidism because of the influence of human chorionic gonadotropin (hCG) acting as a thyroid stimulator.[7] Treatment is, therefore, usually considered to be needed for most women who are pregnant with hyperthyroidism.

So how to do this? The treatment of hyperthyroidism has not changed for more than 50 years. We may be better informed and better able to use the same old treatments but there has not been a fundamental shift in the approach. It remains antithyroid drugs, radioiodine and surgery. Each has well-known advantages and disadvantages and the informed young women does not like any of them. And right she is. What a terrible choice to have to make when carrying a precious child. Radioiodine is out straightaway for obvious reasons. Surgery, the original treatment for Graves' disease is never anything to rush into unless you are a surgeon. That leaves antithyroid drugs. Or does it? Let us first deal with antithyroid drugs. The US Food and Drug Administration (FDA) has now black boxed propylthiouracil (PTU) because of the unacceptable increased risk for liver failure, especially in children;[8] therefore, its use as first-line treatment is no longer recommended.[9] The first drug of choice is now methimazole. But methimazole in pregnancy has been well established to cause what has become known as a methimazole embryopathy (see *Table 1*)[10] and potentially involves many different tissues. So the thyroid community came up with the suggestion to switch to PTU for the first trimester of pregnancy and then to switch back to methimazole after organ formation is completed.[9]

This scenario assumes that you see the patient in early pregnancy. But that is unlikely to be before 6 weeks—after a good deal of human development has taken place. In essence, using this approach requires a switch to PTU at 6 weeks and then a return to methimazole at 12 weeks with barely time to even determine the correct dose. A better way is to switch antithyroid drugs when the woman is planning a pregnancy although this ignores the matter of unexpected pregnancies. If this approach does not sound difficult enough, who says PTU is safe? There are good experimental data showing the teratogenic effects of PTU[11] and recently Peter Laurberg's group in Denmark

Table 1: Examples of Defects Seen in Methimazole Embryopathy

Skin	Aplasia Cutis
Gut	Choanal atresia
	Omphalocele
	Patent intellointestinal duct
Heart	Ventricular septal defects
Head	Dysmorphic facies

have shown that there are PTU-associated birth defects in the face, neck, and urinary system after PTU exposure.[12] These tended to be less severe than after methimazole but still mostly required surgical correction. In my view that ends the recommended logic. Clearly neither antithyroid drug is a great choice.

So are there more options for the treatment of hyperthyroidism in pregnancy? There are in fact two other choices. The first is not to get pregnant. But of course it may be too late for that approach. But it is the advice that should be offered to those young women already diagnosed with hyperthyroidism. Delay until you are appropriately treated. And if you are in a hurry? Or if your eggs are aging? Then go ahead and have surgery. It is now safer than ever before if you go to a high volume thyroid surgeon.

The second extra choice is to do nothing. If the disease is mild, the chance of major complications is small and as the immune suppression of pregnancy develops in the second trimester the disease will almost certainly dissipate.[13] But physicians are really bad at doing nothing. Get used to it. ■

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