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Therapeutic Drug Monitoring of Antithyroid Drugs in Pregnancy:

The Knowledge Gaps

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Abstract

Despite being a common condition in pregnancy, and despite propylthiouracil (PTU) being perceived as safer than methimazole, there are virtually no epidemiological controlled studies on malformation rate an neurobehavioral outcomes with the former. This knowledge gap must be filled to ensure fetal safety.

Keywords

antithyroid; therapeutic drug monitoring; malformations; pregnancy; thyrotoxicosis

Because the thalidomide era there is a commonly held perception among both patients and physicians that many drugs are a human teratogens. In studies conducted in our institution we have shown that women exposed to non-teratogenic drugs believe they have a 25% risk of major malformations, which is a risk equal in magnitude to that of thalidomide.[1] In reality, the risk for major malformations in the general population ranges between 1–3%. As a result of this misperception, a large number of women refuse to take drugs in pregnancy, even if such refusal may endanger their lives.

The Motherisk Program at the Hospital for Sick Children and the University of Toronto counsels women and health professionals on the safety/risk of medicinal drugs, chemicals, radiation and infection during pregnancy and lactation. Presently we deal with up to 200 calls daily from women, their families and health professionals.[2]

Over the years we have become painfully aware of large knowledge gaps related to thyroid diseases and their treatments during pregnancy and lactation. In this report we briefly review these issues and identify critical unanswered questions.

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Hyperthyroidism in Pregnancy

Hyperthyroidism is second only to diabetes as a common endocrinopathy in pregnancy.[3] Large numbers of women need antithyroid drugs to ensure their well being, yet these medications, if they cross the human placenta, may disrupt fetal thyroid development similarly to their disruption of the function of the adult thyroid. This illustrates a potential maternalfetal conflict, because untreated thyrotoxicosis in pregnancy is associated with increased rates of various complications (Table 1).

Typically, thyrotoxicosis tends to be aggravated in the first trimester of pregnancy, improve in the second, and recur within one year postpartum.[4] The goals of maternal treatment are to maintain free thyroxine (T_4) at the upper level of the normal range with the minimal possible doses of antithyroid drugs. In fact, in about 30% of women antithyroid drugs may be discontinued in the last few weeks of pregnancy.

Maternal-Fetal Pharmacokinetics of Antithyroid Drugs

The critical first question that must be addressed is whether the main antithyroid drugs, propylthiouracil (PTU) and methimazole (MMI), cross the human placenta. Experiments with the dually perfused human term placenta documented transfer at both low and high levels of PTU (4 and 40 mcg/gmL and MMI (1.5 and 15 mcg/mL). Both drugs documented relatively similar transfer and placental clearance rates, corresponding to similar clinically documented effects on maternal and fetal thyroid function.[5]

In studying the pharmacokinetics of PTU in pregnancy, there were consistently lower serum concentrations in the third trimester than among non pregnant women.

Cord serum concentrations of PTU are consistently higher than maternal, suggesting slower clearance rate from the fetus.[6]

Fetal Safety

In practice, there is presently clear preference of PTU over MMI due to perceived “limited placental transfer” of the former. In agreement with the similar placental transfer documented above, clinical studies illustrate no differences in mean fetal free T_4 or fetal TSH, 6% low FT_4 with PTU and 7% with MMI, with no apparent correlation between maternal doses and fetal thyroid function.[7] Hence, kinetically, there is little reason to prefer PTU over MMI.

In monitoring potential adverse fetal effect, in a study of 241 cases of fetal exposure to MMI and 1089 controls, there was no higher overall rate of malformations with MMI, but there were two cases of choanal and esophageal atresias (a malformation that originates at weeks 3–7 of gestation).[8] The literature also reports several cases of congenital aplasia-cutis with local lack of skin due to MMI.

It is quite surprising that despite its wide clinical use in pregnancy, there is no epidemiological controlled study of the potential teratogenic effect of PTU. Yet, animal studies have shown PTU to induce fetal hypothyroidism, with permanent effects on neurologic functions secondary to impaired synaptic transmission. The clinical literature describes numerous cases of fetal goiter secondary to PTU, often reversible upon discontinuation of the drug.[9]

The fetus is dependent on the mother for its thyroid hormone supply for the first half of the pregnancy. It is critical to establish whether PTU and MMI can adversely affect brain

development. Here too only a small 30-year-old study exists that looked at child intellectual development after PTU, suggesting no adverse effects.[10] In contrast, large studies exists with MMI, where intellectual achievements were similar to unexposed controls, corroborating lack of evidence of any deleterious effects of thyroid function in the offspring.[11]

Breastfeeding on Antithyroid Drugs

PTU has a much lower milk/plasma concentration ratio (0.1) as compared with MMI. In a small study (n = 11) of breastfed infants whose mothers took 300-75 mg/d, there was no apparent effects on neonatal thyroid function. Yet, 3 neonates exhibited TSH levels above the adult higher range.[12]

MMI has been measured in milk at a weight corrected dose of only 0.14% of the maternal dose. Yet, despite these reassuring data, a study by Motherisk has shown that only 44% of mothers receiving PTU initiated breastfeeding as compared with 84% of controls.[13]

In summary, it appears that whereas PTU and MMI are equivalent in terms of efficacy, there are more reports of congenital malformations with MMI, possibly as an artifact of lack of such studies with PTU. It is critically important to control the mother's hyperthyroidism and avoid thyrotoxicosis.

Presently, there are more data on MMI effects on fetalneonatal neurocognitive function, and there is urgent need for a study of neurodevelopment following PTU. Lastly, it appears that breastfeeding is compatible with both PTU and MMI and treated women should be encouraged to do so.

This review documents that despite wide use of PTU in pregnancy, there is presently an unacceptable void in knowledge of its fetal safety, a gap that should not be difficult to close with so many pregnant women using this drug.

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TABLE 1

Complications of Thyrotoxicosis

- Preterm labor
- Hyper emesis gravidarum
- Pregnancy-induced hypertension
- Thyroid crisis
- IUGR
- Neonatal thyrotoxicosis with goiter
- Neonatal hypothyroidism

Typical: aggravation in 1st trimester, improvement in 2nd, recurrence within 1 yr postpartum.