

## COMMENTARY

# The Use of Antithyroid Drugs in Pregnancy and Lactation

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### Antithyroid Drug (ATD) Therapy of Hyperthyroidism in Pregnancy

The management of hyperthyroidism in the pregnant woman has been the topic of several recent reviews (1–6) and case series (7–8). These papers have discussed maternal-fetal thyroid relationships, the epidemiology of maternal hyperthyroidism, causes of gestational thyrotoxicosis, the clinical and laboratory diagnosis of hyperthyroidism in pregnancy, therapy with ATDs, surgery,  $\beta$  adrenergic blocking drugs, and iodides, as well as the consequences of inadvertent radioiodine therapy and the implications of breast feeding. The purpose of this discussion is to provide an in depth examination of the use of ATDs in the pregnant hyperthyroid woman, rather than to present comprehensive guidelines for the treatment of hyperthyroidism during pregnancy furnished in other reviews (1–6). The subject continues to engender controversy because of the lack of prospective clinical trials and the relative rarity of the condition, occurring in only 1 of 1000–2000 pregnancies (7, 8). With more women receiving radioiodine before conception, the frequency may be even lower in the future.

#### Risks of untreated hyperthyroidism

When one discusses the risks and benefits of ATD therapy in the management of the hyperthyroid pregnant women, the risks to the mother and fetus of untreated hyperthyroidism must also be considered. These risks appear to be directly related to the control or, more likely, the severity of the maternal hyperthyroidism. In a 1989 retrospective analysis of 181 hyperthyroid pregnant women (8), the subjects were separated into 3 groups: women who were euthyroid at presentation and remained that way (group 1,  $n = 34$ ), women who were hyperthyroid at presentation but who were controlled during the pregnancy (group 2,  $n = 90$ ), and women whose hyperthyroidism was not controlled (group 3,  $n = 57$ ). The odds ratio (OR) for low birth weight ( $<2500$  g)

infants was not elevated in group 1 compared with normal control women. Group 2 women had an OR for low birth weight infants of 2.4 [95% confidence interval (CI) 1.4–4.1], and the OR was 9.2 (95% CI 5.5–16) in group 3 women. Similarly, prematurity was more common in groups 2 and 3 [OR in group 2, 2.8 (CI 0.33–23.5); OR in group 3, 16.5 (CI 2.1–130)] compared with group 1. Eclampsia was also more common in group 3 women (OR 4.7, CI 1.1–19.7). In this study there was no increase in the frequency of infants who were small for gestational age, although Mitsuda *et al.* (9) found a higher frequency of small-for-gestational-age infants in women who were thyrotoxic for more than 30 weeks during the pregnancy (26.7% *vs.* 7.7% among women who were euthyroid throughout pregnancy). Davis, *et al.* (7) found that 50% (4 of 8) of the infants born to untreated hyperthyroid women were stillborn *vs.* no stillbirths in the 36 treated euthyroid women. Also, 62% (5 of 8) of untreated hyperthyroid women had congestive heart failure *vs.* 3% (1 of 36) of treated euthyroid women. Interestingly, another study found that the altered hemodynamics seen in pregnant hyperthyroid women with congestive heart failure improved but did not normalize with restoration of a euthyroid state (10). This may be one explanation for the development of preeclampsia even in women whose hyperthyroidism is controlled during pregnancy (8).

It is uncertain whether untreated Graves' disease is associated with a higher frequency of congenital abnormalities. Mitsuda *et al.* (9) described congenital abnormalities in 6 of 230 (2.6%) infants born to mothers with Graves' disease (3 with ventricular septal defect, 1 with cleft lip and palate, 1 with polydactyly, and 1 with diastasis recti abdominis). This rate was similar to the malformation rate in normal pregnancies, but it is not specified whether the mothers' hyperthyroidism was controlled or not. In another report from Japan examining the relationship of fetal malformations to thyroid status in the first trimester (11), the rate of fetal malformations was 6% (3 of 50; imperforate anus, anencephaly, and cleft lip: 1 each) in untreated hyperthyroid women, 1.7% (2 of 117; ear lobe malformation and omphalocele) in treated hyperthyroid women, and 0% (0 of 126) in treated euthyroid women. In a report from the U.S. (12), the overall rate of fetal malformations was 3% (6 of 185): 3 of 99 (3%) of babies were born to women who were hyperthyroid during

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the first trimester (pulmonic stenosis, ventricular septal defect, patent ductus arteriosus: 1 each), and 3 of 96 (3%) born to women who were euthyroid in the first trimester (inguinal hernia in 2, hydrocephalus in 1). These data suggest that there may be a small increase in the rate of congenital anomalies in women with untreated or incompletely treated hyperthyroidism in the first trimester, but more information is clearly needed.

#### *Thionamide drug therapy of hyperthyroidism*

ATD therapy is obviously indicated for hyperthyroidism when it is moderate or severe. Although there is no generally accepted definition of moderate or severe hyperthyroidism, it would be reasonable to treat women whose free  $T_4$  levels are more than 2.5 ng/dL if the upper limit of normal is 2.0 ng/mL. However, for an asymptomatic woman whose pregnancy is progressing satisfactorily and whose serum free  $T_4$  is minimally above 2.5 ng/dL, careful clinical follow-up without antithyroid therapy may be appropriate. It should be noted that all prior studies linking hyperthyroidism to adverse pregnancy outcomes have reported a correlation with elevations of maternal thyroid hormone levels rather than the presence or absence of maternal symptomatology. Certainly, in milder cases, when free  $T_4$  and/or free  $T_3$  serum levels are only slightly elevated, it may be appropriate to follow the patient expectantly, given that hyperthyroidism tends to spontaneously improve over the course of the gestation (1–6), and that neonatal hypothyroidism is seen more often if the mother is euthyroid rather than mildly hyperthyroid (see below) (13). It might also be reasonable to measure free  $T_4$  by equilibrium dialysis in borderline cases, because some free  $T_4$  assays may report erroneously high free  $T_4$  levels in situations of increased  $T_4$  binding such as pregnancy (14). Throughout gestation, communication with the patient's obstetrician is important for assessment of the health of the pregnancy, which must be correlated with maternal thyroid status for optimal ATD dose titration.

Both propylthiouracil (PTU) and methimazole (MMI) have been used in pregnancy and are equally effective in the management of hyperthyroidism in this setting (12, 13, 15). In the U.S., PTU has traditionally been preferred because of MMI's purported increased passage across the placenta and breast epithelium, and because of a reported association between MMI use and aplasia cutis as well as other rare anomalies (see below). However, MMI or its precursor carbimazole are used widely throughout the world to treat pregnant women.

#### *Which drug: PTU or MMI?*

*Transplacental passage.* In the only *in vivo* human study to formally examine the possible placental transfer PTU and MMI, 9 pregnant women ingested  $^{35}\text{S}$ -labeled compounds 2 h before the elective termination of pregnancies that ranged in gestational age from 8 to 20 weeks (16). Only seven of the nine women had complete data. For MMI ( $n = 2$ ) or carbimazole ( $n = 3$ ), the ratio of fetal serum or cord blood MMI levels to maternal drug levels ranged from 0.72 to 1, indicating a high rate of drug transfer. For PTU, the ratio ranged from 0.27 to 0.35 ( $n = 2$ ), indicating a substantially lower transfer rate. These investigators also obtained drug transfer data from pregnant rats that supported these observations. The differ-

ences in placental passage were mainly attributed to the known disparity in drug binding to albumin ( $\text{PTU} \gg \text{MMI}$ ) and in lipid solubility, as well as possible differences in maternal/fetal volumes of distribution, excretion, and metabolism of each compound (16).

More recently, a study using isolated perfused human placenta found no difference in the rate or extent of transplacental passage between PTU and MMI (17). Even though PTU is highly protein bound [61% to human serum albumin (17)], transfer rates across the placenta were independent of the perfusate protein concentration, suggesting that there is highly efficient placental extraction of unbound drug. Failure to achieve a steady-state with a single dose of drug was offered as the likely explanation for the differences that were observed between this study and the earlier report by Marchant *et al.* (16). Although it is uncertain whether this *in vitro* model is completely representative of *in vivo* events, a lack of a difference in placental transfer of PTU and MMI is consistent with clinical observations showing similar fetal outcomes with either drug, in terms of thyroid function and congenital anomalies (12, 15), and with data showing that cord blood PTU levels were similar to or higher than simultaneously obtained maternal serum PTU levels (18).

*Possible drug-related congenital anomalies.* Aplasia cutis is a congenital localized absence of skin, typically present as a 0.5–3 cm isolated, punched out, midline lesion at the vertex or occipital area of the scalp (19). The lesions may close spontaneously or skin grafting may be required in more severe cases. It occurs spontaneously in approximately 1 in 2000 births (20), is often familial, and can occur alone or in association with other anomalies. In 1972, Milham and Elledge (21) reported that of 12 cases of aplasia cutis that occurred in Washington state in a 6-month period, 2 mothers had taken MMI. Subsequently, additional cases were reported in association with MMI (20, 22). Although Van Dijke *et al.* presented circumstantial evidence that there may be no association between MMI use and aplasia cutis (20), and Momotani *et al.* (11) found no cases among the offspring of 243 MMI-treated mothers, cases continue to be reported (23–28). Furthermore, Martinez-Frias *et al.* (29) reported a 3-fold increase in the frequency of this anomaly in regions of Spain where there was illegal use of MMI in animal feed as a fattening agent, providing epidemiological evidence for an association.

Perhaps of greater concern than aplasia cutis are recent descriptions of a MMI embryopathy (8 cases), which includes aplasia cutis, choanal atresia, tracheal-esophageal fistulae, hypoplastic nipples, facial anomalies, and psychomotor delay (reviewed in Refs. 30, 31). When considering the significance of all of these reports, it must be emphasized that there are no case reports of aplasia cutis or other congenital anomalies in association with PTU exposure. This is particularly significant because PTU is the preferred drug therapy of hyperthyroidism in pregnancy in the U.S.

The data suggesting that PTU crosses the placenta more easily than previously thought would seem to remove PTU's advantage over MMI in pregnancy. On the other hand, the rare but probable real association between MMI usage and fetal anomalies makes MMI a less attractive first line alternative. All

things being equal, PTU is probably still the first choice for the treatment of hyperthyroidism in pregnancy, although MMI remains a reasonable second-line agent in the case of an allergic reaction, intolerance, or poor response to PTU.

#### Practical considerations

When the diagnosis of moderate to severe hyperthyroidism is made, therapy with 100 mg PTU every 8 h should be initiated. Lower doses should be used in milder cases, because baseline thyroid function is a major factor in the rate of drug response. If the patient has been taking MMI before she becomes pregnant, switching to PTU would be reasonable before a planned conception or if the pregnancy is diagnosed in the first trimester during the period of organogenesis. The patient's thyroid function should be monitored monthly, and the drug dose adjusted to maintain the serum free  $T_4$  at the very upper limit of the normal range or slightly above normal. Indeed, the ATD dose should probably be tapered if the TSH rises into the normal range. On the other hand, if the severe hyperthyroidism persists, there should be no hesitation to increase the dose in an effort to control the hyperthyroidism to the appropriate pregnancy target. Doses in the range of 600–800 mg/day are needed occasionally, possibly related to poor compliance (32) or altered PTU pharmacodynamics in pregnancy; in one study, the pharmacokinetics of PTU in pregnancy appeared to be normal (33), whereas others suggested that peak serum PTU levels and area under the curve were lower during pregnancy compared with levels in the same women when they were postpartum (18) or compared with nonpregnant controls (34). Limited data for MMI in pregnancy also suggest that drug clearance may be more rapid than in nonpregnant women (35). Despite these caveats, Wing *et al.* (12) found that the median maximal and minimum doses of PTU (450 mg and 100 mg daily, respectively) and MMI (40 mg and 10 mg daily, respectively), were similar to what might be required in nonpregnant patients. However, if the requirement for high doses of PTU or MMI persists during pregnancy, thyroidectomy may be warranted (1–6).

As thyroid function improves, the dose of PTU may be gradually tapered, and when it is in the range of 50–100 mg daily, it is often possible to discontinue the drug altogether. As alluded to above, and as proposed by Daniels (2) low doses of ATDs should be discontinued if serum TSH levels become normal (2), given the relationship between maternal and fetal thyroid function noted above. In one retrospective report of 30 PTU-treated women, 10 were able to discontinue it before the end of pregnancy (36).

#### Theoretical considerations

It is clear that overzealous treatment of maternal hyperthyroidism can lead to fetal hypothyroidism (37) and goiter (38, 39), although most cases of hypothyroidism are really transient episodes of subclinical hypothyroidism, with mild hyperthyrotropinemia and normal serum free  $T_4$  and  $T_3$  levels (13, 15, 40). Momotani *et al.* (13, 15) have reported the most extensive data documenting the relationship between maternal and neonatal thyroid function. In one report (13), no cases of neonatal hypothyroxinemia or elevated serum TSH

were seen in the offspring of treated women whose serum free  $T_4$  levels remained elevated. There was a strong relationship between maternal and fetal thyroid function, illustrated by rates of transient neonatal hypothyroxinemia of 10, 36, and 100% when the mother's free  $T_4$  was maintained in the upper one third of the normal range, the lower two thirds of the normal range, or below the normal range, respectively. Importantly, there were no differences in cord blood free  $T_4$  and TSH in infants exposed to PTU ( $n = 34$ ) vs. MMI ( $n = 43$ ), and there was no relationship between the dose of either ATD and neonatal thyroid function. This latter observation and the close relationship between maternal and fetal thyroid function might be explained by the possibility that fetal thyroid function may be under the influence of maternal thyroid stimulating immunoglobulins, as suggested by Mortimer *et al.* (41) and by Momotani *et al.* (13, 15). This may also provide a rationale for using higher ATD doses to control maternal thyroid function, if need be, rather than fail to control the disease for fear of inducing fetal hypothyroidism.

On the other hand, data from Haddow *et al.* (42) suggest that even mild maternal hypothyroidism may have an impact on the subsequent intellectual capacity of the infant, which is potentially reversible with thyroxine therapy. However, it does not appear that any of the women in the study by Haddow *et al.* (42) were hypothyroid because of ATD usage during pregnancy. Follow-up data from infants exposed to either PTU or MMI *in utero* have not revealed any differences in intelligence quotient (IQ) when compared with age-matched controls (43) or unexposed siblings (44), but since maternal thyroid function during the index pregnancy is not reported in these studies, it is difficult to know whether any of the children were born to mothers who were hypothyroid during gestation.

Is there a role for combined thyroxine and ATD therapy to prevent maternal hypothyroidism or fetal complications of maternal ATD exposure? In a metaanalysis of the literature (45), the frequency of neonatal goiter was lower when women received combined therapy (1/165 or 0.6%) than when they received ATDs alone (18/417 or 4.3%). In another report (40), there were no differences in cord blood  $T_4$ ,  $T_3$ , or TSH in neonates born to mothers ( $n = 7$ ) who had been treated with combined PTU and thyroid hormone (liotrix)(mean PTU dose 129 mg/day) or PTU alone ( $n = 4$ )(mean PTU dose 150 mg/day). This small study showed that combined therapy does not necessarily prevent neonatal hypothyroxinemia, but also showed that PTU doses are not necessarily higher when adjunctive thyroid hormone therapy is used.

ATD and thyroxine therapy in pregnancy is currently anathema because it could lead to inadvertent overdosing of ATDs (6). However, this notion might need reassessment if it could be shown that maternal hypothyroidism, a strong predictor of fetal hypothyroxinemia (13), could be prevented. In one report for example, 32% of women treated with ATDs alone became hypothyroid at some point during their pregnancy (cited in Ref. 45); in another report, the frequency of hypothyroidism defined by a low free  $T_4$  at term was 25% (13). In women with either overt hyperthyroidism or such mild disease that ATDs could be discontinued, adding thyroxine to their ATD therapy would not be sensible. However,

in women who require drug doses above the minimum (e.g. more than 150–200 mg/day for PTU or more than 10–15 mg/day for MMI), the addition of thyroxine to prevent hypothyroidism has some theoretical appeal, especially in the first trimester. However, only prospective studies with long-term follow up data would be able to address this question.

### ATD Therapy of Hyperthyroidism during Lactation

The question of the safety of lactation during ATD therapy arises in several clinical situations. The activity of Graves' disease fluctuates through pregnancy, with improvement in the third trimester and subsequent reduction or discontinuation of ATD therapy, only to be followed by worsening of the disease in the postpartum period with resumption of ATD therapy. Some women with Graves' disease may require continuous ATD therapy until delivery and would like to begin nursing immediately. Others may have previously stopped ATD therapy late in pregnancy and are currently nursing, but subsequently experience an exacerbation of hyperthyroidism requiring ATD initiation; however, they wish to continue breast-feeding. In addition, Graves' disease may first occur in the postpartum period, either as the initial manifestation of hyperthyroidism or following postpartum thyroiditis (46). Again, if such women are currently nursing, they often desire to continue even if ATD therapy is required.

In the past, women taking ATD therapy have been advised against breast-feeding because of the presumption that the concentrations of these drugs in breast milk were sufficient to affect the infant's thyroid. This recommendation derives from studies of thiouracil, one of the first thiourea compounds used for treatment of thyrotoxicosis. In 1944, Williams *et al.* (47) reported that the thiouracil concentration in breast milk was 3 times higher than that in serum 2 h after oral administration of 1 g thiouracil to two lactating women. Although thiouracil treatment of hyperthyroidism was soon discontinued for other reasons, no studies of the currently used ATD drugs were published until 20 yr ago.

#### ATD pharmacokinetics during lactation

In 1980, Kampmann *et al.* published a report, with the auspicious title "Propylthiouracil in Human Milk: Revision of a Dogma," documenting that PTU was not concentrated significantly in breast milk. Nine women (seven without thyroid disease and two with Graves' disease, already treated with PTU) were given 200 mg PTU, and the serum and milk PTU concentrations were measured for 4 h. The mean total amount of PTU excreted in breast milk over that period was 0.025% (range 0.007–0.077%) of the administered dose, with the milk concentration being only approximately 10% of simultaneously collected serum concentrations (48), in agreement with an earlier study (49). Using these data, the authors calculated that a lactating mother treated with 200 mg PTU three times a day would transmit 149  $\mu\text{g}$  of PTU a day to her infant, which for a 4-kg infant, is equivalent to a daily dose of 3 mg for a 70-kg adult (48).

Subsequent studies on the transfer of MMI or cabimazole (CM) into milk have shown that a higher proportion of an orally administered dose of these drugs to the mother appears in the milk. The mean milk to serum ratio of MMI

concentration is 1.0 (50–52) with a mean excretion in breast milk over an 8-h period equal to 0.1–0.17% of an orally administered dose (51, 52). This is four to seven times higher than that for PTU. After a single 40-mg MMI dose to the mother, an infant may potentially receive 70  $\mu\text{g}$ , which for a 4-kg infant is equivalent to 1.2 mg for a 70-kg adult (51). Due to the higher potency of MMI, this dose could theoretically affect the infant's thyroid. However, in general, these early studies were performed by administration of a single dose of MMI to lactating women who did not have thyroid disease and, therefore, were not in a steady-state. A very recent study measured serum MMI levels in infants who were breast-fed by thyrotoxic mothers receiving 20–30 mg of MMI daily. Serum MMI levels in the babies were less than 0.03  $\mu\text{g}/\text{mL}$  2 h after the mother ingested the dose (53), far below the therapeutic range (52).

From a pharmacokinetic view, higher passage of MMI or CM *vs.* PTU into breast milk could be anticipated from the properties of the drugs. MMI is minimally bound to serum proteins, whereas PTU is more extensively protein-bound in serum, mostly to albumin (54). In addition, MMI is not ionized in serum (pH 7.4) whereas PTU, a weak acid, is more ionized in serum (pH 7.4) than in the more acidic breast milk (pH 6.8). This would inhibit its transfer from serum into the lipid-rich breast milk (48).

Based upon the data available in the early 1980s, several authors (49, 50, 52) recommended that if a woman chose to breast-feed, PTU rather than MMI or CM should be used. However, these early studies simply addressed passage of ATD in breast milk, but did not assure the safety of breast-feeding during ATD therapy. As noted by one author, "Because breast-feeding is important both from a physiological as well as a psychological view point it seems important to study thyroid function of newborn infants during lactation when mothers are given antithyroid treatment for hyperthyroidism" (55).

#### Clinical studies

Over the last 2 decades, several such studies have been published, which include almost 200 infants of thyrotoxic lactating mothers taking PTU, MMI, or CM (Table 1; Refs. 48, 53, 55–58). The methodologies of these reports vary, with some having a rigorous schedule of thyroid function testing of the infant and others, a more variable surveillance. In addition, other factors independent of maternal ATD dosage may influence thyroid function of the infant. The most important of these is the transplacental passage of maternal immunoglobulins that can stimulate the infant's thyroid in the early weeks of life (58).

There are several conclusions that can be drawn from a review of the studies in Table 1. First, maternal use of either MMI (doses up to 20 mg/day) or PTU (up to 600–750 mg/day) during lactation does not affect the infant's thyroid hormone levels significantly. The only three reported infants who had distinctly high serum TSH concentrations or low serum  $T_4$  levels were tested during the first week of life and were born to mothers who had been treated with PTU during gestation and continued therapy postpartum (55, 58). In fact, at delivery, two of these infants had even more suppression of thyroid function, as evidenced by lower levels of  $T_4$  and

**TABLE 1.** Studies of Thyroid Function (TFT) and development of infants of thyrotoxic lactating mothers treated with ATD

	Number of infants	Maternal ADT dose	Study duration	Schedule of infants' TFT testing	Infants' outcomes
Kampmann (48)	1	PTU 200–300 mg q.d. Started during pregnancy	5 months	Not provided	Normal TFTs
Lamberg (55)	13 (1 set of twins)	11 women: CM 5–15 mg q.d. 1 woman: PTU 25 mg q.d. Started during pregnancy	3 weeks	4, 7, 14, and 21 days of life	Normal TFTs in 12; 1 infant (PTU) had decreased, T <sub>4</sub> at 4 days and normal T <sub>4</sub> at 21 days
Momotani (1989, Ref. 56)	8	PTU 50–300 mg q.d. Started during pregnancy	3 weeks to 8 months	Tested only 1 time postpartum, not standardized	Normal TFTs
Azizi (1995, Ref. 57) <sup>a</sup>	12	MMI 5 mg q.d. Started during pregnancy	1 month	Once after 1 month	Normal TFTs
	17	MMI 10 mg q.d. Started 2–8 months postpartum when hyperthyroidism developed*	1 month	Baseline and after 1 month	Normal TFTs (including infant of 1 mother with TSH 24 mU/L)
	6	MMI 20 mg q.d. for 1 month; 10 mg q.d. for 1 month; 5 mg q.d. for 4 months Started 2–8 months postpartum when hyperthyroidism developed	6 months	Baseline, 2 weeks, and 1, 2, 4, and 6 months	Normal TFTs (including infant of 1 mother with TSH 102 mU/L)
Momotani (2000, Ref. 58)	11	PTU 300–750 mg q.d. 2 women started during pregnancy; 11 started 1–6 months postpartum when hyperthyroidism developed	3.5–9 months	Variable	Normal TFTs in 8; 2 had high TSH within 1 week postpartum, which then became normal
Azizi (2000, Ref. 53)	51	5 mg q.d. Started during pregnancy	6 months	Monthly	Normal TFTs
	88	10–20 mg q.d. for 1 month; 10 mg q.d. for 1 month; 5–10 mg q.d. for 10 months Started 2–8 months postpartum when hyperthyroidism developed	12 months	Baseline, 1, 2, 4, 8, and 12 months	Normal TFTs (including 6 infants whose mothers had TSH levels 19–102 mU/L); Normal IQ scores and physical growth in 14 tested children

TFT, Thyroid function test.

<sup>a</sup> This study has been extended to a larger group of children (53).

higher TSH values in cord blood. However, thyroid function returned to normal within the first month after birth, despite the continuation of maternal ATD during lactation (55, 58). Therefore, this transient suppression of neonatal thyroid function most likely represented the time required for clearance of PTU received via transplacental passage, rather than by transmission through breast milk. In addition, even if the mother becomes hypothyroid presumably because of ATD overtreatment, the thyroid function of the breast-fed infant remains normal as demonstrated by Azizi *et al.* (53, 57). These authors reported six women taking MMI (10 mg daily, 1 woman; 20 mg daily, 5 women) who developed elevated serum TSH levels (19–102 mU/L) and decreased serum T<sub>4</sub> levels (3–32 nmol/L) 1 month after treatment; the infants' corresponding serum TSH (1.0–2.6 mU/L) and T<sub>4</sub> (138–154 nmol/L) levels were normal.

Second, the intellectual and somatic development of children whose mothers received MMI while breast-feeding has been studied, although no such reports have been published for PTU. Using the Wechsler Preschool and Primary School of Intelligence and Goodendough tests, Azizi *et al.* (53) measured verbal and performance IQ scores and their respective subscales in 14 children of thyrotoxic mothers and 17 controls between the ages of 48–74 months. The IQ scores and phys-

ical growth did not differ between the two groups (53). Although Azizi has recently extended these studies to a larger group of 34 children whose mothers received MMI during lactation and found no difference in somatic or intellectual growth (53). This still represents a small sample size that may be insufficient to exclude type II error. However, given the normal thyroid function in these infants, it seems reasonable to infer that their thyroid hormone levels were sufficient for normal postnatal brain development.

Finally, potential allergic effects associated with ATD therapy, such as rash, agranulocytosis, hepatic dysfunction, and autoimmune sequelae, have not been reported in infants who breast-fed while their mothers were treated with ATD. However, because most of these adverse reactions are rare (except rash), and the number of reported children is only approximately 200, a potentially serious reaction remains a possibility.

In summary, maternal ATD use during lactation appears to be safe, whether it is continued after gestation or initiated in the postpartum period. For MMI, doses of up to 20 mg daily have been documented not to affect infants' thyroid function (53, 57). For PTU, the number of reported infants is smaller and thyroid function was followed in only three infants whose mothers were taking high doses (750 mg daily, 1 woman; and 600 mg daily, 2 women) (58). Therefore, to be

prudent, PTU doses used during lactation should be 450 mg or less. A mother should take her ATD dose just after breastfeeding, which should provide a 3–4 h interval before she lactates again. Although maternal thyroid hormone levels must be monitored with appropriate ATD adjustment, it appears that the child's thyroid function does not need to be checked regularly as long as somatic and mental development are progressing normally.

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