

Thyroid Function and Intellectual Development of Infants Nursed by Mothers Taking Methimazole

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ABSTRACT

For many years, breast-feeding was forbidden if antithyroid drugs were being used. Recently, limited studies have shown the relative safety of propylthiouracil and methimazole (MMI). It is not known whether MMI therapy of lactating mothers for 1 yr is safe for breast-fed infants and does not cause alterations in thyroid function and intellectual development. Between 1988 and 1998, 139 thyrotoxic lactating mothers and their infants were studied. Fifty-one thyrotoxic lactating mothers were treated with MMI during pregnancy, and MMI was continued during breast-feeding. Eighty-eight mothers were given 10 mg MMI (n = 46) or 20 mg MMI (n = 42) daily for 1 month, 10 mg daily for the second month, and 5–10 mg daily thereafter. Serum T₄, T₃, and TSH concentrations were measured in thyrotoxic lactating mothers and their infants, before and at 1, 2, 4, 8, and 12 months. Serum MMI was measured in the infants of thyrotoxic lactating mothers taking 20 mg MMI. Thyroid function, urinary iodine, thyroid antibodies, intelligence quotient (IQ), verbal and functional components (Wechsler and Goodenough tests) were performed on 14 children of thyrotoxic lactating mothers between 48 and 74 months of age and on 17 controls.

Mean ± SD of FT4I in thyrotoxic lactating mothers treated with 10 mg MMI for 1 month decreased from 19.4 ± 4.1 to 11.6 ± 4.4 and from

20.5 ± 4.7 to 9.8 ± 1.5 when treated with 20 mg MMI. Values for FT3I decreased from 462 ± 52 to 194 ± 52 with 10 mg MMI and from 481 ± 92 to 171 ± 38 with 20 mg MMI. FT4I and FT3I were normal from the third to the twelfth months. In all infants FT4I, FT3I, and TSH concentrations were normal before and up to 12 months of MMI therapy in their lactating mothers. The lowest T₄ and T₃ values were 108 and 1.87 nmol/L, and the highest TSH value was 4.0 mU/L. Serum MMI levels in infants were less than 0.03 µg/mL. Six mothers receiving 20 mg MMI had increased serum TSH concentrations ranging from 26–135 mU/L after 1 month of treatment. Their infants were euthyroid with serum TSH values less than 2.6 mU/L. At 48–74 months of age, height, weight, FT4I, FT3I, TSH, and antithyroid antibody titers were not different than controls. The mean IQ was 107 ± 14 vs. 106 ± 16 (Goodenough test) and 103 ± 10 vs. 103 ± 16 (Wechsler test) for infants of thyrotoxic lactating mothers and control infants, respectively. Similarly, there was no difference in verbal and performance IQ and their components between infants of thyrotoxic lactating mothers and control children.

No deleterious effects occur in thyroid function and physical and intellectual development of breast-fed infants whose lactating mothers were treated with doses of MMI up to 20 mg daily. (*J Clin Endocrinol Metab* 85: 3233–3238, 2000)

THIONAMIDE DRUGS are the mainstay of treatment for thyrotoxicosis during pregnancy; however, the use of these agents during breast-feeding is controversial. For many years breast-feeding was forbidden if antithyroid drugs were being used (1). It has been well established that both methimazole (MMI) and propylthiouracil are transferred into the breast milk (2–4). Recent studies have shown that propylthiouracil crosses into the milk only in small amounts (2, 5). Therefore, lactating women with Graves' disease who are receiving propylthiouracil have been advised that breast-feeding their infants is safe (5–8). The situation with MMI is less clear, however, because this drug is transferred into breast milk—extremely well (3, 4, 9). There are two clinical studies and one case report (10) on the safety of breast-feeding for infants whose mothers were treated with modest doses of carbimazole (11) or MMI (12). However, the doses used were small, and only six patients with an initial daily dosage of 20 mg MMI were included (12). Furthermore, long-term follow-up of infants was not done. We, therefore, undertook the present study to evaluate the long-term effect of MMI therapy of mothers with hyperthyroidism on thyroid

function of their breast-fed infants and their subsequent physical and intellectual outcome during preschool years.

Subjects and Methods

The study was performed between April 1988 and March 1998 in Tehran, Iran. We began this research by evaluating women with thyrotoxicosis who received MMI therapy during pregnancy and were permitted to breast-feed exclusively after delivery while receiving 5 mg MMI daily. The safety of this dose of MMI on breast-fed infants was determined. Women who developed thyrotoxicosis during the postpartum period were given 10 mg MMI daily and continued breast-feeding. The safety of breast-feeding was demonstrated, and the initial dose of MMI was increased to 20 mg per day.

Selection of lactating mothers with thyrotoxicosis and control subjects

One hundred thirty-nine thyrotoxic lactating mothers and their infants were studied. Fifty-one thyrotoxic lactating mothers were treated with 5–20 mg MMI during pregnancy and were allowed to continue taking 5 mg MMI during breast-feeding. Eighty-eight thyrotoxic lactating mothers were diagnosed as hyperthyroid within 2–8 months of delivery (24% from 3–4 and 76% from 5–8 months postpartum). Twenty-seven thyrotoxic lactating mothers (31%) had a history of thyrotoxicosis before pregnancy. All had overt symptoms and signs of thyrotoxicosis including weakness, fatigue, weight loss, nervousness, tachycardia, hyperactivity, diffuse goiter, warm and moist skin, stare, lid lag, and tremor. We excluded cases with mild symptoms and signs of thyrotoxicosis and those with T₃/T₄ ratio less than 20 ng/µg or a sedimentation rate of over 30 mm/h. However, we did not perform thyroid RAI uptake

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measurements because all mothers were breast-feeding. Therefore, definitive distinction between Graves' hyperthyroidism and destructive thyrotoxicosis could not be made. We identified 38 normal breast-fed infants, 2–8 months of age, whose mothers were euthyroid, without acute or chronic illnesses, who had attended health maintenance clinics; blood samples had been ordered by pediatricians for different reasons not related to thyroid disease.

For evaluation of physical and neuropsychological development, we recruited 14 children of thyrotoxic lactating mothers and 17 controls between the age of 48 and 74 months. To counter the effect of parental education and socioeconomic status, the control group consisted of children with parental education and socioeconomic levels close to children of thyrotoxic lactating mothers. Using the two-factor index of social position scores of Hollingshead (13), the computed scores were 28 ± 6 and 29 ± 5 (not significant) for parents of case and control groups, respectively.

Study procedures

Fifty-one women who were treated with MMI during pregnancy were allowed to continue breast-feeding, and their infants were evaluated monthly until 6 months after delivery. MMI therapy was continued until 12 months after delivery in all but one mother, and the average number of lactating months per infant while a mother was taking MMI was 11 months in this group. Of 88 thyrotoxic lactating mothers who were first diagnosed and treated after delivery, 46 mothers received 5 mg MMI twice a day during the first 2 months, and 42 mothers were given 10 mg MMI twice a day during the first month and 5 mg twice daily during the second month of therapy. All 88 mothers received a maintenance dose of 5–10 mg MMI from the third until the twelfth months after initiation of therapy. Mothers were allowed to continue breast-feeding, with supplements given to infants older than 6 months of age. The average number of lactating months per infant while a mother was taking MMI was 13 months in this group. Mothers and their infants were evaluated before and at 1, 2, 4, 8, and 12 months after initiation of MMI therapy. At each visit, symptoms of hyper- or hypothyroidism were sought and both mother and infant were examined and blood samples collected for thyroid function tests. In six infants 5–6 months of age, blood samples for MMI measurement were obtained 2 h after breast-feeding. Mothers were on 10 mg MMI twice a day and instructed to take 10 mg 2 h before breast-feeding.

Fourteen children of thyrotoxic lactating mothers and 17 controls were recruited at 48–74 months of age. Histories and physical examinations were performed, and height and weight were recorded. Blood and urine samples were collected for thyroid function tests and urinary iodine measurement, respectively. The intelligence quotient (IQ) was evaluated by Wechsler Preschool and Primary School of Intelligence (WPPSI) and Goodenough tests (14, 15). WPPSI provides a full-scale score, a verbal score, and a performance score, and scores on 11 subtests. IQ tests were performed by the same psychologist, to minimize subjective interpretation of the tests. The psychologist did not know whether the children were from thyrotoxic lactating mothers treated with MMI or control children.

The study was approved by the appropriate human research review committee, and informed consent was obtained from the parents of each child.

Assay methods

Serum T_4 and T_3 were measured by RIA, and serum TSH by IRMA. T_3 -resin uptake was measured, and FT4 and FT3 indices were calculated

(16). All kits were Spectria, obtained from Orion Diagnostica (Finland). We measured antithyroid peroxidase (TPO) and antithyroglobulin (Tg) antibodies by immunoenzymometric assay (Radium, Italy). The urinary iodine level was measured by a digestion method (17). Serum MMI concentration was determined using high-performance liquid chromatography with electrochemical detection (18). The sensitivity of the MMI assay was $0.03 \mu\text{g/mL}$ (263 nmol/L).

Reference ranges of serum parameters for euthyroid adult subjects are: T_4 , 58–167 nmol/L; T_3 , 1.2–3.1 nmol/L; TSH, < 0.1–5.0 mU/L; FT4I, 4.5–12.5; FT3I, 70–200; anti-TPO, < 100 IU/mL; anti-Tg, < 100 IU/mL.

Statistical analysis

Geometric means and SD are used to summarize the results. We compared continuous variables using the unpaired and paired Student's *t* tests and Z test.

Results

Breast-feeding period

The infants of 51 mothers with thyrotoxicosis during pregnancy who were maintained on 5 mg MMI daily had normal serum T_4 , T_3 , and TSH concentrations from 1–6 months postpartum.

Table 1 demonstrates the FT4I and FT3I values before and after MMI therapy in 46 thyrotoxic lactating mothers first treated after delivery with 10 mg MMI daily and their infants. After 1 month of therapy, 29 of 46 (63%) had a normal FT4I, one had a low FT4I and an increased TSH, and 16 had an elevated FT4I. Mean FT4I decreased from 19.4 ± 4.1 to 11.4 ± 6.4 ($P < 0.001$). Two months after treatment with 10 mg MMI daily, only two thyrotoxic lactating mothers had FT4I values above the normal range and the mean of the FT4I had decreased to 8.7 ± 2.6 . The mean FT3I decreased from 642 ± 58 to 194 ± 52 in the first month and to 167 ± 29 in the second month of therapy ($P < 0.001$). Twenty-one (46%) and six (13%) thyrotoxic lactating mothers had elevated FT3I at 1 and 2 months of MMI treatment, respectively. All thyrotoxic lactating mothers had normal FT4I and FT3I from the third month up to the twelfth month after initiation of therapy. In the infants, serum T_4 , T_3 , and TSH concentrations before and 1 month after MMI administration to their mothers were all within the normal range and did not change significantly over the following month of observation: T_4 , 157 ± 33 vs. 154 ± 24 nmol/L; T_3 , 3.04 ± 0.29 vs. 2.96 ± 0.25 nmol/L; and TSH 1.6 ± 0.7 vs. 1.5 ± 0.8 mU/L, before and after MMI treatment, respectively (Fig. 1). The lowest serum T_4 and T_3 concentrations in the MMI group were 122 and 1.83 nmol/L, respectively, and the highest TSH concentration was 3.6 mU/L.

In 42 thyrotoxic lactating mothers first treated after delivery who received 20 mg MMI daily, the mean serum FT4I and

TABLE 1. Free thyroid indices before and after MMI treatment in thyrotoxic lactating mothers, first treated 2–8 months after delivery

Initial MMI dose (mg/day) ^a	Thyroid index	Before	MMI treatment (months)				
			1	2	4	8	12
10 (n = 46)	FT4I	19.4 ± 4.1^b	11.4 ± 6.4	8.7 ± 2.6	8.5 ± 2.8	8.4 ± 2.7	8.2 ± 2.2
	FT3I	642 ± 58	194 ± 52	167 ± 29	158 ± 30	153 ± 27	154 ± 29
20 (n = 42)	FT4I	20.5 ± 4.7	9.8 ± 1.5	8.3 ± 2.4	8.4 ± 2.9	8.5 ± 2.5	8.3 ± 2.6
	FT3I	451 ± 42	171 ± 38	152 ± 26	154 ± 31	156 ± 23	153 ± 25

^a MMI dose: first month, 10 or 20 mg; second month, 10 mg both groups; third to 12th month, 5–10 mg.

^b All values are mean \pm SD; values for both FT4I and FT3I were significantly decreased from 1 to 12 months after treatment, as compared with initial values, $P < 0.001$.

FT3I decreased significantly after 1 month of therapy: FT4I, 20.5 ± 4.7 vs. 9.8 ± 1.5 ($P < 0.001$); and FT3I, 451 ± 92 vs. 171 ± 38 ($P < 0.001$), before and after MMI treatment, respectively (Table 1). By the end of the first month of therapy, seven patients had abnormal thyroid function tests: in one patient the serum T_4 was 174 and T_3 was 3.99 nmol/L; and in one patient the serum T_4 was normal and the serum T_3 elevated to 3.76 nmol/L; and five thyrotoxic lactating mothers had increased serum TSH and decreased FT4I (Table 2). The dose of MMI was appropriately adjusted and the serum FT4I, FT3I, and TSH concentrations remained within the normal range in all thyrotoxic lactating mothers until 1 yr after the onset of MMI treatment. Serum T_4 , T_3 , and TSH concentrations in 42 breast-fed infants 1 month after maternal MMI therapy with 20 mg daily were all within normal limits. The values were: T_4 , 152 ± 19 and 148 ± 24 nmol/L; T_3 , 3.11 ± 0.29 and 3.04 ± 0.32 nmol/L; and TSH, 1.8 ± 1.4 and 2.4 ± 1.9 mU/L, before and after MMI therapy of their mothers, respectively (Fig. 1). The lowest serum T_4 , T_3 , and the highest TSH concentrations in this group were 108 nmol/L, 1.87 nmol/L, and 4.0 mU/L, respectively. The serum MMI level in all six infants was less than $0.03 \mu\text{g}/\text{mL}$ ($293 \text{ nmol}/\text{L}$), 2 h after they were breast-fed.

The T_4 , T_3 , and TSH serum concentrations in 88 infants of thyrotoxic lactating mothers who were first treated after delivery, 1 month after MMI therapy of their mothers, compared with values in the control infants (T_4 , 154 ± 30 , and T_3 , 3.09 ± 0.31 nmol/L; and TSH, 1.3 ± 1.0 mU/L), were not significantly different, and all values remained within the normal range in the children of thyrotoxic lactating mothers during 1 yr of MMI therapy.

Six thyrotoxic lactating mothers had low serum T_4 and high serum TSH concentrations 1 month after MMI therapy (five receiving 20 mg and one receiving 10 mg daily). Only two mothers complained of weight gain and weakness. Serum T_4 , T_3 , and TSH concentrations in all six infants were in the normal range (Table 2). All six mothers required MMI at reduced doses until the end of 12 months of therapy.

Two mothers continued 20 mg/day MMI for 2 months. The serum T_4 , T_3 , and TSH serum concentrations in their

infants were 9.8 and $10 \mu\text{g}/\text{dL}$, 200 and 230 ng/dL, and 2.8 and 3.2 mU/L, respectively.

Psychological testing in the children

There was no significant difference in age, sex, height, weight, serum T_4 , T_3 , and TSH and urinary iodine concentrations and anti-Tg and anti-TPO titers between 14 children of thyrotoxic lactating mothers and 17 control children. Individual values for all children were within the normal range (only one child in the control group had an elevated anti-TPO level of 150 IU/mL). Information concerning parental education, socioeconomic status, number of siblings, and number of hours spent for sports and outdoor activities were similar in both groups.

Table 3 shows the results of IQ scores with Goodenough and Wechsler tests. There were no significant differences in full-scale, verbal, and performance IQ scores between children of thyrotoxic lactating mothers and those from the control group. Subscales of verbal and performance IQ scores are shown in Fig. 2. Scores in all subsets of verbal IQ (information, vocabulary, mathematics, similarities, comprehension, and sentences) and performance IQ (animal house, picture completion, mazes, geometric design, and block design) were similar in both groups of children.

There was no difference in IQ between the children of thyrotoxic lactating mothers who began MMI treatment during pregnancy and those whose mothers began MMI during the postpartum period. There was no statistically significant correlation between the IQ score in the children and the initial daily dose of MMI in their mothers during the breast-feeding period.

Discussion

The current study demonstrates that treatment of hyperthyroidism with a daily dose of 5–20 mg MMI in lactating mothers does not alter the thyroid function of their breast-fed infants. In addition, we have shown that children whose thyrotoxic lactating mothers were treated with MMI while breast-feeding them had physical and mental development

FIG. 1. Serum T_4 , T_3 , and TSH concentrations in 46 breast-fed infants of treated with an initial dose of 10 mg MMI daily (----) and 42 breast-fed infants of mothers treated with an initial dose of 20 mg MMI daily (—). The dose of MMI was 5–10 mg after the first month and continued until the end of the first year of treatment. Values for both groups of infants were in the normal range up to 12 months after treatment of their mothers.

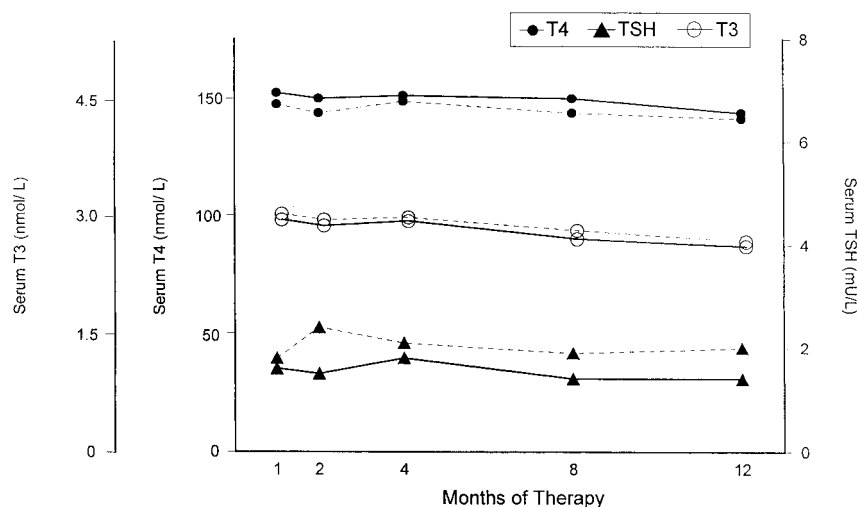


TABLE 2. Serum T₄, T₃, and TSH concentrations 1 month after MMI therapy in six thyrotoxic lactating mothers, who became hypothyroid, and in their infants

Case no.	MMI dose (mg/day)	Mother			Infant		
		T ₄ (nmol/L)	T ₃ (nmol/L)	TSH (mU/L)	T ₄ (nmol/L)	T ₃ (nmol/L)	TSH (mU/L)
1	10	32	1.69	24	138	3.15	2.2
2	20	24	2.30	19	136	3.23	1.0
3	20	58	1.84	42	153	3.00	1.8
4	20	41	2.23	68	149	3.15	1.9
5	20	13	1.08	100	154	3.84	1.7
6	20	3	2.46	102	142	3.07	2.6

TABLE 3. Comparison of the mean (\pm SD) values for Goodenough and Wechsler IQ scores in children 48–74 months of age, breast-fed while their mothers were taking MMI and in the control group

IQ test	Case (n = 14)	Control (n = 17)	P
Goodenough	107 \pm 14 ^a	106 \pm 16	NS
Wechsler			
Verbal IQ	102 \pm 12	108 \pm 18	NS
Performance IQ	106 \pm 11	100 \pm 17	NS
Full-scale IQ	103 \pm 10	103 \pm 16	NS

^a All the values are mean \pm SD.
NS, Not significant.

and thyroid function comparable with sex- and age-matched control children at 48–74 months of age.

More than 50 yr ago, it was reported that the concentration of thiouracil in milk was three times higher than the plasma concentration (19). These data were extended by inference to the newer antithyroid drugs, propylthiouracil (introduced in 1946) and MMI (introduced in 1949), and for many decades the use of antithyroid drugs for the treatment of thyrotoxicosis in breast-feeding mothers was abandoned (1, 20). Women taking either of these drugs were advised by their physicians not to breast-feed for the fear of causing hypothyroidism in the infant. In 1979, Low *et al.* (2), and in 1980, Kampmann *et al.* (5), reported that less than 0.1% of the administered dose of propylthiouracil was detected in the milk of lactating women. Since these observations, there have been a few reports describing the use of propylthiouracil in the treatment of thyrotoxicosis in breast-feeding mothers (5–8). A total of 15 infants have had normal thyroid function tests while their mothers were being treated with 50–300 mg propylthiouracil daily.

There has been more scepticism in the use of MMI and carbimazole during breast-feeding, because studies of excretion of these compounds in the milk have demonstrated a milk to plasma drug ratio of approximately 1 (3, 4). It is estimated that after a single dose of 40 mg MMI the breast-fed infant may receive as much as 70 μ g MMI, an amount that could theoretically affect the infant's thyroid function (7). However, Lamberg *et al.* (11) reported 11 infants whose mothers were treated with carbimazole in dosages ranging from 5–15 mg daily during pregnancy and were permitted to breast-feed after delivery. All 11 newborns had normal serum TSH and T₄ concentrations during the 3 weeks of study, and two infants continued to have normal values at 3 and 4 months of age during continued breast-feeding. The dose of carbimazole used in this study was equivalent to 3.3–10 mg MMI daily. We have previously reported that in 35 infants of lactating mothers with thyrotoxicosis who were receiving

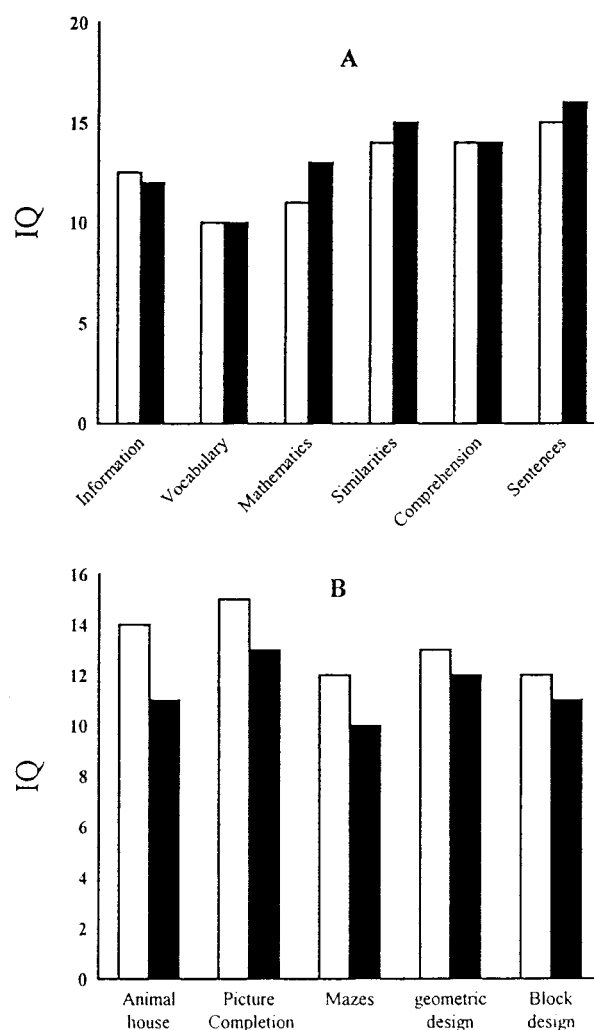


FIG. 2. Wechsler test scores in the 14 children between 48 and 74 months of age, who were breast-fed while mothers were taking MMI (\square), and in 17 controls (\blacksquare). There is no statistical difference in the subsets of verbal IQ (A) and performance IQ (B) between the two groups.

5–20 mg MMI daily, serum concentrations of T₄, T₃, and TSH were within the normal range 1 month after the initiation of therapy (12). Thyroid function tests in the six breast-fed infants whose mothers were receiving 20 mg MMI daily for the first month, 10 mg for the second month, and 5 mg for an additional 4 months remained within normal range.

In the present study, we have extended our experience in a larger number of lactating mothers with thyrotoxicosis

treated with MMI and their breast-feeding infants. We have observed that MMI treatment of 88 lactating women, who developed thyrotoxicosis 2–8 months after delivery, for 1 yr does not cause alterations in thyroid function of their infants. Of interest are the results of thyroid function tests in infants whose mothers had biochemical evidence of hypothyroidism 1 month after MMI treatment. Serum T_4 , T_3 , and TSH concentrations remained within the normal range in all six children while their mothers had marked increase in serum TSH concentrations.

It has been shown that mean peak milk MMI concentrations after a dose of 40 mg is $0.72 \pm 0.07 \mu\text{g/mL}$ at 1 h (4) and following a 15-mg dose is $0.32 \pm 0.1 \mu\text{g/mL}$ at 2 h (21). The half-life of MMI in milk is 4.2 ± 0.8 h, and the mean MMI concentration decreases to $0.03 \pm 0.01 \mu\text{g/mL}$ after 12 h. From the available data (4, 7, 21), it can be calculated that following a 20-mg dose of MMI, the infant may receive approximately 35 μg MMI. This amounts to 5 $\mu\text{g/kg}$ for a 5-month-old infant weighing 7 kg (or 350 μg MMI in a 70-kg man). Therefore, it is not surprising that in the present study the serum MMI levels in the infants were less than 0.03 $\mu\text{g/mL}$.

The administration of a low-dose of 10 mg MMI daily resulted in normalization of thyroid function for most of the thyrotoxic mothers after 1 month of therapy. This finding is in agreement with our previous observations that thyrotoxic patients in Iran respond well to lower doses of both MMI and propylthiouracil (22, 23). We have suggested that environmental iodine intake may affect the response to antithyroid drugs. Others have also reported that euthyroidism can be achieved by low-dose MMI treatment in thyrotoxic patients, although the control of hyperthyroidism is slower in comparison with larger doses (24).

We have also shown that physical growth, thyroid function, and IQ scores are similar in children whose mothers received MMI while breast-feeding compared with control children between 48 and 74 months of age. However, due to small sample size in both groups, we can not conclude with certainty that no differences between two groups exist. It is of interest that IQ scores in all children whose mothers received MMI while breast feeding are within the normal range of 91–130, that was observed in 73 Tehranian schoolchildren tested by our group in another study (25).

Thyroid hormone is essential for brain development during intrauterine life and brain function after birth. It plays important roles in neurogenesis, neuronal migration, axon and dendrite formation, myelination, synaptogenesis, and the regulation of specific neurotransmitters (26, 27). Therefore, lack of thyroid hormone any time from midgestation through the first few years of life may disturb neural connectivity and reduce the capability of neural transmission, affecting intellectual function and mental processes. The integrity of the hypothalamic-pituitary-thyroid axis in both mother and fetus during pregnancy and that of the newborn during the first 2 yr of life is of great importance. Subtle but important alterations in neuropsychological development have been reported in children born of mothers with undiagnosed hypothyroidism during pregnancy (28) and in children who were diagnosed with congenital hypothyroidism by screening programs and treated within the first 2 months

of life (29). In addition, it has been suggested that transient neonatal hyperthyrotropinemia may adversely affect long-term intellectual development, at least in iodine-deficient regions (30) (Azizi, F., M. Afkhami, A. Sarshar, M. Nafarabadi, submitted for publication). Therefore, normal thyroid function and an unaltered IQ score and its subscales in children of MMI-treated thyrotoxic lactating mothers suggest that the use of MMI during breast-feeding did not cause thyroid dysfunction during the neonatal period and that subsequent performance on neuropsychological tests remained normal.

On the basis of the present findings and other reports in the current literature, we conclude that both propylthiouracil and MMI can be safely administered during lactation. However, the potential risk of thyroid dysfunction in rare instances may exist, and careful monitoring of both mother and infant must be carried out. Serum T_4 and TSH determinations every 4 weeks while the thyrotoxic lactating mothers are taking initial doses of an antithyroid drug is reasonable.

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