

# Effects of Propylthiouracil and Methimazole on Fetal Thyroid Status in Mothers with Graves' Hyperthyroidism

NAOKO MOMOTANI, JAEDUK YOSHIMURA NOH, NAOFUMI ISHIKAWA, AND KUNIIHIKO ITO

*Ito Hospital, 3-6 Jingumae, 4-Chome, Shibuya-Ku, 150 Tokyo, Japan*

## ABSTRACT

Thionamide therapy is a mainstay of the treatment of hyperthyroidism complicated by pregnancy, but it can expose the fetus to hypothyroidism. In terms of fetal thyroid status, propylthiouracil (PTU) has been preferred over methimazole (MMI) based on experimental data on limited transplacental passage, and lower doses have been recommended. However, neither of these practices is supported by convincing clinical evidence.

We compared the effect of maternal ingestion of PTU with that of MMI on fetal thyroid status using cord sera at delivery in 77 mothers with Graves' hyperthyroidism who were receiving thionamides and whose free  $T_4$  ( $FT_4$ ) levels were within the normal range. We also examined the dose effects on fetal thyroid status in these women. Thirty-four women were taking PTU (group P), and 43 were taking MMI (group M).

Neither the mean fetal  $FT_4$  nor the mean fetal TSH level was significantly different between the two groups. No significant difference in the occurrence of low  $FT_4$  levels or high fetal TSH levels was found between group P and group M (low  $FT_4$ , 6% vs. 7%; high TSH, 21% vs. 14%). Little relationship was observed between maternal doses and fetal thyroid status; in fact, when low doses of both PTU (100 mg daily or less) and MMI (10 mg daily or less) were administered, high TSH levels in the fetus were observed in 7 of the 34 fetuses (21%) and in 6 of the 43 fetuses (14%), respectively. Higher doses were associated with normal or low fetal TSH levels.

These findings demonstrate that in terms of fetal hypothyroidism-inducing potential, there is little reason to choose PTU over MMI. Individualized, not uniformly low, doses of these drugs may prevent fetal hypothyroidism. (*J Clin Endocrinol Metab* 82: 3633-3636, 1997)

THE RISKS OF pregnancy related to Graves' hyperthyroidism are prevented by using antithyroid drugs of the thionamide type. The fetus directly benefits from maternal ingestion of these drugs when hyperthyroidism develops due to TSH receptor antibodies transferred from the mother. However, it has been well established that these drugs can expose the fetus to the risk of hypothyroidism. In fact, screening for congenital hypothyroidism revealed that 25% of transient neonatal hypothyroidism was due to maternal ingestion of propylthiouracil (PTU) (1).

Based on the experimental study by Marchant *et al.* demonstrating the limited transplacental passage of [ $^{35}$ S]PTU compared to [ $^{35}$ S]MMI after a single oral dose given to normal women (2), the prevailing view has been that PTU is less likely than methimazole (MMI) to induce hypothyroidism in the fetus. They found a persistent fetal to maternal ratio of less than 1 after [ $^{35}$ S]PTU administration (2). However, there has been little clinical evidence that the incidence of neonatal hypothyroidism is smaller in infants whose mothers received PTU compared with that in infants whose mothers received MMI. On the other hand, Gardner and his colleagues reported that cord serum PTU concentrations were consistently higher than maternal serum PTU concentrations during the treatment of hyperthyroidism (3).

It is generally believed that the higher the dose of thio-

namides, the higher the risk of fetal hypothyroidism; therefore, small doses (usually 150 mg PTU or less daily) have been recommended (4). However, some infants are born without hypothyroidism even though the mother receives large doses of thionamides, and as little as 50 mg PTU daily can cause high TSH levels in neonates (5, 6).

In this study, we compared the suppressive effect of maternal ingestion of PTU with that of MMI on fetal thyroid status by examining cord sera of euthyroid mothers with Graves' hyperthyroidism during thionamide therapy. The dose effects on fetal thyroid status were also studied in these women.

## Subjects and Methods

Of 249 pregnant women with Graves' disease who continued PTU or MMI until delivery, 77 women had taken the drugs for at least 4 weeks, had normal free  $T_4$  ( $FT_4$ ) levels at delivery and were delivered at term. None of them had a history of radioiodine therapy or surgery for Graves' disease. Of these 77, 34 were treated with PTU (group P), and 43 were treated with MMI (group M). PTU and MMI tablets contained 50 and 5 mg, respectively. PTU was administered in divided doses when the dosages were higher than 50 mg, and once when they were 50 mg or lower. MMI was administered in divided doses when the dosages were higher than 15 mg, and once when they were 15 mg or lower. Thirty-two healthy women who had no history of thyroid disease and who were delivered at term served as normal controls. Blood samples were obtained from the women and from the umbilical cords of their respective infants at the time of delivery. Informed consent for blood drawing was obtained from every mother who was studied.

Each pair of serum samples was assayed for  $FT_4$ , TSH, and antibodies that inhibit TSH binding (TBIAb). Normal ranges for maternal  $FT_4$ , maternal TSH, cord  $FT_4$ , and cord TSH levels based on data obtained from the normal group were 7.7-15.6 pmol/L, 0.3-3.5  $\mu$ U/L, 10.4-19.9

Received October 22, 1996. Revision received February 11, 1997. Re-revision received April 15, 1997. Accepted July 16, 1997.

Address all correspondence and requests for reprints to: Naoko Momotani, M.D., Ito Hospital, 3-6 Jingumae, 4-Chome, Shibuya-Ku, 150 Tokyo, Japan.

pmol/L, and 1.8–21.1 mU/L, respectively. FT<sub>4</sub> levels were measured with the Amerlex Free T<sub>4</sub> RIA Kit (Amersham Medical, UK), and TSH levels were measured using the Boots-Celltech Sucrose TSH immunoradiometric assay (Celltech Diagnostic, Slough, UK). TBLAb levels were measured by RRA using the TRAb Kit (Baxter, Tokyo, Japan), which was originally developed by Shewring and Smith (7).

Statistical significance was analyzed by Wilcoxon and  $\chi^2$  tests. Differences were considered significant at a level of  $P < 0.05$ .

## Results

### Fetal thyroid status

There was no significant difference in the mean fetal FT<sub>4</sub> level between group P and group M ( $13.8 \pm 2.6$  vs.  $14.2 \pm 3.0$  pmol/L; Fig. 1). The incidence of fetal FT<sub>4</sub> levels below the normal range was 2 in 34 (6%) in group P and 3 in 43 (7%) in group M. The difference was not significant. The mean FT<sub>4</sub> level in either test group was not significantly different from that in the healthy group ( $15.2 \pm 2.4$  pmol/L;  $P < 0.05$ ; Fig. 1).

The difference in the mean fetal TSH level between group P and group M was not significant ( $15.0 \pm 13.4$  vs.  $12.6 \pm 10.9$  mU/L; Fig. 2). The incidence of TSH levels above the normal range in group P fetuses was 7 in 34 (21%), and that in group M fetuses was 6 in 43 (14%). The difference was not significant. The single highest TSH value was 75.9 mU/L in group P. The differences in both the mean TSH levels and the incidences of high fetal TSH levels were still insignificant between the two groups when this case was excluded. The mean fetal TSH level in group P was significantly higher than that in the healthy group ( $7.4 \pm 4.7$  mU/L;  $P < 0.05$ ), and the difference between the mean fetal TSH level in group M and that in the healthy group was insignificant (Fig. 2).

All infants with low FT<sub>4</sub> or high TSH levels were clinically euthyroid, and none had goiters at birth. None of them was hypothyroid at the screening test for congenital hypothy-

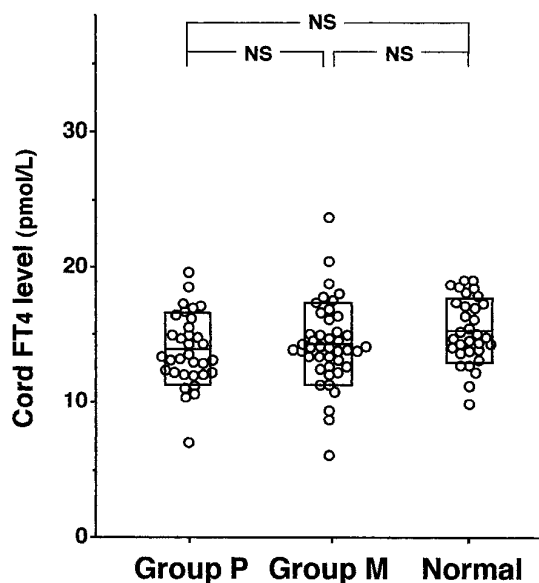


FIG. 1. Individual cord FT<sub>4</sub> levels and the mean  $\pm$  1 SD level in group P, to which PTU was administered; in group M, to which MMI was administered; and in healthy subjects. The differences in the mean level among group P, group M, and the healthy subjects were not significant.

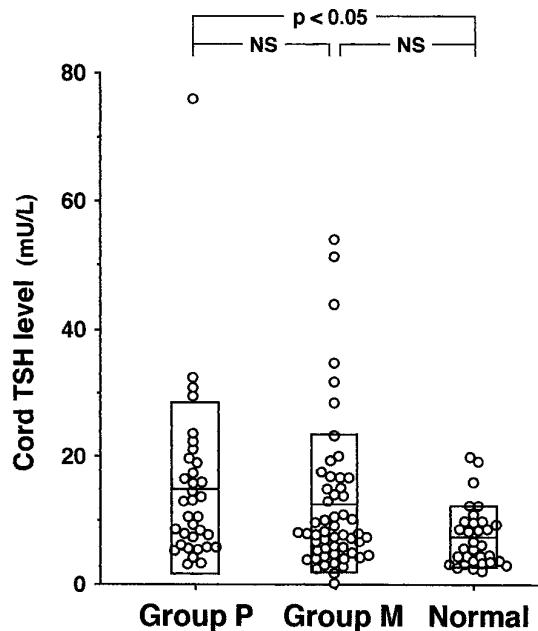


FIG. 2. Individual cord TSH levels and the mean  $\pm$  1 SD level in group P, to which PTU was administered; in group M, to which MMI was administered; and in healthy subjects. The difference in the mean level between groups P and M was not significant. The mean level in group P was significantly higher than that in the healthy subjects. The difference in the mean level between group M and the healthy subjects was insignificant.

roidism using capillary blood specimens obtained 4 or 5 days after birth. This test was conducted at a variety of institutions around Tokyo and at all times measured TSH. Depending on the institution, occasionally either T<sub>4</sub> or FT<sub>4</sub> was also measured.

### Relationship between drug doses and fetal thyroid status

Table 1 shows the relationship between the daily maternal doses of PTU or MMI and fetal TSH levels. In group P, mothers were receiving 25–200 mg PTU daily. Thirty of the 34 mothers in group P were receiving 100 mg PTU or less daily. Seven of the fetuses (23%) from these 30 mothers had TSH levels above the normal range, and the other 23 fetuses (77%) had normal TSH levels. In 4 mothers who were taking more than 100 mg PTU daily, all the fetal TSH levels were within the normal range. MMI doses in group M ranged from 2.5–20 mg daily. In 41 of the 43 mothers in this group, the doses were 10 mg or less. Six of the fetuses (15%) from these 41 mothers showed high TSH levels, and the other 35 fetuses (85%) had normal TSH levels. Four of the 6 fetuses with a high TSH level in group M were from mothers taking 5 mg MMI or less daily. Both of the fetuses whose mothers were taking 20 mg daily had a low TSH level.

### Maternal FT<sub>4</sub> and TSH concentrations

Maternal FT<sub>4</sub> concentrations ranged from 9.1–15.6 pmol/L in group P and from 7.7–15.6 pmol/L in group M. The mean maternal FT<sub>4</sub> levels in groups P and M were  $13.5 \pm 1.6$  and  $12.5 \pm 2.0$  pmol/L, respectively; the difference was significant ( $P < 0.05$ ). Maternal TSH values were below normal in

**TABLE 1.** Cord TSH levels and daily thionamide doses in mothers with normal FT<sub>4</sub> concentrations at delivery

PTU				MMI			
Dose (mg)	Above normal fetal TSH	Normal fetal TSH	Below normal fetal TSH	Dose (mg)	Above normal fetal TSH	Normal fetal TSH	Below normal fetal TSH
200	0	2	0	20	0	0	2
150	0	2	0	15	0	0	0
100	5	2	0	10	2	2	0
75	0	1	0	7.5	0	1	0
50	2	19	0	5	3	12	0
25	0	1	0	2.5	1	20	0

26 subjects in group P and 21 subjects in group M, within the normal range in 8 subjects in group P and 19 subjects in group M, and above the normal range in no subject in group P and in 3 subjects in group M. Mothers had low TSH levels significantly more often in group P than in group M.

#### Maternal TBIAb levels

Maternal mean TBIAb levels in groups P and M were not significantly different ( $17.6 \pm 11.8\%$  vs.  $22.0 \pm 10.8\%$ ).

### Discussion

As we have reported previously, thyroid status in fetuses of mothers with normal FT<sub>4</sub> levels receiving thionamides was suppressed, although mildly, at a substantial frequency (8). This observation and the significant correlation between maternal and fetal thyroid status (8) suggest that thionamide doses sufficient to maintain mothers in a euthyroid state are somewhat excessive for the fetuses.

No difference was found between fetal thyroid status in PTU-treated women (group P) and that in MMI-treated women (group M) despite the fact that maternal thyroid status in the former group was not lower than that in the latter group. Therefore, it is evident that PTU is not less potent than MMI in inducing fetal hypothyroidism when treating Graves' hyperthyroidism in pregnancy. This observation seems to contradict the finding of Marchant *et al.* that PTU showed smaller transference from the mother to the fetus and lower infant serum/maternal serum ratios than MMI when the drugs were administered in a single dose (2). It has been appreciated that the limited transplacental passage of PTU is due to its binding to serum protein about 80% of the time (9). MMI does not bind to protein in serum (10). A possible explanation for the similarity of the suppressive effect of PTU to that of MMI found in our study may be that in clinical use, the drugs are given by repeated administration (multiple doses). In this situation, the concentration in the fetus is likely to be close to or even higher than that in the mother [as reported by Gardner *et al.* (3)], provided that placental transfer is rapid compared with drug elimination and that back diffusion of the drug from fetus to mother is the predominant pathway of drug elimination from the fetus, as has been reported to be the case with other drugs. TBIAb levels in group P were similar to those in group M, indicating that differences in the activity of Graves' hyperthyroidism are unlikely to affect the result.

There has been a report by Mortimer *et al.* that fetal thyroid status was inversely related to maternal drug dosage in 10

PTU-treated and 6 carbimazole-treated women with Graves' disease, although they did not make their data available (11). In our patients with Graves' disease, higher doses did not result in high TSH levels in the fetus, and lower doses were accompanied by high fetal TSH levels at a substantial frequency in both groups P and M (21% and 14%, respectively). Consistent with our observation, Gardner *et al.* and Cheron *et al.* did not find a significant correlation between PTU doses and fetal thyroid status (3, 12). A close correlation in both TSH receptor antibody activities and serum thionamide concentrations between the fetus and the mother in patients with Graves' disease indicates that the fetal thyroid is under the influence of the same stimulatory and inhibitory factors as the maternal thyroid (3, 8). As a result, there is a significant correlation between fetal and maternal thyroid function (8). When maternal hyperthyroidism is due to autonomously functioning thyroid nodules, the dose relationship is likely to be seen, because the fetus does not suffer from hyperthyroidism in this case.

The significant correlation of fetal thyroid status with maternal thyroid status coupled with the fact that there are variations in doses necessary to maintain individual mothers in the same thyroid status suggests that a lack of relationship between maternal doses and fetal thyroid status is reasonable. Of course, in some cases, noncompliance may be another reason for the lack of correlation between dose of thionamides and maternal/fetal thyroid function. Doses higher than those in our study would not cause fetal hypothyroidism as long as maternal FT<sub>4</sub> levels are in a high normal range or above (8).

The reason why the thyroid status of some fetuses was suppressed, though mildly, whereas that of others was not remains unclear. Refetoff *et al.* reported the occurrence of hypothyroidism in only one infant in each of two sets of dizygotic twins born to mothers treated with thionamides during gestation (13). This may be another example of the individual variability. Differences, if any, in transplacental passage of both drugs and TSH receptor antibodies among the patients may not be the only factor responsible for the individual variation, as there is a good correlation in both of these factors between the fetus and the mother (3, 8). The cause may be multifactorial. Subtle individual variability in serum concentrations, in transplacental passage of both drugs and antibodies, and in susceptibility to drugs or antibodies may produce significant differences.

Recent studies on neuropsychological outcomes in early treated congenital hypothyroidism have shown that intel-

lectual retardation, if it ever occurs, can be caused only by severe hypothyroidism (14, 15). Therefore, transient mild hypothyroidism due to maternal thionamide therapy is unlikely to affect normal brain development. In fact, previous studies on the intellectual development of children exposed to thionamide therapy have shown no discernible retardation (16, 19). However, it may be best to keep the fetus in a euthyroid state because any subtle developmental defects may have been missed in these studies. Currently, maternal thyroid status, but not thionamide dose, may be the most convenient and reliable marker in avoiding fetal hypothyroidism (8). It is advisable to keep maternal FT<sub>4</sub> in a high normal to slightly hyperthyroid range at least near term as thyroid hormones become increasingly important for normal brain development.

There has been another reason for some clinicians to choose PTU. Aplasia cutis, a localized defect of the skin on the vertex of the scalp, the prognosis of which is benign, has been associated with MMI administration in a small number of cases (20, 21). However, statistical investigation refutes the causal relationship of maternal ingestion of MMI with aplasia cutis in the fetus (22, 23).

MMI is commonly chosen for routine management of thyrotoxic patients because of its more rapid and reliable efficacy and possible lower incidences of major side effects (24–26), although Wing and her colleagues did not find a significant difference in the time needed to normalize FT<sub>4</sub> indexes in pregnant patients (27).

We conclude that when maternal FT<sub>4</sub> levels are used as an index of fetal thyroid function, PTU and MMI are comparable in the treatment of hyperthyroidism due to Graves' disease, at least in terms of the fetal thyroid.

### Acknowledgments

We are indebted to Dr. K. Iwakura and many other obstetricians for their kind cooperation.

### References

- Dussault JH. 1993 Neonatal screening for congenital hypothyroidism. *Clin Lab Med.* 13:645–652.
- Marchant B, Brownlie BEW, Hart DM, Horton PW, Alexander WD. 1977 The placental transfer of propylthiouracil, methimazole and carbimazole. *J Clin Endocrinol Metab.* 45:1187–1193.
- Gardner DF, Cruikshank DP, Hays PM, Cooper DS. 1986 Pharmacology of propylthiouracil (PTU) in pregnant hyperthyroid women: correlation of maternal PTU concentrations with cord serum thyroid function tests. *J Clin Endocrinol Metab.* 62:217–220.
- Cooper DS. 1991 Treatment of thyrotoxicosis. In: Braverman LE, Utiger RD, eds. *Werner and Ingbar's the thyroid: a fundamental and clinical text*, 6th ed. Philadelphia: Lippincott; 887–916.
- Davis LE, Lucas MJ, Hankins GDV, Roark ML, RN, Cunningham FG. 1989 Thyrotoxicosis complicating pregnancy. *Am J Obstet Gynecol.* 160:63–70.
- Momotani N, Yamashita R, Yoshimoto M, Noh J, Ishikawa N, Ito K. 1989 Recovery from foetal hypothyroidism: evidence for the safety of breast-feeding while taking propylthiouracil. *Clin Endocrinol (Oxf).* 31:591–595.
- Shewring G, Smith BR. 1982 An improved radioreceptor assay for TSH receptor antibodies. *Clin Endocrinol (Oxf).* 17:409–417.
- Momotani N, Noh J, Oyanagi H, Ishikawa N, Ito K. 1986 Antithyroid drug therapy for Graves' disease during pregnancy. *N Engl J Med.* 315:24–28.
- Kampmann JP, Hansen JEM. 1983 Serum protein binding of propylthiouracil. *Br J Clin Pharmacol.* 16:549–552.
- Cooper DS, Bode HH, Nath B, Saxe V, Maloof F, Ridgway EC. 1984 Methimazole pharmacology in man: studies using a newly developed radioimmunoassay for methimazole. *J Clin Endocrinol Metab.* 58:473–479.
- Mortimer RH, Tyack SA, Galligan JP, Perry-Keene DA, Tan YM. 1990 Graves' disease in pregnancy: TSH receptor binding inhibiting immunoglobulins and maternal and neonatal thyroid function. *Clin Endocrinol (Oxf).* 32:141–152.
- Cheron RG, Kaplan MM, Larsen PR, Selenkow HA, Crigler Jr JF. 1981 Neonatal thyroid function after propylthiouracil therapy for maternal Graves' disease. *N Engl J Med.* 304:525–528.
- Refetoff S, Ochi Y, Selenkow HA, Rosenfield RL. 1974 Neonatal hypothyroidism and goiter in one infant of each of two sets of twins due to maternal therapy with antithyroid drugs. *J Pediatr.* 85:240–244.
- Simons WF, Fuggle PW, Grant DB, Smith I. 1994 Intellectual development at 10 years in early treated congenital hypothyroidism. *Arch Dis Child.* 71:232–234.
- Dubuis J-M, Glorieux J, Richer F, Deal CL, Dussault JH, Vliet GV. 1996 Outcome of severe congenital hypothyroidism: closing the developmental gap with early high dose levothyroxine treatment. *J Clin Endocrinol Metab.* 81:222–227.
- McCarroll AM, Hutchinson M, McAuley R, Montgomery DAD. 1976 Long-term assessment of children exposed *in utero* to carbimazole. *Arch Dis Child.* 51:532–536.
- Burrow GN, Klatskin EH, Genel M. 1978 Intellectual development in children whose mothers received propylthiouracil during pregnancy. *Yale J Biol Med.* 51:151–156.
- Messer PM, Hauffa BP, Olbricht T, Benker G, Kotulla P, Reinwein D. 1990 Antithyroid drug treatment of Graves' disease in pregnancy: long-term effects on somatic growth, intellectual development and thyroid function of the offspring. *Acta Endocrinol (Copenh).* 123:311–316.
- Eisenstein Z, Weiss M, Katz Y, Bank H. 1992 Intellectual capacity of subjects exposed to methimazole or propylthiouracil *in utero*. *Eur J Pediatr.* 151:558–559.
- Burrow GN. 1975 The thyroid in pregnancy. *Med Clin North Am.* 59:1089–1098.
- Mandel SJ, Brent GA, Larsen PR. 1994 Review of antithyroid drug use during pregnancy and report of a case of aplasia cutis. *Thyroid.* 4:129–133.
- Momotani N, Ito K, Hamada N, Ban Y, Nishikawa Y, Mimura T. 1984 Maternal hyperthyroidism and congenital malformation in the offspring. *Clin Endocrinol (Oxf).* 20:695–700.
- Van Dijke CP, Heydendael RJ, De Kleine MJ. 1987 Methimazole, carbimazole, and congenital skin defects. *Ann Intern Med.* 106:60–61.
- Cooper DS. 1984 Antithyroid drugs. *N Engl J Med.* 311:1353–1362.
- Cooper DS. 1985 Propylthiouracil levels in hyperthyroid patients unresponsive to large doses. *Ann Intern Med.* 102:328–331.
- Okamura K, Ikenoue H, Shiroozu A, Sato K, Yoshinari M, Fujishima M. 1987 Reevaluation of the effects of methylmercaptoimidazole and propylthiouracil in patients with Graves' hyperthyroidism. *J Clin Endocrinol Metab.* 65:719–723.
- Wing DA, Millar LK, Koonings PP, Montoro MN, Mestman JH. 1994 A comparison of propylthiouracil *versus* methimazole in the treatment of hyperthyroidism in pregnancy. *Am J Obstet Gynecol.* 170:90–95.