Treatment of Graves' Disease with Antithyroid Drugs in the First Trimester of Pregnancy and the Prevalence of Congenital Malformation

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Background: Several reports have suggested that propylthiouracil (PTU) may be safer than methimazole (MMI) for treating thyrotoxicosis during pregnancy because congenital malformations have been associated with the use of MMI during pregnancy.

Objectives: We investigated whether *in utero* exposure to antithyroid drugs resulted in a higher rate of major malformations than among the infants born to a control group of pregnant women.

Methods: We reviewed the cases of women with Graves' disease who became pregnant. The pregnancy outcomes of 6744 women were known, and there were 5967 live births. MMI alone had been used to treat 1426 of the women, and 1578 women had been treated with PTU alone. The 2065 women who had received no medication for the treatment of Graves' disease during the first trimester served as the control group. The remaining women had been treated with potassium iodide, levothyroxine, or more than one drug during the first trimester. The antithyroid drugs were evaluated for associations with congenital malformations.

Results: The overall rate of major anomalies in the MMI group was 4.1% (50 of 1231), and it was significantly higher than the 2.1% (40 of 1906) in the control group ($P = 0.002$), but there was no increase in the overall rate of major anomalies in the PTU group in comparison with the control group (1.9%; 21 of 1399; $P = 0.709$). Seven of the 1231 newborns in the MMI group had aplasia cutis congenita, six had an omphalocele, seven had a symptomatic omphalomesenteric duct anomaly, and one had esophageal atresia. Hyperthyroidism in the first trimester of pregnancy did not increase the rate of congenital malformation.

Conclusions: *In utero* exposure to MMI during the first trimester of pregnancy increased the rate of congenital malformations, and it significantly increased the rate of aplasia cutis congenita, omphalocele, and a symptomatic omphalomesenteric duct anomaly. **(*J Clin Endocrinol Metab* 97: 2396–2403, 2012)**

Thyrotoxicosis occurs in approximately 0.2% of pregnancies, and the most common cause of thyrotoxicosis is Graves' disease (1, 2). Graves' disease is common in young women of childbearing age, and poorly controlled Graves' disease during pregnancy can cause serious complications in both the mother and the fetus. A number of observational studies have consistently linked hyperthyroidism during pregnancy with an increased risk of low birth weight (3), preterm birth (4, 5), and congenital malformations (6, 7). Propylthiouracil (PTU) and methima-

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Abbreviations: CI, Confidence interval; CMZ, carbimazole; FT_4, free T_4; MMI, methimazole; OR, odds ratio; PTU, propylthiouracil.

zole (MMI)/carbimazole (CMZ) are the treatments of choice, and PTU and MMI/CMZ have similar transplacental transfer kinetics (8). Evidence regarding the impact of antithyroid drugs on pregnancy outcomes remains inconclusive. Several case reports have suggested that PTU may be safer than MMI during pregnancy because of the occurrence of congenital malformations associated with the use of MMI during pregnancy (aplasia cutis congenita, choanal atresia, and intestinal anomalies) (9–12). However, a casual relationship between MMI and malformations cannot be excluded. It has been suggested that thyrotoxicosis might itself be a teratogen because fetal loss and intrauterine growth retardation have been observed in untreated hyperthyroid pregnant women (12). In a recent study in 2010, Clementi *et al.* (13) investigated the use of MMI/CMZ and PTU for associations with congenital malformations and found that prenatal exposure to MMI/CMZ was significantly associated with choanal atresia, omphalocele, and total situs inversus and/or dextrocardia. PTU, MMI, and potassium iodide are the drugs currently used to control maternal hyperthyroidism in Japan. The objective of this study was to investigate whether *in utero* exposure to MMI or PTU resulted in a higher rate of major malformations than among the infants born to a control group of pregnant women. We reviewed the cases of 6744 pregnant women with Graves' disease and classified them into three groups according to whether they received MMI, PTU, or no medication for the treatment of Graves' disease in the first trimester of pregnancy (0–12 wk gestation). We then investigated whether *in utero* exposure to MMI or PTU in the first trimester of pregnancy increased the rate of giving birth to an infant with a congenital malformation.

Subjects and Methods

We reviewed the cases of 6941 women with Graves' disease who became pregnant between January 1, 1999, and December 31, 2010, and the pregnancy outcome of 6744 (97%) women was known. The diagnosis of Graves' disease was based on the clinical examination and laboratory data. There were 5967 live births, 30 perinatal losses, 657 miscarriages, and 90 abortions. All of the deliveries were attended by obstetricians. During the mothers' first visit after delivery, a physician interviewed them about the congenital malformations diagnosed by the obstetricians, using a structured questionnaire (shown in the Supplemental Data, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org) to obtain details about the outcome of the pregnancy, gestational age at delivery, birth weight, and the presence and type of major or minor birth defects in their infant. If a malformation was reported, the doctor corresponded with the gynecologist, and we were able to determine whether there were any life-threatening anomalies in the fetus. Total or subtotal thyroidectomy had been performed to treat 1008 of the mothers before or during their current pregnancy, and 380 mothers underwent I-131 treatment before their current pregnancy. Women who still had hypothyroidism after thyroidectomy or I-131 treatment were treated with levothyroxine. The other women with hyperthyroidism were treated with MMI, PTU, or potassium iodide during their current pregnancy. We classified mothers and infants into three groups according to whether the mothers received MMI, PTU, or no medication (control group) for the treatment of Graves' disease in the first trimester of pregnancy (0–12 wk gestation). The MMI group refers to women treated with MMI alone during the first trimester of pregnancy, and the PTU group refers to women treated with PTU alone during the first trimester of pregnancy. The remaining women had been treated with potassium iodide, levothyroxine, or more than one drug during the first trimester. We evaluated the thyroid hormone status of the mother during the first trimester of pregnancy by reviewing the free T_4 (FT_4) level spot data obtained by measurements in each woman during 0 to 12 wk of each gestation. We investigated the clinical characteristics of the mothers in each of the three groups: the MMI group, the PTU group, and the control group. Then we calculated the rate of congenital malformations based on the number of infants in each group, *i.e.* the number of live births plus the number of perinatal losses.

Laboratory methods

Until March 2002, the FT_4 levels were measured by a chemiluminescent enzyme immunoassay (Lumipulse FT_4; Fuji Rebio Inc., Tokyo, Japan; manufacturer's reference limits, 0.75–1.75 ng/dl), and thereafter they were measured by an electrochemiluminescence immunoassay (ECLusys FT_4; Roche Diagnostics GmbH, Mannheim, Germany; manufacturer's reference limits, 0.8–1.6 ng/dl). Based on the results of our previous study of a large population, the reference interval for FT_4 at 0–12 wk gestation was 0.77–1.91 ng/dl. Mothers were considered hyperthyroid if their FT_4 level was above the reference range, euthyroid if their FT_4 level was within the reference range, and hypothyroid if their FT_4 level was below the reference range. We classified mothers in three groups according to their FT_4 level measured during the first 12 wk of gestation.

Statistical methods

Associations between the antithyroid drugs and malformations were evaluated in a 2×2 table. The odds ratio (OR), 95% confidence interval (CI), and *P* values were computed for each association. Multivariate logistic regression analyses were performed to compare the proportions of infants born with congenital malformations to mothers in the groups treated with each of the antithyroid drugs and to the mothers who were not treated with any antithyroid drugs during the first trimester of pregnancy. Maternal age and mother's thyroid status in the first trimester of pregnancy were also included in these models to adjust for confounding.

The statistical analyses were performed with JMP software, version 8.0.2 (SAS Institute Inc., Cary, NC). A *P* value of <0.05 was considered significant.

Results

During the first trimester of pregnancy, 1426 women were treated with MMI alone and 1578 with PTU alone, and the

2065 women who received no medication for the treatment of Graves' disease during the first trimester served as the control group. The remaining 1675 women had been treated with potassium iodide (394 women), levothyroxine (838 women), or more than one drug during the first trimester (443 women). Of the 2065 women in the control group, 1695 were in remission after treatment with antithyroid drugs for Graves' disease before their pregnancy, and all of the others had been treated for Graves' disease before their pregnancy: 55 had undergone radioiodine treatment, 311 had undergone thyroidectomy, and four had undergone both surgery and radioiodine.

Table 1 shows the clinical characteristics of the mothers in each of the three groups. The mean age of the MMI group was significantly lower than in the control group (31.8 *vs.* 32.6 yr; $P < 0.0001$). Then, we investigated the rate of congenital malformations in each group. The numbers of infants (including live births and perinatal losses) and the prevalence of infants with a congenital malformation in each group are summarized in Table 2. The overall rate of infants with a congenital malformation was 2.5% (152 of 5997 infants). The rate of malformed infants born to the women in the MMI group was 4.1% (50 of 1231 infants). The rate of malformed infants born to the women in the PTU group was 1.9% (26 of 1399 infants). The rate of malformed infants born to mothers in the control group was 2.1% (40 of 1906 infants). The overall rate of major malformations in the MMI group was significantly higher than in the control group ($P = 0.002$, Fisher's exact test), but there was no increase in the overall rate of major anomalies in the PTU group in comparison with the control group ($P = 0.709$). The dosage of the antithyroid drug did not differ significantly according to whether or not the mothers delivered a child with a congenital malformation: MMI group, $P = 0.13$; PTU group, $P = 0.84$. With multivariate logistic regression analysis, the mothers treated with MMI during pregnancy had higher odds of giving birth to an infant with a congenital malformation (OR, 2.28; 95% CI, 1.54–3.33; $P = 0.0002$) than mothers who did not receive any medication for the treatment of Graves' disease. On the other hand, no increased risk of giving birth to an infant with a congenital malformation was found among the mothers treated with PTU (OR, 0.66; 95% CI, 0.41–1.03; $P = 0.079$). The distribution of the congenital malformations in each group is shown in Table 2. Nine of 5997 newborns had aplasia cutis congenita, eight had an omphalocele, and eight had a symptomatic omphalomesenteric duct anomaly that required surgery. All of these three anomalies were curable. One of the newborns with aplasia cutis congenita also had a symptomatic omphalomesenteric duct anomaly. One newborn in the MMI group who had esophageal atresia also had small intestine obstruction due to a congenital malformation, and the infant died at 48 d after delivery. Detailed information regarding the mothers of the infants with each of the malformations is provided in Tables 3–5. Seven of the nine newborns with aplasia cutis congenita had been exposed to MMI alone, one had been exposed to MMI during the first 4 wk of gestation (and to potassium iodide thereafter), and one had been exposed to MMI in the first 7 wk of gestation (and to PTU thereafter). Six of the eight newborns with omphalocele had been exposed to MMI alone, and two had been exposed to MMI during the first 7 wk of gestation (and to PTU thereafter). All eight infants required surgical correction, and all were curable. Seven of the eight newborns with a symptomatic omphalomesenteric duct anomaly were exposed to MMI alone, and one was exposed to MMI during the first 9 wk of gestation (and to PTU thereafter). A multivariate analysis that included the age and FT_4 level of the mothers showed that prenatal exposure to MMI in the first trimester was significantly associated with the birth of an infant with aplasia cutis congenita, an omphalocele, and an omphalomesenteric duct anomaly ($P < 0.0001$, $P = 0.0013$, $P = 0.0001$, respectively). None of the other malformations listed in Table 2, including ventricular septal defect and atrial septal defect, were associated with the exposure to any of the antithyroid drugs. Next, we investigated the rate of congenital malformations according to maternal thyroid status in each group. Table 6 shows the rate of infants with a congenital malformation according

TABLE 1. Maternal age, FT_4 level, and pregnancy outcome in the first trimester of pregnancy of exposed group and control group

	Control group (without medicine)	MMI	PTU
Total patients (n)	2065	1426	1578
Maternal age (yr)	32.6 (4.3)	31.8 (4.3)[a]	32.9 (4.0)
FT_4 (ng/dl)	1.29 (0.41)	1.41 (0.91)[b]	1.48 (0.81)[a]
Pregnancy outcome (n)			
Live birth	1895	1226	1392
Perinatal loss	11	5	7
Miscarriage	146	165	166
Abortion	13	30	13
Prescribed after conception (n)		34	39
Prescribed before conception (n)		1392	1539
Dosage of antithyroid drugs (mg/d)		5 (8.1)	100 (113)

Data are expressed as number of patients (n) or mean (SD).

[a] $P = 0.0062$, *vs.* control group.

[b] $P < 0.0001$, *vs.* control group.

TABLE 2. The number and prevalence of malformed infants in each of the exposed groups and the control group (multiple malformations included)

	Control group (without medicine)	MMI group	PTU group	All patients
Total no.	1906	1231	1399	5997
Mean birth weight (g)	2990	2939	3005	2990
Mean gestation length (wk)	39.1	39	39.1	39.3
Congenital malformation, yes (%)	40 (2.1%)	50 (4.1%)	26 (1.9%)	152 (2.5%)
OR (95% CI)	1	2.28 (1.54–3.33)	0.66 (0.41–1.03)	1.15 (0.68–1.86)
P value		0.0002	0.0786	0.58
Ventricular septal defect	11 (27.5%)	9 (18%)	8 (31.0%)	33 (18.1%)
Atrial septal defect	1 (2.5%)	0	2 (7.7%)	4 (2.2%)
Patent ductus arteriosus	0	4 (8%)	1 (3.9%)	6 (3.3%)
Cheiloschisis, palatoschisis	2 (5.0%)	0	1 (3.9%)	5 (2.8%)
Accessory ear	1 (2.5%)	2 (4%)	0	3 (1.6%)
Complete situs inversus	0	0	1 (3.9%)	1 (0.5%)
Omphalocele	0	6 (12%)	0	8 (4.4%)
Omphalomesenteric duct anomalies	0	7 (14%)	0	8 (4.4%)
Aplasia cutis congenita	0	7 (14%)	0	9 (4.9%)
Others	25 (62.5%)	15 (30%)	13 (50.0%)	75 (41.2%)
Trisomy 21	2	3	2	
Syndactyly	1	0	3	
Intestinal malrotation	3	0	1	
Congenital cardiovascular deformity	3	0	0	
Ventricular dilatation	3	1	0	
Congenital megacolon	2	0	0	
Imperforate anus	2	1	1	
Hydronephrosis	0	1	2	
Craniosynostosis	1	1	0	
Kidney dysplasia	1	1	0	
Biliary atresia	1	1	0	
Talipes varus	1	0	0	
Diaphragmatic hernia	1	0	0	
Hypoplasia of the patella	1	0	0	
Arachnoid cyst hemorrhage	1	0	0	
Transposition of the great vessels	1	0	0	
Cataracta congenita	1	0	0	
Aortic stenosis	1	0	0	
Pulmonary artery stenosis	1	0	0	
Fallot's tetralogy	0	1	1	
Sturge-Weber syndrome	0	1	0	
Thoracocyllosis	0	1	0	
Hearing loss	0	1	0	
Esophageal stenosis	0	1	0	
Esophageal atresia	0	1	0	
Small bowel obstruction	0	1	0	
Spina bifida occulta	0	1	0	
Talipes valgus	0	0	1	
Brachydactyly	0	0	1	
Situs inversus viscerum	0	0	1	
Schistorhachis	0	0	1	
Hypospadias	0	0	1	

to maternal thyroid status in the first trimester of pregnancy in each group. The thyroid hormone level in 1105 of the 1906 mothers who had not received any treatment (control group) was measured during the first 12 wk of gestation, and the other 801 patients first came to our hospital after 12 wk of gestation. In the control group, there was no significant difference between the rate of giving birth to an infant with a congenital malformation of the mothers with hyperthyroidism and the mothers with euthyroidism, and there was no significant difference between the rate of giving birth to an infant with a congenital malformation of the mothers with hypothyroidism and the mothers with euthyroidism. The results were the same in the PTU group. In the MMI group, the rate of giving birth to an infant with a congenital malformation of the women with hyperthyroidism was 4.5% (nine of 202), and the rate of giving birth to an infant with a congenital malformation of the euthyroid mothers was 3.8% (31 of

TABLE 3. Details of the mothers of the eight newborns with aplasia cutis congenita

Age (yr)	Treatment	Time treatment started before conception (months)	Treatment period (g.w.)	MMI dose (mg)	FT_4 (ng/dl)	Thyroid status
26	MMI	4	Until 13 wk	5	1.08	Euthyroid
31	MMI	8	Until 17 wk	15	1.18	Euthyroid
30	MMI	15	Until 18 wk	5	1.08	Euthyroid
32	MMI	9	Until 27 wk	5	1.12	Euthyroid
33	MMI	19	Until 31 wk	5		Unknown
32	MMI	154	Until 37 wk	10	1.48	Euthyroid
29	MMI	120	Until delivery	5	1.74	Euthyroid
29[a]	MMI, PTU	1	Switched to PTU at 9 wk	25	0.23	Hypothyroid

g.w., Gestational week.

[a] Mother of a newborn with omphalomesenteric duct anomaly.

814). The difference between the rate of giving birth to an infant with a congenital malformation of the mothers with hyperthyroidism and the mothers with euthyroidism was not significant ($P = 0.68$, Fisher's exact test). On the other hand, 75 mothers were hypothyroid, and the rate of giving birth to an infant with a congenital malformation of the hypothyroid mothers was 9.3% (seven of 75) and was significantly higher than the rate of the euthyroid mothers ($P = 0.03$, Fisher's exact test). However, the results of the multivariate analysis, which included maternal treatment during the first trimester of pregnancy, maternal thyroid status, and maternal age, showed that maternal thyroid status had no effect on the rate of giving birth to an infant with a congenital malformation (OR, 0.86; 95% CI, 0.63–1.1; $P = 0.28$).

Discussion

This is the largest study in Japan to investigate whether *in utero* exposure to MMI or PTU in the first trimester of pregnancy increases the risk of giving birth to an infant with a congenital malformation. The results indicated that exposure to MMI during the first trimester of pregnancy increases the risk of giving birth to an infant with a congenital malformation. The incidences of aplasia cutis congenita, omphalocele, and a symptomatic omphalomesenteric duct anomaly in the infants who had been exposed to MMI in the first trimester were higher than expected. There was one infant with esophageal atresia born to a mother treated with MMI. The mother was euthyroid during the first trimester. The low frequency of choanal atresia and esophageal atresia in Japan may be the reason why there was only one infant with esophageal atresia in our study. The risk exposure period is considered to be between 10 and 15 gestational weeks for aplasia cutis congenita, between 3 and 8 wk for omphalocele, and up to 7 wk for omphalomesenteric duct anomaly. One of the nine newborns with both aplasia cutis congenita and omphalomesenteric duct anomaly had been exposed to MMI in the first 7 wk of gestation and to PTU thereafter, which means that the exposure to PTU occurred during the risk exposure period for aplasia cutis congenita. No specific birth defects, such as aplasia cutis congenita, omphalocele, or symptomatic omphalomesenteric duct anomaly, were found in the infants exposed to PTU alone.

An unusual pattern of congenital malformations including choanal atresia, gastrointestinal anomalies such as esophageal atresia and tracheoesophageal fistula, minor facial and skin dysmorphic features, growth restriction, and developmental delay have been reported in several

TABLE 4. Details of the mothers of the eight newborns with omphalocele

Age (yr)	Treatment	Time treatment started before conception (months)	Exposed period (g.w.)	MMI dose (mg)	FT_4 (ng/dl)	Thyroid status
32	MMI	72	Until 22 wk	2.5	1.28	Euthyroid
33	MMI	51	Until 22 wk	20	0.42	Hypothyroid
28	MMI	17	Until 31 wk	7.5	1.54	Euthyroid
34	MMI	69	Until 33 wk	20	0.60	Hypothyroid
28	MMI	18	Until delivery	30	0.96	Euthyroid
28	MMI	3	Until delivery	30	2.06	Hyperthyroid
36	MMI, PTU	34	Switched to PTU at 7 wk	10	1.80	Euthyroid
36	MMI, potassium iodide	35	Switched to potassium iodide at 7 wk	15	1.11	Euthyroid

g.w., Gestational week.

TABLE 5. Details of the mothers of the eight newborns with an omphalomesenteric duct anomaly

Age (yr)	Treatment	Time treatment started before conception (months)	Exposed period (g.w.)	MMI dose (mg)	FT_4 (ng/dl)	Thyroid status
35	MMI	83	Until 8 wk	15	0.35	Hypothyroid
31	MMI	7	Until 13 wk	5		Unknown
34	MMI	190	Until 14 wk	15	0.93	Euthyroid
30	MMI	72	Until 21 wk	15	0.31	Hypothyroid
31	MMI	18	Until delivery	15	1.03	Euthyroid
33	MMI	40	Until delivery	12.5	1.26	Euthyroid
39	MMI	156	Until delivery	2.5	1.04	Euthyroid
29[a]	MMI, PTU	1	Switched to PTU at 9 wk	25	0.23	Hypothyroid

g.w., Gestational week.

[a] Mother of a newborn with aplasia cutis congenita.

infants whose mothers were treated with MMI or CMZ during pregnancy (10, 14–16). It has been suggested that these malformations may represent a rare MMI embryopathy. In MMI embryopathy, exposure occurred before the seventh week of gestation. Aramaki *et al.* (17) reported a case of multiple anomalies, including ocular coloboma and nipple hypoplasia, in a newborn who had been prenatally exposed to MMI. Over a three-decade period, more than 20 cases of aplasia cutis congenita have been reported as possibly associated with MMI or CMZ exposure during pregnancy (12, 18–24). Although case reports are important in recording suspected adverse effects, they suffer from the weakness of being anecdotal evidence. However, it should be borne in mind that only one such case has ever been described after PTU exposure (25, 26).

The data in the literature have been insufficient to draw any definitive conclusions as to the teratogenic potential of MMI. The most unbiased method available for obtaining data on the teratogenicity of any substance in humans is to acquire data prospectively, before outcome of pregnancy is known. Di Gianantonio *et al.* (27) prospectively investigated the outcome of the pregnancy of 241 women counseled by 10 teratology information services because of MMI exposure and compared the outcome with that of 1089 women referred to the services because of exposure to nonteratogenic drugs. The results showed no increase in the overall rate of major anomalies in the MMI-exposed group in comparison with the control group, but two of the eight infants with a congenital malformation in the MMI group had a specific anomaly, choanal atresia and esophageal atresia. In a recent study, Clementi *et al.* (13) investigated MMI/CMZ and PTU for associations with congenital malformations based on data from the International Clearinghouse for Birth Defects Surveillance and Research. They performed a case-affected control analysis, and the study included 18,131 cases with malformations and reported first-trimester exposure to medication. A total of 127 subjects had been born to mothers with known first-trimester antithyroid drug exposure (PTU, 47; MMI/CMZ, 80). Clementi *et al.* concluded that prenatal exposure to MMI/CMZ was significantly associated with choanal atresia, omphalocele, and total situs inversus and/or dextrocardia. Rosenfeld *et al.* (28) followed up 115 PTU-exposed pregnancies and 1141 controls and found that the rate of major malformations in the two groups was comparable. We have to bear in mind that there may have been some reporting bias based on the widely held belief that PTU is unlikely to cause congenital malformations. There is also the question of whether hyperthyroidism (in addition to or instead of the medication) increases the risk of birth defects (29, 30). Women with untreated or inadequately treated hyperthyroidism have a higher incidence of fetal loss; higher rates of cesarean delivery and placental abruption, preterm labor, and low birth weight; and an increased risk of delivering an infant with a minor congenital malformation (7, 31). The results of our study showed that maternal hyperthyroidism had little effect on the rate of birth of infants with a congenital malformation or even on the rate of birth of infants with a specific congenital anomaly such as aplasia cutis congenita or ompha-

TABLE 6. Congenital malformations according to maternal thyroid status in the first trimester of pregnancy in each group

Group	Total no.	Maternal thyroid status (first trimester)[a]		
		Hyperthyroidism	Euthyroidism	Hypothyroidism
Control group	1105	2/112 (1.8%)	18/973 (1.9%)	0/20 (0.0%)
MMI	1091	9/202 (4.5%)	31/814 (3.8%)	7/75 (9.3%)
PTU	1263	7/277 (2.5%)	17/950 (1.8%)	0/36 (0.0%)

[a] Data are expressed as number of infants with a malformation.

locele. The rate of birth of infants with a congenital malformation by the women with hypothyroidism was higher than that by the euthyroid women; however, the number of hypothyroid mothers was relatively small.

This study had several limitations. Because we focused on the presence of major malformations based on information obtained from the mothers, minor dysmorphic features may have been underreported. Also, the questionnaire may have missed some abnormalities because it asks broad questions. Aplasia cutis congenita and omphalocele are very rare malformations, and their birth prevalences are only 1:33,000 (22) and 1:6,000, respectively (32, 33). Most omphalomesenteric duct anomalies are asymptomatic, but symptomatic cases require surgical correction, and their true prevalence remains unknown (34). Large sample sizes are required to estimate the risk of rare malformations in prospective cohort studies of exposed pregnancies. Our study was retrospective, and because the number of cases may have been insufficient to reach statistical levels, especially for the infants who had been exposed to PTU, we cannot exclude the possibility of mere chance accounting for the results. Our study was unable to rule out the possibility that genetic factors or other teratogens caused the malformations. However, the association we found between MMI/CMZ exposure and omphalocele is consistent with previous reports (13).

In summary, exposure to MMI during the first trimester of pregnancy increased the risk of congenital anomalies, including the risk of the rare anomalies aplasia cutis congenita, omphalocele, and a symptomatic omphalomesenteric duct anomaly. It seems preferable to treat Graves' disease with PTU because it appears to be safer to use in the fertile period; however, the reported risk of hepatotoxicity in both the mother and the child is a concern.

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