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Clinical Research Article

Exposure to Propylthiouracil in the First Trimester of Pregnancy and Birth Defects: A Study at a Single Institution

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Abstract

Context: Medical treatment of Graves disease during the first trimester has been the subject of controversy ever since treatment with an antithyroid drug during the first trimester was reported to possibly be associated with an increased risk of birth defects in newborns.

Objective: We investigated whether the incidence of birth defects among newborns born to mothers with Graves disease (GD) treated with propylthiouracil (PTU) during the first trimester of pregnancy was higher than in a control group that was not exposed to any medication.

Methods: We reviewed the cases of 1913 women with GD who gave birth between January 1, 2015, and May 31, 2019. Detailed information concerning the outcome of pregnancy and the presence of birth defects was collected at the first visit after the delivery and again 1 year after delivery. We classified the mothers and infants into 3 groups according to the treatment the mother had received for GD in the first trimester of pregnancy: a group in which the mothers had been treated with PTU alone (PTU group), a group in which the mothers had not been treated with any medication (control group), and a group in which the mothers had received some other medical treatment, such as thiamazole, potassium iodide, or 2 or more drugs (other treatment group).

Results: The incidence of malformed infant births was 5.5% (30/541 infants) in the PTU group and 5.7% (27/ 475 infants) in the control group. There were no specific birth defects in the PTU group, and there were no significant differences between PTU dosages or maternal thyroid function according to whether mothers had delivered a child with a birth defect.

Conclusion: The results of our retrospective study showed that treatment with PTU during the first trimester of pregnancy did not increase the incidence of birth defects among newborns.

Graves disease (GD) is common in young women of childbearing age, and preconception counseling regarding the risks and benefits of the treatment options, such as antithyroid drug (ATD) treatment, radioiodine therapy, and thyroidectomy, should be offered to GD patients who wish to conceive in the future. Treatment with thiamazole (MMI) during the first trimester of pregnancy has been reported to possibly be associated with increased risk of congenital anomalies, including the specific congenital anomalies MMI embryopathy, choanal atresia, aplasia cutis, and esophageal atresia [1-6]. The results of our previous observational study in Japan did not show an association between congenital anomalies and propylthiouracil (PTU) treatment during the first trimester of pregnancy [5]. The information on birth defects in that study was collected at the first visit after delivery (usually within 3 months after delivery). Registry-based studies in Denmark and Korea, however, showed an increased incidence of congenital anomalies in infants born to mothers exposed to PTU in comparison with an unexposed control group [2, 4]. The study in Denmark examined the prevalence of birth defects registered before age 2 years, and the study in Korea reviewed the prevalence of birth defects registered before age 1 year. There may be delays in diagnosing some birth defects, and birth defects associated with maternal PTU treatment may not be diagnosed until around age 1 or 2 years.

In this study we investigated whether the incidence of birth defects increased among newborns born to mothers treated with PTU during the first trimester of pregnancy in comparison with an unexposed control group based on information collected 1 year after delivery.

Materials and Methods

We reviewed the cases of 1913 women with GD who gave birth between January 1, 2015, and May 31, 2019. The diagnosis of GD was based on the clinical examination and laboratory data. All of the deliveries were attended by obstetricians. Pregnant patients being treated at our institution were informed during their pregnancy that they would be asked about the outcome of their pregnancy after delivery. During the mothers' first visit after delivery, a physician interviewed them about the birth defects diagnosed by the obstetricians. The physician used a structured questionnaire 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. One year after delivery, a physician used a structured questionnaire to interview them again. If a birth defect was reported, the physician corresponded with the gynecologist, and we were able to determine whether the fetus had any life-threatening anomalies.

We classified the mothers and infants into 3 groups: a PTU group, a control group, and an other-treatment group. The mothers in the PTU group had been treated with PTU alone during the first trimester of pregnancy (0-12 weeks' gestation). The mothers in the control group had not been treated with any medication for GD in the first trimester of pregnancy. The women in the other-treatment group had been treated with MMI, potassium iodide (KI), levothyroxine (LT4), or 2 or more drugs during the first trimester. We evaluated the thyroid hormone status of the mother during the first trimester of pregnancy by reviewing the free thyroxine (FT4) level and thyrotropin (TSH) level spot data obtained by measurements made in each woman during 0 to 12 weeks of each gestation. We investigated the clinical characteristics of the mothers in the PTU group and the control group. Then we calculated the rates of birth defects based on the number of infants. We also calculated the rates of birth defects in the infants of the mothers treated with MMI alone (MMI group) and with KI alone (KI group). This study was approved by the local ethics committee. All participants gave their informed consent to participation in the study.

Laboratory methods

TSH, free triiodothyronine (FT3), and FT4 levels were measured by electrochemiluminescence immunoassays (ECLusys TSH [ID:AB_2756377] and ECLusys fT4 [ID:AB_2861411], respectively; Roche Diagnostics GmbH). The manufacturer's reference limits were TSH 0.2 to 4.5 mIU/L and FT4 0.8 to 1.6 ng/dL. Based on the results of a previous large population study, the reference intervals for maternal TSH and FT4 in the first trimester of pregnancy were 0.01 to 3.35 mIU/L and 0.77 to 1.91 ng/dL, respectively.

Statistical analysis

The statistical analysis was performed with JMP software v14.0 (SAS Institute Inc). Dichotomous data were compared by using the chi-square test or Fisher exact test, whichever was appropriate, and were expressed as percentages. *P* values of less than .05 were considered significant.

Results

During the first trimester of pregnancy, 541 with PTU alone, and the 475 women who received no medication for the treatment of GD during the first trimester served as the control group. The remaining 897 women had been treated with MMI alone (23 women), KI alone (109 women), LT4 alone (651 women) or more than one drug during the first trimester (114 women). Of the 475 women in the control group, 427 were in remission after ATD therapy for GD before their pregnancy, and all the others had been treated for GD before their pregnancy: A total of 37 had undergone radioiodine treatment and 11 had undergone thyroidectomy. OF the 651 women treated with LT4 in the first trimester, 274 had undergone radioiodine treatment, 121 had undergone thyroidectomy, and 256 were in remission and required LT4 for subclinical or overt hypothyroidism.

There were no significant differences between the PTU group and the control group with regard to mean maternal age, gestational weeks at birth, and neonatal birth weight, but the maternal FT4 and TSH levels in the first trimester of pregnancy were significantly lower in the PTU group compared to the control group (*P* < .005). The incidences of birth defects 1 year after birth in each group are summarized in Table 1.

The incidence of malformed infants was 5.5% (30/541 infants) in the PTU group and 5.7% (27/475 infants) in the control group. One of the newborns in the PTU group who had hypospadias also had hydronephrosis. Two newborns in the control group had 2 birth defects: One had a ventricular septal defect and retractile testis and the other had an inguinal hernia and hydrocele testis. The incidence of malformed infants in the MMI group was 0% (0/23 infants), and it was 3.7% in the KI group (4/109 infants). There was no increase in the overall incidence of birth defects in the PTU group in comparison with the control group (*P* = .92). The comparison between the PTU group and KI group (30/541 vs 4/109) yielded a *P* value of .64 by Fisher exact test and a *P* value of .42 by chi-square test. The comparison between the PTU group and the MMI group (30/541 vs 0/23) yielded a *P* value of .24. There was no increase in the overall incidence of birth defects in the PTU group in comparison with the KI group or MMI group. The difference in PTU dosage according to whether mothers delivered a child with birth defects was not statistically significant (*P* = .15; Table 2).

The number of birth defects that were newly added based on the results of the second interview and questionnaire was 6 in the PTU group (3 cases of cryptorchidism and 1 case each of microtia, omphalocele, and congenital heart disease) and 3 in the control group (1 case each of aproctia, congenital heart disease, and congenital hearing loss).

Next, we investigated whether there were any associations between maternal thyroid function during the first trimester and birth defects in the newborns. The results showed no significant differences between the serum FT4 levels of the group of mothers who gave birth to an infant with a birth defect and the group of mothers who gave birth to an infant with no birth defects in either the PTU group or the control group (see Table 2).

Discussion

Medical treatment of GD during the first trimester of pregnancy has been the subject of controversy ever since treatment with MMI during the first trimester of pregnancy was reported to possibly be associated with an increased risk of birth defects in newborns [7].

Some observational studies have found no association between exposure to ATDs and birth defects [8-12]. The number of cases in these studies may have been insufficient to reach statistical levels; however, 915 patients were exposed to PTU in one study, which seems to have been a sufficient number [11]. In 2012, we reported finding that exposure to MMI during the first trimester of pregnancy was associated with an increase in the incidence of congenital malformations, and it significantly increased the incidence of aplasia cutis congenita, omphalocele, and a symptomatic omphalomesenteric duct anomaly. The proportion of malformed infants born to the women in the PTU group in the same study was 1.9% (26/1399 infants), and it was not significantly different from the proportion of malformed infants born to GD mothers not treated with medication (2.1%, 40/1906 infants) [5]. The registry-based studies from Denmark and Korea showed an increased risk of birth defects in newborns when their mothers were exposed to PTU in early pregnancy [2, 4]. The study from Denmark showed that PTU was associated with birth defects in the face and neck region and in the urinary system. In the study from Korea, PTU was found to be associated with birth defects in the genital organs and the musculoskeletal system. In an additional study from Denmark, the difference in risk of general birth defects in the PTU group was not shown to be statistically significant in comparison with the control group, but the increased risk of birth defects in the urinary system remained [1]. The discrepancy between the results in Denmark and Korea may be attributable to

Table 1. Prevalence of birth defects in each of the exposed groups

Group	Control (unexposed)	PTU	MMI	KI
Total No.	475	541	23	109
Maternal age, y	35 (31-38)	34 (31-37)	34 (29-36)	34 (32-38)
First trimester				
Maximal medication dose, mg/d[a]	0	87.5 (50-150)	2.5 (1.43-5)	19 (5.5-38)
Maternal FT4, ng/dL[a]	1.36 (1.23-1.5)	1.29 (1.13-1.49)[b]	1.35 (1.18-1.73)	1.40 (1.17-2.1)
Maternal TSH, mIU/L[a]	0.74 (0.18-1.34)	0.47 (0.02-1.37)[b]	1.18 (0.68-1.83)	0.10 (0.01-1.53)
Gestational wks at birth	39.4 (38.4-40.3)	39.4 (38.4-40.3)	39.3 (37.9-40.9)	39.4 (38.6-40.3)
Birth weight, g	3014 (2786-3254)	3014 (2802-3234)	2888 (2732-3189)	2981 (2768-3294)
Birth defects, %	27 (5.7%)	30 (5.5%)	0 (0%)	4 (3.7%)

Defects by group:

Control (unexposed)		PTU		KI	
Ventricular septal defect	5	Ventricular septal defect	4	Ventricular septal defect	1
Atrial septal defect	1	Pulmonary valve stenosis	1	Omphalocele	1
Congenital cardiac disease	1	Congenital cardiac disease	2	Inguinal hernia	1
Omphalocele	3	Omphalocele	2	Hirschsprung disease	1
Inguinal hernia	1	Inguinal hernia	4		
Hydronephrosis	2	Hydronephrosis	5		
Tethered cord syndrome	1	Polydactyly	1		
Aproctia	1				
Small-intestinal stenosis	1				
Biliary tract abnormality	1				
Hypospadias	1	Hypospadias	2		
Retractile testicle	1	Cryptorchidism	6		
Hydrocele testicle	1				
Testicular dysgenesis	1				
Ovarian cyst	1				
Nasolacrimal duct obstruction	1				
Cheiloschisis, palatoschisis	1	Cheiloschisis, palatoschisis	1		
Microtia	1	Microtia	1		
Accessory ear	1	Accessory ear	1		
Congenital hearing loss	3	Congenital hearing loss	1		

Abbreviations: FT4, free thyroxine; KI, potassium iodide; MMI, thiamazole; PTU, propylthiouracil; TSH, thyrotropin.

[a]Median (interquartile range).

[b]*P* < .005, significantly lower in the PTU group compared to the control group.

Table 2. Characteristics of mothers in the propylthiouracil group who delivered a child with a birth defect

	With birth defects	Without birth defects	P
No.	30	511	
Age, y	35 (31-38)	34 (31-37)	NS
Maximal dose of PTU, mg/d[a]	100 (50-150)	75 (50-150)	NS
No. of patients whose thyroid hormone level was determined in first trimester	29	467	
FT4, ng/dL[a]	1.36 (1.22-1.60)	1.29 (1.13-1.48)	NS
TSH, mIU/L[a]	0.39 (0.05-1.42)	0.48 (0.02-1.37)	NS

Abbreviations: FT4, free thyroxine; NS, not significant; PTU, propylthiouracil; TSH, thyrotropin.
[a]In the first trimester; median (interquartile range).

racial differences or genetic differences. Our own study was an observational study, and we collected information regarding the infants at the mother's first visit after delivery and 1 year after delivery. Because our hospital is a specialized center for thyroid disorders, it was difficult to recruit healthy control individuals without any thyroid disease. The mothers in the control group in this study had not been treated for GD with any medication in the first trimester of pregnancy. Six birth defects had been newly diagnosed in the PTU group after 1 year, but there was no change in the results of the investigation of whether there was an association between birth defects and PTU exposure. There were 6 newborns with cryptorchidism in the PTU group. Cryptorchidism is one of the most common congenital abnormalities, and its prevalence in the general population is 1% to 9% [13, 14]. The prevalence of cryptorchidism in the PTU group in our study was 2.4% (6/255 male newborns) and not higher than in the general population. There were 3 newborns with cryptorchidism in the LT4 group, and its prevalence was 1.0% (3/307 male newborns). The *P* value for the comparison between the PTU group and the LT4 group (6/255 vs 3/307) was .20. We concluded that cryptorchidism was unrelated to PTU exposure in the first trimester of pregnancy.

Our observational study did not reveal any associations between maternal PTU exposure in early pregnancy and birth defects in the newborns. There were no infants with birth defects in the MMI group, but that may have been because of the small number of cases of exposure to MMI. Since 2005, we have been treating GD patients with PTU or KI before conception to avoid MMI exposure during early pregnancy, and that is why the number of patients in the MMI group was so small. GD patients treated with MMI who cannot tolerate PTU because of adverse effects have been switched from MMI to KI as soon as they conceived [15].

The limitation of this study was the small number of cases both in the PTU-exposed group and the control group. Large sample sizes are required to estimate the risk of rare malformations in studies of exposed pregnancies.

Our study was retrospective, and because the number of cases may have been insufficient to reach statistically meaningful levels, we cannot rule out the possibility that mere chance accounted for the results. However, the results were consistent with the findings in an earlier study conducted on a larger cohort that was reported from our institution. Further studies are needed to confirm the associations between specific birth defects and maternal exposure to PTU.

Additional Information

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