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Severity of Birth Defects After Propylthiouracil Exposure in Early Pregnancy

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Background: Propylthiouracil (PTU) used in the treatment of maternal hyperthyroidism in early pregnancy may be associated with a higher prevalence of birth defects in the face and neck region and in the urinary system but the severity of these complications remains to be elucidated.
Methods: Review of hospital-registered cases of birth defects in the face and neck region and in the urinary system after PTU exposure in early pregnancy. We obtained information on maternal redeemed prescription of PTU and child diagnosis of birth defect from nationwide registers for all children born in Denmark between 1996 and 2008 ($n = 817{,}093$). The children were followed until December 31, 2010 (median age, 8.3 years) and the Cox proportional hazards model was used to estimate adjusted hazard ratio (HR) with 95% confidence interval (CI) for having a birth defect after PTU exposure versus nonexposed children ($n = 811{,}730$).
Results: Fourteen cases of birth defects were identified in the face and neck region and in the urinary system after PTU exposure in early pregnancy; 11 children were exposed to PTU only ($n = 564$), whereas 3 children were born to mothers who switched from methimazole (MMI)/carbimazole (CMZ) to PTU in early pregnancy ($n = 159$). Among children exposed to PTU only, the adjusted HR for having a birth defect in the face and neck region was 4.92 (95% CI 2.04–11.86) and in the urinary system 2.73 (1.22–6.07). Looking into details of the 14 cases, 7 children were diagnosed with a birth defect in the face and neck region (preauricular and branchial sinus/fistula/cyst) and 7 children had a birth defect in the urinary system (single cyst of kidney and hydronephrosis). Surgical treatment was registered in 6 of the cases with a birth defect in the face and neck region and 3 of the cases with a birth defect in the urinary system. Two of the children with a birth defect in the urinary system also had other birth defects (genital organs).
Conclusions: We report details on possible PTU-associated birth defects. They tend to be less severe than the defects observed after MMI/CMZ exposure. Yet, the majority of affected children had to undergo surgery.

Introduction

In addition to methimazole (MMI) and its prodrug, carbimazole (CMZ), propylthiouracil (PTU) is one of the thionamides available for the treatment of hyperthyroidism (1). A major concern in the management of hyperthyroidism in pregnancy is the risk of birth defects in children exposed to antithyroid drugs (ATDs) in early pregnancy (2,3). In a Danish population-based cohort study of 817,093 children, we recently reported that both MMI/CMZ and PTU exposure in early pregnancy were significantly associated with a higher prevalence of having one or more birth defect diagnosed before the age of 2 years but the spectrum of defects differed by type of thionamide (4). The birth defects described after MMI/CMZ exposure were similar to previous reports and in line with the MMI/CMZ embryopathy (5), but the finding that PTU was also associated with a higher prevalence of birth defects was new and intriguing and in contrast to a recent large Japanese study (6) and the general consensus (7). In the Danish study, PTU exposure in early pregnancy was associated with a significantly higher prevalence of birth defects in the urinary system and in the face and neck region (4).

Maternal hyperthyroidism in pregnancy should be adequately treated to prevent maternal and fetal complications (8–10). Currently, the only widely accepted ATDs are MMI/CMZ and PTU (1). When having to choose between MMI/CMZ and PTU, it is imperative to quantify the type and severity of the birth defects associated with each drug. In the present study, we describe in detail the cases of PTU-associated birth defects in the face and neck region and in the urinary system.

If the PTU-associated birth defects are less severe, they may not have been detected at the time of the child's birth. In

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the present study, we therefore expanded the follow-up period and also included cases of such birth defects reported for the first time after the age of 2 years. To quantify the severity of the birth defects observed, we obtained information on complicating surgery and infections. In addition, we obtained detailed information about the mothers, including maternal use of other drugs in early pregnancy.

Materials and Methods

Study design and information sources

We describe in detail cases of birth defects in the face and neck region and in the urinary system after PTU exposure in early pregnancy. Cases were diagnosed before the age of 2 years and identified in our previous population-based cohort study (4). Moreover, we identified and describe cases of such birth defects diagnosed after the age of 2 years and up to December 31, 2010.

Information was obtained from the Danish National Hospital Register (DNHR) (11), which stores nationwide data on both inpatient and outpatient visits to any Danish hospitals since 1995 according to the *International Classification of Disease, Tenth Revision* (*ICD-10*), and from the Danish National Prescription Register (DNPR) (12), which stores data on all redeemed prescriptions of drugs since 1995 according to the anatomic therapeutic classification (ATC). We obtained information on child characteristics at birth from the Medical Birth Registry (MBR) (13) and information on maternal characteristics at the time of the child's birth from Statistics Denmark.

All data were linked in Statistics Denmark and were made available only in an encrypted form. The study was approved by the Danish Data Protection Agency.

Exposure and outcome

The start of pregnancy was the first day of last menstrual period and on average, conception would have taken place 2 weeks after the pregnancy start estimated in this study (14).

Information on maternal ATD treatment was obtained from the DNPR using the following ATC codes: H03BA02 (PTU), H03BB01 (CMZ), and H03BB02 (MMI). As previously described in detail (4), we defined that a child had been exposed to ATD in early pregnancy if the mother had redeemed at least one prescription for ATD in the period ranging from 6 months before pregnancy start to the end of gestational week 10. According to the type of ATD prescribed in this period, the children were categorized as exposed to PTU (only prescriptions of PTU), exposed to MMI/CMZ (only prescriptions of MMI and/or CMZ), or exposed to PTU and MMI/CMZ (both prescription of PTU and MMI/CMZ). In addition, two control groups were identified: the ''no ATD in pregnancy'' group (maternal redeemed prescriptions of ATD more than 1 year before the pregnancy start and/or 1 to 5 years after birth of the child) and the nonexposed group (no maternal redeemed prescriptions of ATD or thyroid hormone 1995–2008 and no maternal hospital diagnosis of hyperthyroidism or hypothyroidism 1977–2008).

Diagnosis of a birth defect in the child was obtained from the DNHR from 1995–2010 using the following *ICD-10* codes: DQ18 (birth defects of the face and neck) and DQ60-64 (birth defects of the urinary system). Median age at the end of follow-up (December 31, 2010) was 8.3 years (range, 0–15 years).

Statistical analyses

χ^2 Test was used to compare the prevalence of birth defects by exposure groups and the Cox proportional hazards model was used to estimate hazard ratio (HR) with 95% confidence interval (CI) for a diagnosis of a birth defect in the urinary system and in the face and neck region, respectively, in children exposed to PTU in early pregnancy versus nonexposed children. The children were followed from birth to the first diagnosis of a birth defect, emigration, death, or December 31, 2010, whichever came first. The adjusted model included type of pregnancy (singleton/multiple), birth year and sex of the child, as well as the following maternal covariates obtained at the time of the child's birth: age, parity, income, cohabitation, origin, and geographical residence (East/West Denmark). Robust standard errors were used to account for multiple pregnancies.

Statistical analyses were performed using STATA version 11 (StataCorp, College Station, TX).

Results

A total of 14 cases of birth defects in the face and neck region and in the urinary system were identified after PTU exposure in early pregnancy; 11 children were exposed to PTU only, whereas 3 children were born to mothers who switched from MMI to PTU in early pregnancy (Table 1). Among children with birth defects in the face and neck region after PTU exposure ($n = 7$), 5 children were diagnosed before the age of 2 years, and 2 additional cases were identified when including later diagnoses of birth defects. In the group of children with a birth defect in the urinary system after PTU exposure ($n = 7$), 6 cases were diagnosed before the age of 2 years and 1 additional case was identified later with a diagnosis of birth defect (Table 1).

Among children exposed to PTU only ($n = 564$), the adjusted HR for having a birth defect in the face and neck region diagnosed at any age during follow-up was 4.92 (95% CI 2.04–11.86) compared to the nonexposed group ($n = 811{,}730$). On the other hand, no cases were observed in the MMI/CMZ exposed group (Table 1). The adjusted HR for having a birth defect in the urinary system was 2.73 (1.22–6.07) in children exposed to PTU only and 2.09 (1.09–4.02) in children exposed to MMI/CMZ only in comparison to the nonexposed group.

Table 2 lists characteristics for each of the 14 cases with possible PTU-associated birth defects. None of the children died during follow-up. In the group of children with birth defects in the face and neck region, 3 children had a diagnosis of preauricular sinus/cyst (case 2, 4, and 5). They all had surgery performed for the birth defect, and 2 of the children had reports of complicating infections (case 2 had a diagnosis of abscess of the external ear and redeemed a prescription for dicillin, and case 4 had a diagnosis of both purulent and chronic otitis media and penicillin was prescribed). One child (case 7) had a diagnosis of sinus/cyst/fistula of the branchial cleft. This child had surgery performed and had reported complicating infection (diagnosis of cutaneous abscess of face and prescription of penicillin). The remaining 3 children (case 1, 3, and 6) had an unspecified diagnosis of the birth defect but additional information was available. The first child (case 1) had the surgical procedure code of resection of cyst/fistula of ductus thyroglossus registered; the second child (case 3) had a diagnosis of cutaneous abscess of face

Table 1. Prevalence of Birth Defects in the Face and Neck Region and in the Urinary System Diagnosed Before or After the Age of Two Years According to Antithyroid Drug Exposure in Early Pregnancy

	PTU		*MMI/CMZ*		*PTU and MMI/CMZ*		*No ATD in pregnancy*		*Nonexposed*		
Children (n)	*564*		*1097*		*159*		*3543*		*811,730*		
Birth defects[b]	n	%	n	%	n	%	n	%	n	%	p[a]
Face and neck (DQ18)	5	0.89	0	0	2	1.26	6	0.17	1,557	0.19	<0.001
<2 years old[c]	3		0		2		0		625		
≥2 years old[d]	2		0		0		6		932		
Urinary system (DQ60-64)	6	1.06	9	0.82	1	0.63	15	0.42	3,151	0.39	<0.001
<2 years old[c]	5		9		1		11		2,431		
≥2 years old[d]	1		0		0		4		720		

[a]*p* value from the χ^2 test: PTU vs. MMI/CMZ vs. PTU and MMI/CMZ vs. No ATD in pregnancy vs. nonexposed.
[b]Percentage (%) is the percentage of all children within the column.
[c]Diagnosed before the age of 2 years.
[d]Diagnosed from the age of 2 years and up to December 31, 2010.
PTU, propylthiouracil; MMI/CMZ, methimazole/carbimazole; PTU and MMI/CMZ, both propylthiouracil and methimazole/carbimazole use in early pregnancy; no ATD in pregnancy, antithyroid drug (ATD) use but not during the pregnancy; nonexposed, never ATD use.

Table 2. Birth Defects of the Face and Neck Region and the Urinary System in Children Exposed to Propylthiouracil in Early Pregnancy

Case	*Birth (year)*	*Gender (f/m)*	*Ga (weeks)*	*Bw (grams)*	*Birth defect* (ICD-10)		*Age*[a] *(years)*	*Contacts*[b] (n)	*Surgery*[c] *(yes/no)*	*Infection*[d] *(yes/no)*
Face and neck cases										
1	1996	Female	39	3250	DQ188	Face and neck, other specified	1.5	3	Yes	No
2	1997	Male	40	3800	DQ181	Preauricular sinus/cyst	9.9	6	Yes	Yes
3	2003	Male	38	3350	DQ188	Face and neck, other specified	3.4	4	Yes	Yes
4	2004	Male	38	3490	DQ181	Preauricular sinus/cyst	1.6	7	Yes	Yes
5	2005	Female	41	3410	DQ181	Preauricular sinus/cyst	0.7	2	Yes	No
6	2006	Male	39	3210	DQ188	Face and neck, other specified	1.4	2	No	No
7	2007	Female	37	3050	DQ180	Sinus/fistula/cyst of branchial cleft	0.3	8	Yes	Yes
Urinary system cases										
8	1997	Male	40	3400	DQ620	Congenital hydronephrosis	0	3	No	No
9	1998	Male	36	2440	DQ610	Single cyst of kidney	0	3	No	No
10	2002	Male	37	2660	DQ642	Posterior urethral valve[e]	4.2	5	Yes	No
11	2003	Male	39	3200	DQ620	Congenital hydronephrosis	0	2	No	No
12	2005	Male	41	4200	DQ620	Congenital hydronephrosis[f]	0.1	11	Yes	Yes
					DQ622	Megaureter				
13	2007	Male	37	3230	DQ610	Single cyst of kidney	0	4	No	No
					DQ620	Congenital hydronephrosis				
14	2008	Male	40	3360	DQ620	Congenital hydronephrosis	0.4	6	Yes	Yes

[a]Age at diagnosis of the birth defect.
[b]Number of hospital contacts related to the birth defect up to December 31, 2010.
[c]Registration of surgery related to the birth defect up to December 31, 2010.
[d]Registration of a diagnosis of infection or redeemed prescription of antibiotic related to the birth defect up to December 31, 2010.
[e]Also diagnosed with the birth defects DQ540 glandular hypospadia and DQ541 penile hypospadia.
[f]Also diagnosed with the birth defects DQ531 undescended testis and DQ555 aplasia testis.
PTU, propylthiouracil; Ga, gestational age; bw, birth weight; *ICD-10*, *International Classification of Disease, Tenth Revision.*

and redeemed prescriptions of dicillin; and the third child (case 6) had a diagnosis of localized enlarged lymph nodes but had no report of additional surgery or infection.

The children with birth defects of the urinary system were all boys, and these birth defects were predominantly congenital hydronephrosis (Table 2). Two of the children also had birth defects of the genital organs (case 10 and 12) and three children underwent surgery (case 10, 12, and 14). Considering the structural defects leading to hydronephrosis, additional information was available for case 10 (diagnosis of posterior urethral valve and surgical procedure code of resection of urethral valve), case 12 (diagnosis of megaureter and surgical procedure code of dilatation of the ureter ostium), and case 14 (surgical procedure code of nephrostomia and pyeloureterostomia with division of the ureteropelvic junction). Considering complicating urinary infections, one child (case 12) had redeemed prescriptions for trimetoprim after surgery had been performed, and one child (case 14) had been hospitalized with a diagnosis of acute pyelonephritis before surgery was performed.

Table 3 describes characteristics of the mothers. One mother redeemed a prescription for tolfenamic acid (nonsteroidal anti-inflammatory drug; NSAID) 20 days before the pregnancy start (case 1) and had a hospital diagnosis of osteoarthritis of the hips. Other than this, none of the mothers had other chronic diseases other than thyroid disease reported. In the group of children with birth defects in the urinary system, the majority of the mothers gave birth to their first child. Considering maternal smoking, two of seven mothers reported smoking during pregnancy in each group. Only one mother had another origin than Danish and was from Vietnam.

Table 4 lists details on maternal ATD treatment during pregnancy. The majority of mothers had started PTU treatment before the pregnancy (Table 4), but in some cases ($n=5$), PTU treatment was initiated in early pregnancy. In this latter group, three mothers (case 1, 2, and 12) had no redeemed prescription of ATD prior to the pregnancy start, findings compatible with first time treatment of hyperthyroidism initiated in early pregnancy. Three mothers (case 1, 4, and 14) switched from MMI to PTU in early pregnancy, whereas the remaining children were exposed only to PTU. One mother (case 4) had a redeemed prescription of thyroid hormone as well as ATD 10 days prior to the pregnancy start (block plus replacement therapy), but none of the mothers redeemed prescriptions of thyroid hormone during the pregnancy.

Discussion

Principle findings

We report details on 14 cases of birth defects potentially caused by PTU exposure in early pregnancy. Birth defects in the face and neck region were diagnosed in 7 children, the majority being preauricular and branchial sinus, fistula, and cysts. All cases except 1 were treated surgically. Birth defects of the urinary system were diagnosed in 7 children, the majority being congenital hydronephrosis. It was treated surgically in less than half of the cases. None of the children had birth defects in both the face and neck region and in the urinary system, but 2 of the children with birth defects of the urinary system also had birth defects of the genital organs. Detailed review of maternal characteristics did not indicate competing causes.

The period of organogenesis

The embryonic period is the early period of human development that lasts until the end of gestational week 10 when calculated from the first day of the last menstrual period (or to the end of embryonic week 8 when calculated from the time of conception). It is during the embryonic period that tissues and organs develop including structures of the face and neck region (15) and the urinary system (22). During gestational week 6–10 (embryonic week 4–8), tissues and organs rapidly develop, and it is the period that is most sensitive to teratogenic exposures and abnormal development (3). By the end of gestational week 10, all major organ systems are established (14). The fetal period, from gestational week 11 to the birth of the child, is characterized by growth and further maturation and differentiation of tissues and organs.

Birth defects of the face and neck

Birth defects in the face and neck region may reflect disturbances in the complex development of the branchial apparatus, which is an embryological structure consisting of the branchial arches, the branchial pouches, the branchial clefts, and the branchial membranes. The branchial apparatus begins to develop in gestational week 6 (embryonic week 4), and a developmental abnormality can form a fistula, sinus, or cyst depending on the degree of completion (15). Two types of birth defects may arise in the region of the ear: abnormalities of the first branchial cleft or preauricular sinus and cysts. Abnormalities of the first branchial cleft are duplications of the external auditory canal and classified as type I and type II defects (16). The auricle arises after the fusion of six hillocks from the first and second branchial arches. Preauricular sinus and cysts were first time described in 1864 and result from failure of the auricular hillocks to fuse (17). In contrast to abnormalities of the first branchial arch, the preauricular sinus typically does not involve the facial nerve or the parotid gland (17,18). The clinical presentation is often a small pit near the auricle usually on the anterior margin of the ascending limb of the helix. It is often asymptomatic but can become infected. It occurs either sporadically or inherited. It has been described as part of different syndromes, and it may be associated with renal anomalies (19,20). However, none of the cases we described also had birth defects of the urinary system.

Birth defects of the urinary system

Congenital anomalies of the kidney and urinary tract (CAKUT) is the term used to describe the spectrum of malformations affecting the kidney, the urinary tract, or both. CAKUT is the leading cause of urinary tract infections, chronic kidney disease, and renal failure in children (21). The development of the kidneys and the urinary tract starts in gestational week 5 (embryonic week 3), and the kidney is capable of producing urine from approximately 10 weeks of gestation (22). Malformations of the urinary system are often detected *in utero* by ultrasound (1%–2% of fetuses), but many abnormalities resolve spontaneously during pregnancy

Table 3. Maternal Characteristics at the Time of the Child's Birth

Case	Age (years)	Parity[a]	Cohabitation	Income quartile[b]	Educational level[c]	Smoking in pregnancy[d]	Origin	Other drug(s) used in early pregnancy[e]	Other disease(s)	Pregnancy complications
Face and neck cases										
1	27	3	Unmarried	2nd	Basic	Yes	Danish	Tolfenamic acid	Artrosis coxae	Abortus imminens, gestational edema
2	35	4	Unmarried	3rd	Low	Yes	Danish	None	None	None
3	37	2	Married	3rd	Middle	No	Danish	Sulfamethizole	None	Cesarean section
4	28	2	Unmarried	1st	Basic	Unknown	Danish	Thyroid hormone	None	Cesarean section
5	28	2	Married	2nd	Low	No	Danish	Propranolol	None	Asphyxia
6	33	2	Married	3rd	High	No	Danish	None	None	Asphyxia
7	40	2	Unmarried	3rd	Middle	No	Danish	Metoclopramide, sumatriptan	None	Abortus imminens
Urinary system cases										
8	27	1	Unmarried	4th	Middle	Yes	Danish	None	None	None
9	39	3	Married	2nd	Low	Unknown	Vietnamese	None	None	None
10	35	1	Unmarried	4th	Basic	No	Danish	Choriogonadotropin, follitropin	None	Multiple pregnancy
11	29	2	Married	3rd	Low	No	Danish	Povidone artificial tears	None	None
12	25	1	Married	2nd	Middle	No	Danish	Metoclopramide, oral contraceptives	None	Abortus imminens, hyperemesis
13	29	1	Married	1st	High	Yes	Danish	None	None	None
14	24	1	Unmarried	1st	Basic	No	Danish	Azelaic acid lotion, sulfamethizole	None	Cesarean section

[a]Previous live and stillbirths including index pregnancy.
[b]Quartiles, 1st quartile lowest.
[c]Highest educational level fullfilled: basic (primary/secondary education only; 9–13 years), low (vocational education and training: 9–13 years), middle (short- or medium cycle higher education: 14–16 years), high (long-cycle higher education: ≥17 years).
[d]Reported current smoking or smoking cessation in the pregnancy.
[e]Prescriptions registered in the period from 1 month prior to pregnancy start to gestational week 11. All prescriptions besides case 1 (tolfenamic acid), case 4 (thyroid hormone), and case 12 (oral contraceptives) were redeemed after the pregnancy start.

Table 4. Maternal Antithyroid Drug Treatment Including Details on the Start of Propylthiouracil Treatment in Relation to the Early Pregnancy Period

Case	Year of child's birth	Year of first ATD prescription	PTU treatment started before or after the pregnancy start[a]	Day of PTU start in pregnancy[b]
Face and neck cases				
1	1996	1996	After	43
2	1997	1996	After	16
3	2003	2000	Before	—
4	2004	2003	After	41
5	2005	1999	Before	—
6	2006	2000	Before	—
7	2007	2005	Before	—
Urinary system cases				
8	1997	1995	Before	—
9	1998	1995	Before	—
10	2002	2001	Before	—
11	2003	2001	Before	—
12	2005	2004	After	54
13	2007	2005	Before	—
14	2008	2005	After	47

[a]Pregnancy start was calculated by subtracting gestational age at birth from the date the child was born.
[b]Days after pregnancy start (first day of last menstrual period) when the first PTU prescription was redeemed.
ATD, antithyroid drug; PTU, propylthiouracil.

and after birth the prevalence is approximately 0.5% (23). Such defects are twice as common in boys, and all the cases we present were boys (23).

The structural abnormality can be either at the level of the kidney, the ureteropelvic junction or in the lower urinary tract affecting the ureter, the bladder or urethra. The majority of the children we describe had a diagnosis of congenital hydronephrosis, and the underlying structural defect was at the ureteropelvic junction, the ureter ostium or the urethra. Renal cystic diseases compromise a heterogeneous group of disorders that can be genetic, developmental or acquired (24). Two children had a birth defect at the level of the kidney (single cyst of kidney). One of these children was followed up to the age of 12 years, but had no hospital contacts in Denmark related to the birth defect after the year of birth. The other child was born in 2007 and was still an outpatient in 2009. In addition to single cyst of the kidney, he also had a diagnosis of congenital hydronephrosis.

PTU exposure and birth defects

We previously reported a significantly higher prevalence of birth defects diagnosed before the age of 2 years after PTU exposure in early pregnancy (4). This finding is in contrast to previous studies (6,25,26) and it questions the current guidelines that often recommend that pregnant women should be switched from MMI/CMZ to PTU in early pregnancy (27). No previous study has shown an increased risk of birth defects in the face and neck region after PTU exposure, possibly because such defects were not included in study outcomes. Two previous studies (28,29) found more cases of birth defects in the urinary system after PTU exposure in line with our findings, but in these studies the prevalence was not statistically different from the prevalence in nonexposed children. Because the reports of an association between PTU exposure in early pregnancy and birth defects are new and question current guidelines (27), it is of clinical importance to review individual cases underlying the overall epidemiologic associations. We included both major and minor malformations. If birth defects are less severe, they may often remain undiagnosed for a longer period of time, and we therefore now expanded the follow-up period to include cases of birth defects diagnosed in the face and neck region and in the urinary system after the age of 2 years, and we found similar associations. The present review of the 14 cases of birth defects after PTU exposure in early pregnancy substantiates data on an individual level in terms of characteristics of both the child and the mother.

It is difficult to estimate the consequences and severity of specific birth defects. All the children we describe had more than one hospital contact related to the birth defect, and many children underwent surgery and/or had complicating infections. In a screening of 10,734 male subjects at a median age of 19 years in Singapore, a total of 121 individuals (1.13%) were found to have a preauricular sinus (20). The majority of these (76%) were previously asymptomatic and those who had experienced symptoms most commonly reported sinus discharge. Only two cases had undergone surgery. Thus, this study from Singapore questions whether the prevalence of such defects after PTU exposure would also be higher if asymptomatic cases were identified.

Considering birth defects of the urinary system, the spectrum of malformations is diverse. A simple renal cyst detected by ultrasound in early pregnancy may resolve without any sequelae (30). On the other hand, prenatally detected hydronephrosis increases the risk of being hospitalized with pyelonephritis during the first year of life (31) and urinary tract obstruction *in utero* may induce renal dysplasia, which is the major cause of chronic renal failure in children (32,33). We previously found that both PTU and MMI/CMZ treatment in early pregnancy were associated with an increased risk of birth defects in the urinary system (4). Thus, in the case where the

mother switched from MMI to PTU in early pregnancy (case 14), it remains uncertain whether the birth defect observed was specific to PTU or related to MMI/CMZ treatment.

Consistent evidence suggests that MMI/CMZ treatment in early pregnancy may be associated with severe malformations previously combined as a specific embryopathy including choanal atresia, esophageal atresia, omphalocele, omphalomesenteric anomalies, and aplasia cutis (4–6). Considering this, the PTU-associated birth defects we describe tend to be less severe, but a longer follow-up period would be warranted to fully clarify the consequences.

Strengths and limitations

The birth year of the children ranged from 1996–2008. Thus, the length of the follow-up period differed, and it cannot be excluded that children born in the later years could have registrations related to the birth defect after the end of follow-up. We only had information on hospital diagnoses and surgical procedure codes, but children with birth defects of the face and neck may have been diagnosed and treated by a specialist in ear, nose, and throat diseases working in private clinics outside the hospital. In addition to this, less severe defects may be undiagnosed or diagnosed years after the birth of the child and therefore not registered as a birth defect. However, we believe this potential misclassification would be independent of the exposure. Considering complicating infections, we did not have information on the treatment with antibiotics during hospitalization, which may underestimate the information obtained. Considering maternal ATD treatment, we only had information on redeemed prescription of drugs, and we had no information on the dose, compliance, or duration of the treatment for mothers with only one prescription registered.

Perspectives

The clinical dilemma in the treatment of maternal hyperthyroidism in pregnancy is the choice between the currently available thionamides, which may all be associated with an increased risk of birth defects (2–4). Consistent evidence suggests that MMI/CMZ treatment in early pregnancy may be associated with severe birth defects (4–6). In the present review of cases of PTU-associated birth defects, these defects resulted in more than one hospital contact and often in surgical treatment, but none of the children died and the number of hospital contacts was limited. Thus, compared with MMI/CMZ, the PTU-associated birth defects seemed less severe, but further studies on the teratogenic role of PTU are needed. Clinicians should be aware of and report possible PTU-associated birth defects.

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