Birth Defects After Early Pregnancy Use of Antithyroid Drugs: A Danish Nationwide Study

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Introduction: Hyperthyroidism in pregnant women should be adequately treated to prevent maternal and fetal complications, but teratogenic effects of antithyroid drug (ATD) treatment have been described. Evidence is still lacking in regard to the safety and choice of ATD in early pregnancy.

Objective: Our objective was to determine to which degree the use of methimazole (MMI)/carbimazole (CMZ) and propylthiouracil (PTU) in early pregnancy is associated with an increased prevalence of birth defects.

Methods: This Danish nationwide register-based cohort study included 817 093 children live-born from 1996 to 2008. Exposure groups were assigned according to maternal ATD use in early pregnancy: PTU (n = 564); MMI/CMZ (n = 1097); MMI/CMZ and PTU (shifted in early pregnancy [n = 159]); no ATD (ATD use, but not in pregnancy [n = 3543]); and nonexposed (never ATD use [n = 811 730]). Multivariate logistic regression was used to estimate adjusted odds ratio (OR) with 95% confidence interval (95% CI) for diagnosis of a birth defect before 2 years of age in exposed versus nonexposed children.

Results: The prevalence of birth defects was high in children exposed to ATD in early pregnancy (PTU, 8.0%; MMI/CMZ, 9.1%; MMI/CMZ and PTU, 10.1%; no ATD, 5.4%; nonexposed, 5.7%; $P < .001$). Both maternal use of MMI/CMZ (adjusted OR = 1.66 [95% CI 1.35–2.04]) and PTU (1.41 [1.03–1.92]) and maternal shift between MMI/CMZ and PTU in early pregnancy (1.82 [1.08–3.07]) were associated with an increased OR of birth defects. MMI/CMZ and PTU were associated with urinary system malformation, and PTU with malformations in the face and neck region. Choanal atresia, esophageal atresia, omphalocele, omphalomesenteric duct anomalies, and aplasia cutis were common in MMI/CMZ-exposed children (combined, adjusted OR = 21.8 [13.4–35.4]).

Conclusions: Both MMI/CMZ and PTU were associated with birth defects, but the spectrum of malformations differed. More studies are needed to corroborate results in regard to early pregnancy shift from MMI/CMZ to PTU. New ATD with fewer side effects should be developed. **(*J Clin Endocrinol Metab* 98: 4373–4381, 2013)**

Hyperthyroidism is one of the most common endocrine disorders in pregnancy. It complicates 0.1% to 0.4% of pregnancies and is most frequently caused by Graves' disease (1). Untreated overt hyperthyroidism may present a risk to the mother and the fetus and has been associated with maternal heart failure (2), preterm birth (3), low birth weight (3), and even fetal death (4). Thus, adequate treatment should be started at the time of diagnosis (5). Antithyroid drug (ATD) is the preferred treatment for hyperthyroidism in pregnant women (5), and the available drugs are thionamides, including propylthiouracil (PTU), methimazole (MMI), and carbimazole (CMZ). CMZ is a prodrug to MMI (6). These drugs all cross the placenta (7), are equally effective in the treatment of hy-

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For editorial see page 4332

Abbreviations: ATC, Anatomical Therapeutic Chemical; ATD, antithyroid drug; 95% CI, 95% confidence interval; CMZ, carbimazole; DNHR, Danish National Hospital Register; DNPR, Danish National Prescription Register; MMI, methimazole; OR, odds ratio; PTU, propylthiouracil; VSD, ventricular septal defect.

perthyroidism in pregnancy (8), and have the same potential to induce fetal hypothyroidism (9).

As recently reviewed in detail (6, 10, 11), an emerging body of literature addresses the possible side effects of ATD treatment in pregnancy, and evidence from a number of studies suggests that MMI/CMZ use in the first trimester of pregnancy may be associated with an increased risk of birth defects. More specifically, a number of birth defects, eg, choanal atresia, esophageal atresia, omphalocele, omphalomesenteric duct anomalies, and aplasia cutis have recurred in case reports over time leading to the term MMI/CMZ embryopathy (10, 12). These findings, in combination with the absence of an association between PTU and birth defects in several studies (13–16), have made PTU the drug of choice in early pregnancy in various guidelines (17). On the other hand, liver failure has been reported in relation to PTU treatment (18), 1 case of aplasia cutis (19) and 1 case of choanal atresia (20) have been reported in children exposed to PTU in utero, and experimental studies have recently cast doubt on the safety of using PTU in early pregnancy (21, 22). As brought forward by several authors (11, 23), no final conclusion on the use of ATD in early pregnancy has been given, and larger studies are needed in particular to ascertain the potential teratogenic role of PTU in early pregnancy.

Information on prescriptions of drugs has been registered in the Danish National Prescription Register (DNPR) since 1995 (24). Using Danish nationwide registers, we identified live-born children exposed to PTU and/or MMI/CMZ in early pregnancy, described the prevalence of birth defects, and estimated the odds ratio (OR) of birth defects in these children and in children born to mothers treated with ATD before or after the pregnancy in comparison with a large group of nonexposed children.

Subjects and Methods

Study population and design

We conducted a population-based cohort study. All Danish citizens are assigned a unique 10-digit personal identification number that is used in all the nationwide registers. All data were linked in Statistic Denmark and were made available only in encrypted form. The study was approved by the Danish Data Protection Agency. Institutional review board permission is not required for register-based studies in Denmark.

In the Danish Civil Registration System (25), we identified all live-born children in Denmark between January 1, 1996, and December 31, 2008 (n = 849 416), and in the Medical Birth Registry (26), we identified their mothers and information on maternal age and parity at the time of the child's birth and gestational age, birth weight, and gender of the child as well as information on whether it was a singleton or multiple pregnancy.

The exposure: ATD

The DNPR (24) holds data on all prescription drugs redeemed from Danish pharmacies since 1995. Prescription information including the patient's personal identification number in encrypted form, the type of drug prescribed according to the Anatomical Therapeutic Chemical (ATC) classification system, and the date of sale is transferred from the pharmacies to the register. Thyroid hormones (ATC H03A) and ATD (ATC H03B) are sold solely as prescription drugs in Denmark, and we identified all prescriptions dispensed between January 1, 1995, and December 31, 2008.

The pregnancy period was estimated by subtracting gestational age at birth from the date the child was born. The registered gestational age was based on the first day of the last menstrual period, because the exact time of conception is unknown. On average, conception would have taken place 2 weeks after the pregnancy start values given in this study. We defined the child as exposed to maternal ATD in early pregnancy if the mother had at least 1 redeemed prescription of ATD in the time period ranging from 6 months before pregnancy start to the end of the 10th gestational week. We identified 1820 children who fulfilled this criterion, and these children were grouped according to the type of ATD treatment in this period: PTU exposure (PTU prescriptions only [n = 511] or MMI/CMZ in the beginning of the period changing to PTU before pregnancy start [n = 53]), MMI/CMZ exposure (MMI/CMZ prescriptions only [n = 1,079] or PTU in the beginning of the period, changing to MMI/CMZ before pregnancy start [n = 18]), and MMI/CMZ and PTU exposure (both MMI/CMZ and PTU prescriptions after pregnancy start: MMI/CMZ followed by PTU [n = 149] or PTU followed by MMI/CMZ [n = 10]). Among children not exposed to maternal ATD in early pregnancy, we predefined the no-ATD-exposure group (n = 3543) as children born to mothers who had solely redeemed prescriptions of ATD more than 12 months before pregnancy start or more than 12 months and less than 5 years after birth of the child. Finally, children born to mothers with no redeemed prescription of ATD or thyroid hormones from 1995 to 2008 and no diagnosis of hyperthyroidism registered from 1977 to 2008 in the Danish National Hospital Register (DNHR) (27) were categorized as nonexposed (n = 811 730). Children who did not fulfill the criteria for any of the exposure groups were not included in the study (3.0%), and most of these children (2.0%) were excluded from the nonexposed group because the mother had redeemed prescriptions of thyroid hormones.

The outcome: birth defects

Diagnosis of birth defects was obtained from the DNHR. The DNHR (27) holds nationwide data on both in- and outpatient visits to any Danish hospital since 1995, and the eighth international classification of disease (ICD-8) has been replaced by ICD-10 since 1994. We included all in- and outpatient visits with a main or additional diagnosis of birth defects (ICD-10: DQ00–DQ99) registered before the child was 2 years old.

Covariates

From Statistic Denmark we obtained information on maternal cohabitation, income, origin, and geographical residence at the time of the child's birth. For cohabitation and origin, we replaced missing values by available information in the preceding or after 5 (origin) or 3 (cohabitation) years, whichever came first. Information on maternal smoking during the pregnancy was

obtained from the DNHR. In the DNHR, we ascertained whether the mother had a diagnosis of preeclampsia/eclampsia (ICD-8: 637.03–637.19 and ICD-10: O14–O15.0) and/or diabetes (ICD-8: 249.00–250.09 and ICD-10: E10.0–E14.9 and O24–O24.9) from 1977 to 2008, and in the DNPR, we obtained information on redeemed prescriptions of antidiabetics from 1995 to 2008 (ATC A10). Children with missing values on maternal covariates were excluded from the study (0.8%).

Statistical analyses

The primary outcome was predefined as a diagnosis of 1 or more birth defects (all types combined) before the child was 2 years old. The secondary outcome was predefined as the specific type of malformations according to ICD-10 subgroup classification. In addition, we listed all individual malformations registered in children exposed to ATD in early pregnancy. The χ^2 test was used to compare the prevalence of birth defects by exposure groups, and logistic regression was used to estimate crude and adjusted ORs with 95% confidence interval (95% CI) for birth defects in the no-ATD-exposure, PTU-exposure, and MMI/CMZ-exposure groups compared with nonexposed children. Robust SEs were used to account for multiple pregnancies.

In supplementary analyses, we addressed the prevalence and types of birth defects in the group of children exposed to both PTU and MMI/CMZ in early pregnancy. In sensitivity analyses, we evaluated potential confounding by maternal smoking and examined the impact of possible intermediates (maternal diabetes, preeclampsia/eclampsia, birth weight, and gestational age). Finally, analyses were restricted to firstborn children and to singleton pregnancies.

Statistical analyses were performed using STATA version 11 (Stata Corp). A 5% level of significance was chosen.

Results

Altogether, 817 093 children were included in the study, and 0.22% of these children were exposed to maternal ATD in early pregnancy (PTU, 0.07%; MMI/CMZ, 0.13%; PTU and MMI/CMZ, 0.02%). In the MMI/CMZ group, a minority of the children were exposed to CMZ (n = 137). Table 1 shows characteristics of the children and their mothers at the time of the child's birth.

Overall prevalence of birth defects

The prevalence of birth defects is described by exposure group in Table 2, which includes the total number of children in each exposure group and the number of children with a diagnosis of 1 or more birth defects before the age of 2 years. Overall, the prevalence of birth defects significantly differed according to exposure group.

Figure 1 illustrates the crude and adjusted ORs with 95% CI for having 1 or more birth defects diagnosed before the age of 2 years according to exposure group. The adjusted model changed the estimates only slightly, and both MMI/CMZ and PTU were associated with an increased prevalence of birth defects in comparison with nonexposed children. On the other hand, children born to mothers with previous or later ATD use, but no ATD treatment in the pregnancy (no ATD exposure in pregnancy), did not have an increased OR of birth defects.

Subgroups of birth defects

The overall prevalence of birth defects was not significantly different for PTU vs MMI/CMZ exposure (P = .437, Figure 1). As our secondary outcome, we examined whether the types of birth defects differed according to type of ATD exposure. All diagnoses of birth defects (DQ00–99) were grouped into 13 overall combined groups (Table 2). In 8 of these groups, the prevalence of birth defects differed significantly according to exposure as also illustrated in Figure 2, where the risk of having birth defects diagnosed in each of the groups are ranked from the highest to the lowest estimated OR. MMI/CMZ was associated with a significantly increased OR of birth defects in a number of organ systems, whereas PTU solely revealed a significant increased OR of face and neck and urinary system malformations. The number of exposed cases was smaller in the PTU group, and the CIs were consequently wider.

MMI/CMZ embryopathy

In Supplemental Table1 (published on The Endocrine Society's Journals Online website at http://jcem.endojournals.org), we added to Table 2 all individual diagnoses of birth defects that were diagnosed in at least 1 exposed child in the MMI/CMZ or PTU group. Notably, various birth defects previously reported in relation to MMI/CMZ embryopathy were registered, including choanal atresia, esophageal atresia, omphalocele, omphalomesenteric duct anomalies, and aplasia cutis. In the MMI/CMZ group, 17 children had at least 1 of these diagnoses, whereas only 1 case occurred in the PTU group (aplasia cutis). The adjusted OR with 95% CI for the risk of having one of these birth defects diagnosed was 21.8 (13.4–35.4) in MMI/CMZ-exposed vs nonexposed children. After the exclusion of these birth defects, both MMI/CMZ and PTU exposure still revealed an increased OR of birth defects (MMI/CMZ, 1.39 [1.11–1.75]; PTU exposure 1.39 [1.02–1.91]).

Both PTU and MMI/CMZ exposure

A subgroup of children (n = 159) were born to mothers who redeemed prescriptions of both MMI/CMZ and PTU after pregnancy start and before the end of the 10th gestational week. In this group, 16 children (10.1%) had a diagnosis of a birth defect, and the adjusted OR with 95% CI for having birth defects diagnosed vs nonexposed was 1.82 (1.08–3.07). Most the children (n = 149) were born

Table 1. Characteristics of the Children and Their Mothers at the Time of the Child's Birth[a]

	No ATD Exposure[b]		ATD Exposure[c]		Nonexposed[d]	
	n	%	n	%	n	%
Children	3543		1820		811 730	
Maternal characteristics						
Age, y						
<25	424	12.0	121	6.7	111 464	13.7
25–29	1160	32.7	565	31.0	283 769	35.0
30–34	1250	35.3	697	38.3	286 729	35.3
35–39	604	17.0	377	20.7	112 040	13.8
≥40	105	3.0	60	3.3	17 728	2.2
Parity[e]						
1	1365	38.5	620	34.1	352 317	43.4
2	1299	36.7	748	41.1	303 350	37.4
3	615	17.4	293	16.1	115 309	14.2
≥4	264	7.4	159	8.7	40 754	5.0
Pregnancy						
Singleton	3393	95.8	1730	95.1	778 727	95.9
Multiple	150	4.2	90	4.9	33 003	4.1
Cohabitation						
Married	2121	59.9	1110	61.0	468 943	57.8
Not married	1422	40.1	710	39.0	342 787	42.2
Income (quartiles)						
1st (lowest)	168	4.7	91	5.0	48 284	5.7
2nd	1323	37.4	621	34.1	266 220	32.7
3rd	1585	44.7	823	45.2	372 086	45.8
4th	467	13.2	285	15.7	128 140	15.8
Origin						
Born in Denmark	2937	82.9	1577	86.7	717 104	88.3
Not born in Denmark	606	17.1	243	13.3	94 626	11.7
Residence[f]						
West Denmark	1985	56.0	973	53.5	442 594	54.5
East Denmark	1558	44.0	847	46.5	369 136	45.5
Smoking during pregnancy[g]						
Yes	803	24.5	351	21.0	148 762	19.8
No	2481	75.5	1317	79.0	603 306	80.2
Child characteristics						
Gender						
Boy	1807	51.0	925	50.8	416 709	51.3
Girl	1736	49.0	895	49.2	395 021	48.7
Gestational age, wk[h]						
<37	280	7.9	168	9.3	52 342	6.5
37–41	3005	85.2	1549	85.4	695 762	86.2
≥42	242	6.9	96	5.3	59 180	7.3
Birth weight, g[i]						
Mean (SD)	3443 (622)		3392 (633)		3494 (602)	

[a] The χ^2 test was used for categorical variables and 1-way ANOVA for continuous variables (no ATD exposure vs ATD exposure vs nonexposed): $P < .001$ except for the variables pregnancy ($P = .146$), residence ($P = .132$), and gender of the child ($P = .278$).

[b] Children born to mothers who only had redeemed prescriptions of ATD >12 months before pregnancy start or >12 months and ≤5 years after the birth of the child.

[c] Children born to mothers with prescriptions of ATD redeemed in the time period ranging from 6 months before pregnancy start to the end of the 10th gestational week.

[d] Children born to mothers with no prescriptions of ATD and/or thyroid hormones redeemed 1995 to 2008 and no diagnosis of hyperthyroidism in the DNHR from 1977 to 2008.

[e] Live births and stillbirths including index pregnancy.

[f] Divided by the Great Belt.

[g] Smoking or smoking cessation during the pregnancy. Children with missing values on maternal smoking were not included (n = 60 073).

[h] Children with missing values on gestational age or registration of gestational age <20 or >45 weeks were not included (n = 4469).

[i] Children with missing values on birth weight or registration of birth weight <500 or >6000 g were not included (n = 7175).

Table 2. Prevalence of Birth Defects According to Maternal ATD Use in Early Pregnancy

	No ATD[a]	MMI/CMZ[b]	PTU[c]	Nonexposed[d]	*P*[e]
Total number of children	3543	1097	564	811 730	
Children diagnosed with birth defects according to ICD-10[f]					
All birth defects (DQ00–99), n (%)	190 (5.36)	100 (9.12)	45 (7.98)	45 982 (5.66)	<.001
Children diagnosed with birth defects according to ICD-10 subgroups, n (%)[g]					
Nervous system (DQ00–07)	5 (0.14)	4 (0.36)	0	1378 (0.17)	.310
Eye (DQ10–15)	2 (0.06)	6 (0.55)	0	1507 (0.19)	.007
Ear (DQ16–17)	2 (0.06)	1 (0.09)	1 (0.18)	487 (0.06)	.688
Other malformations of face and neck (DQ18)	0	0	3 (0.53)	625 (0.08)	<.001
Circulatory system (DQ20–28)	49 (1.38)	26 (2.37)	10 (1.77)	9396 (1.16)	.001
Respiratory system (DQ30–38)	17 (0.48)	14 (1.28)	5 (0.89)	4550 (0.56)	.009
Digestive system (DQ39–45)	3 (0.08)	11 (1.0)	2 (0.35)	2201 (0.27)	<.001
Genital organs (DQ50–56)	22 (0.62)	9 (0.82)	6 (1.06)	6586 (0.81)	.564
Urinary system (DQ60–DQ64)	11 (0.31)	9 (0.82)	5 (0.89)	2431 (0.30)	.001
Musculoskeletal system (DQ65–78)	78 (2.20)	24 (2.19)	15 (2.66)	17 793 (2.19)	.902
Other malformations of musculoskeletal system, (DQ79)	2 (0.06)	8 (0.73)	0	615 (0.08)	<.001
Integumentary system including breast malformations (DQ80–84)	9 (0.25)	7 (0.64)	1 (0.18)	1165 (0.14)	<.001
Others (DQ85–99)	12 (0.34)	10 (0.91)	3 (0.53)	3632 (0.45)	.097

[a] Children born to mothers who only had redeemed prescriptions of ATD >12 months before pregnancy start or >12 months and ≤5 years after birth of the child.

[b] Children born to mothers with prescriptions of MMI or CMZ redeemed in the time period ranging from 6 months before pregnancy start to the end of the 10th gestational week and no PTU exposure.

[c] Children born to mothers with prescriptions of PTU redeemed in the time period ranging from 6 months before pregnancy start to the end of the 10th gestational week and no MMI/CMZ exposure.

[d] Children born to mothers with no prescriptions of ATD and/or thyroid hormones redeemed 1995 to 2008 and no diagnosis of hyperthyroidism in the DNHR from 1977 to 2008.

[e] χ^2 test: no ATD vs MMI/CMZ vs PTU vs nonexposed.

[f] ICD-10 is the 10th edition of the international classification of disease. Data are the numbers of children with a diagnosis of birth defects registered in the DNHR before the age of 2 years.

[g] All birth defects (ICD-10: DQ00–DQ99) were grouped into 13 overall combined groups. ICD-10 did not include the following 4-digit codes: DQ08, DQ09, DQ19, DQ29, DQ46, DQ47, DQ48, DQ49, DQ57, DQ58, DQ59, DQ88, and DQ94.

to mothers who changed from MMI/CMZ to PTU and thus seemed to follow current recommendations. The median time from pregnancy start to the shift to PTU treatment was 44 (range 3–70) days. Table 3 lists information on maternal ATD use and the types of birth defects registered (13 cases). Some birth defects were similar to those described in the Supplemental Table 1 for MMI/CMZ and PTU exposure including choanal atresia, ventricular septal defect (VSD), and malformations of the face and neck region. A small group of children (n = 10) were born to mothers who changed from PTU to MMI/CMZ, and in this group, 3 children had a diagnosis of birth defect (esophageal atresia without fistula, accessory fingers, and unspecified malformation of limb).

Sensitivity analyses (data not shown)

Restricting analyses to the first-born child did not change the results; neither did the exclusion of multiple pregnancies. Adjustment for maternal smoking during the pregnancy did not indicate that our results were confounded by smoking. Also, the associations were unaltered after adjustment for possible intermediates including maternal diabetes (yes/no), preeclampsia/eclampsia (yes/no), birth weight (<2500 or ≥2500 g), and gestational age at delivery (<37, 37–41, or ≥42 wk).

Discussion

In a Danish nationwide cohort study, exposure to either MMI/CMZ or PTU or to both in early pregnancy was associated with an increased prevalence of birth defects. On the other hand, maternal ATD treatment before or after the pregnancy revealed no increased prevalence of birth defects. The spectrum of birth defects differed according to MMI/CMZ and PTU exposure, and some of the

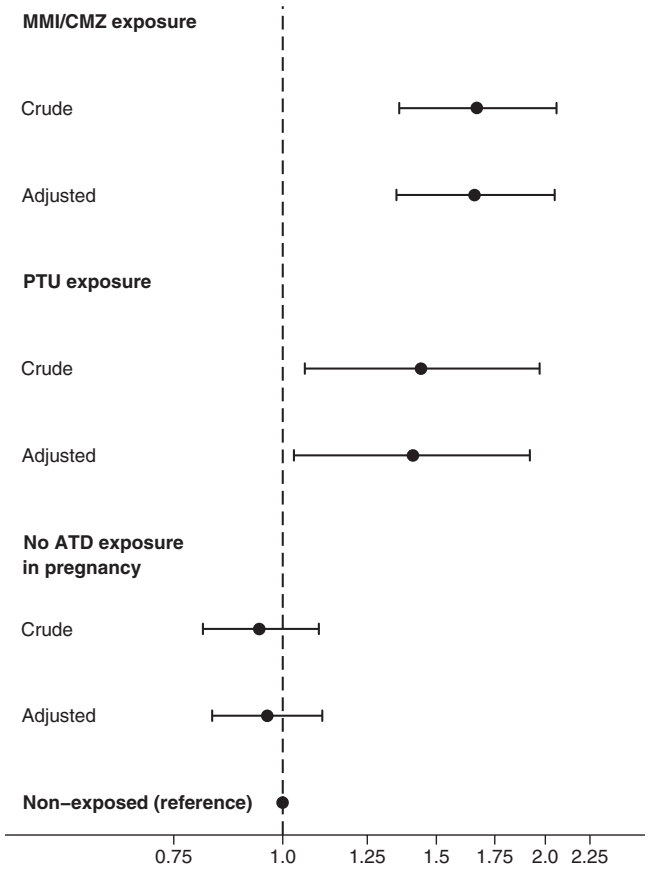

Figure 1. Crude and adjusted odds ratio (AOR) with 95% CI for having one or more birth defects diagnosed before 2 years of age in children exposed to methimazole/carbimazole (MMI/CMZ), propylthiouracil (PTU) and children born to mothers with previously or later antithyroid drug (ATD) use (no ATD exposure in pregnancy) vs nonexposed (never ATD use). Adjusted model included birth year of the child (1996–1997, 1998–2000, 2001–2003, 2004–2006, 2007–2008), gender of the child (boy/girl), singleton/multiple pregnancy and the following maternal variables obtained at the time of the child's birth: age (< 25, 25–29, 30–34, 35–39, ≥ 40 years), parity (1, 2, 3, ≥ 4), cohabitation (married/not married), income (first, second, third, fourth quartile), origin (born in Denmark/not born in Denmark) and residence (East/West Denmark).

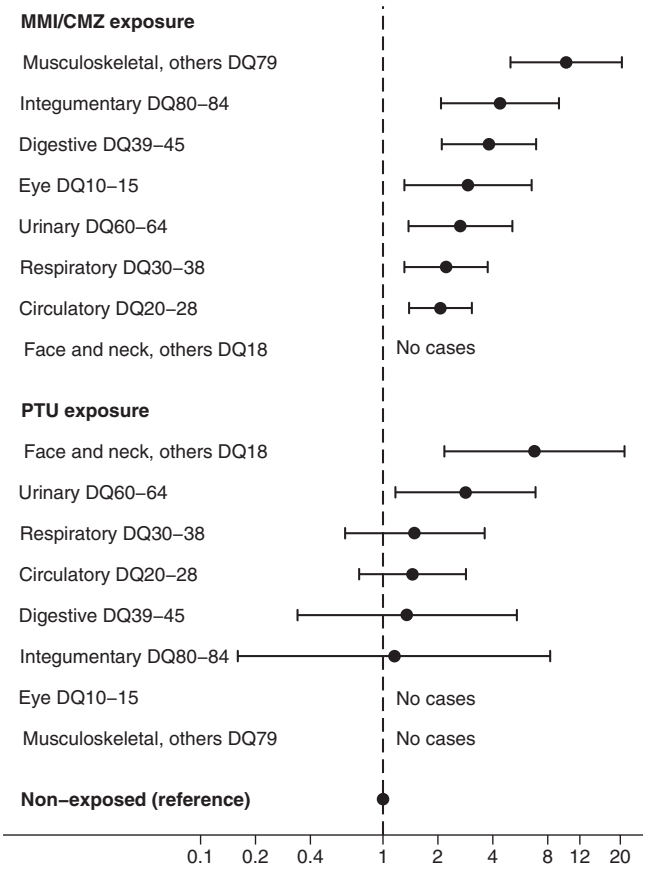

Figure 2. Subgroups of birth defects with significant association to antithyroid drug (ATD) therapy (Table 2). Adjusted OR, ranked for each drug, with 95% CI for birth defects in children exposed to methimazole/carbimazole (MMI/CMZ) or propylthiouracil (PTU) vs nonexposed (never ATD use). Adjusted model included the same variables as in Figure 1.

malformations observed in children exposed to MMI/CMZ were similar to previous reports (10–12).

MMI/CMZ embryopathy

Evidence from many case reports (6, 10, 11), from case-control studies (28, 29), from a review of women with Graves' disease who became pregnant (16), and from a recently published experimental study in zebrafish embryos (30) rather consistently pointed toward a causal relationship between MMI/CMZ exposure and birth defects, although 2 recent population-based studies did not report an association (31, 32).

In Denmark, MMI is the most commonly used drug for treatment of hyperthyroidism in pregnancy. Only a small group of children were exposed to CMZ, and because CMZ is a prodrug to MMI, we combined MMI and CMZ exposure. Our results corroborate previous findings in relation to MMI/CMZ exposure and add weight to the evidence that MMI/CMZ exposure in the teratogenic period of pregnancy might be associated with a specific embryopathy including choanal atresia, omphalocele, esophageal atresia, omphalomesenteric duct anomalies, and aplasia cutis (10, 12). In our study, 1.60% of the MMI/CMZ-exposed children (20 of 1256) developed these malformations, which is very similar to a recent study from Japan (20 of 1231) (16). In the Japanese study (16), none of the children exposed to PTU or to Graves' disease without medical treatment in pregnancy developed these malformations, whereas in our study, 1 case of aplasia cutis occurred among children exposed to PTU and 2 of the cases of choanal atresia and 1 case of esophageal atresia were exposed to both MMI/CMZ and PTU, however, with PTU treatment in less than one-third of the teratogenic period. In our nonexposed group, 583 of 811 730 children (0.07%) and in our no-ATD-exposure group, 2 of 3543 children (0.06%) developed these malformations.

Malformation of the nipples has also been reported as

Table 3. Birth Defects in Children Exposed to Both MMI/CMZ and PTU in Early Pregnancy

Maternal ATD Treatment: Change from MMI/CMZ to PTU in Early Pregnancy[a]		Child Characteristics	
First Prescription of MMI/CMZ[b]	PTU Prescription Redeemed, Days After Pregnancy Start[c]	Birth Year	Diagnosis of Birth Defect[d]
>6 months before pregnancy start	24	2005	DQ531, undescended testicle, unilateral
77 days before pregnancy start	38	2005	DQ673, plagiocephaly
>6 months before pregnancy start	40	2008	DQ650, dislocation of hip, unilateral
131 days before pregnancy start	41	2004	DQ181, preauricular sinus and cyst
19 days after pregnancy start	43	1996	DQ188, other specified malformations of face and neck
>6 months before pregnancy start	47	2008	DQ620, hydronephrosis
>6 months before pregnancy start	50	2006	DQ300, choanal atresia
25 days before pregnancy start	52	2002	DQ105, stenosis and stricture of lacrimal duct
26 days before pregnancy start	54	2002	DQ525, fusion of labia
>6 months before pregnancy start	58	1997	DQ749, malformation of limb, unspecified
138 days before pregnancy start	63	2001	DQ314, laryngeal stridor
>6 months before pregnancy start	63	2000	DQ300, choanal atresia
10 days after pregnancy start	69	2004	DQ210, VSD

[a] Children born to mothers who first redeemed prescriptions of MMI/CMZ (in the time period ranging from 6 months before pregnancy start to the end of the 10th gestational week) and then changed to redeem prescriptions of PTU in early pregnancy (after pregnancy start and before the end of the 10th gestational week).

[b] Number of days before/after pregnancy start when the first MMI/CMZ prescription was redeemed, 1995 to 2008.

[c] Number of days after pregnancy start when the first PTU prescription in the pregnancy was redeemed.

[d] Diagnosis of birth defect registered in the DNHR before the child was 2 years old. The 5-character diagnosis refers to ICD-10 (10th revision of the international classification of disease).

a part of the MMI/CMZ embryopathy (12), but none of the children exposed to ATD in our study were diagnosed with breast malformations. On the other hand, anomalies of the eye occurred more frequently in children exposed to MMI/CMZ, consistent with previous reports (10, 33).

Birth defects of the circulatory system

MMI/CMZ exposure was associated with an increased prevalence of malformations of the circulatory system. PTU exposure was also associated with an increased prevalence, but this did not reach statistical significance. Cases of VSDs have previously been reported in relation to MMI/CMZ exposure (10, 34). In the group of children exposed to only MMI/CMZ in our study, most children had heart septal defects (n = 15) and the prevalence of VSD was 1.0%. One case of VSD occurred in children exposed to both PTU and MMI/CMZ. The prevalence of VSD in children exposed to only PTU was 0.35%, similar to nonexposed children (0.42%).

The recent study from Japan (16) did not detect an increased risk of heart defects in relation to either MMI or PTU. Among PTU-exposed children in our study, 10 children were diagnosed with malformations of the circulatory system including heart septal defects, pulmonary valve stenosis, pulmonary artery stenosis, and patent ductus arteriosus. In a case-control study by Clementi et al (29), PTU exposure was associated with a significantly increased risk of situs inversus with or without dextrocardia and cardiac outflow tract defects, and in a recent experimental study of frog embryos, PTU and not MMI was teratogenic during early embryogenesis with alterations in left-right axis development (22). Another experimental study in mice also suggested that PTU may have teratogenic potential; in this study, blood in the pericardial sac as a feature of abnormal cardiac or vascular function was observed more often in PTU- than in MMI-exposed embryos (21).

Other birth defects

Exposure to either MMI/CMZ or PTU was associated with an increased risk of malformations of the urinary system. In relation to MMI/CMZ, many different malformations occurred, whereas in relation to PTU, a single cyst of the kidney, hydronephrosis, and megaloureter were the only malformations registered. No previous study re-

ported a significant association between urinary system malformations and MMI/CMZ exposure, but a recent review including 72 case reports listed 3 cases of renal anomalies but without further specification (6). In the study by Clementi et al (29), PTU was associated with unilateral kidney a/dysgenesis, and in a case report, a child exposed to PTU had fetal hydrops and urogenital anomalies including vesicovaginal fistula and pyelectasia (35).

In our study population, malformations of the face and neck region occurred more frequently in children exposed to PTU, and in addition, 2 cases were registered in children exposed to both MMI/CMZ and PTU. To our knowledge, no previous study has reported preauricular sinus/cyst and sinus, fistula, and cyst of the branchial cleft in children exposed to PTU.

Methodological considerations

Our study is large and population-based. It was possible to estimate the risk of relatively rare malformations and to avoid differential recall of exposure. We did not have results of maternal thyroid function tests, and we could not test for a possible interaction between ATD treatment and thyroid function abnormality (36). The fact that the pattern of birth defects differed between MMI/CMZ and PTU may, however, suggest that the birth defects were caused by ATD treatment and not by abnormal thyroid function (confounding by indication).

The validity of Danish prescription data has been found to be high (37). We did not have information on the daily dose of medicine, and we do not know whether the women actually took the medicine. However, patients in Denmark are required to pay part of the cost, and the compliance for the use of thyroid medication in pregnancy was previously examined and found to be high (38). The predefined exposure window included prescriptions of ATD redeemed within 6 months before pregnancy start. In post hoc analyses, we evaluated the risk of birth defects when this window was limited to 3 months before pregnancy start and also to the early pregnancy period alone, and associations were similar.

The predictive value and completeness of a diagnosis of birth defects in Danish registers have been evaluated and were reported to be 80% to 90% (39). Our study included only live-born children, which underestimates the incidence of malformations. On the other hand, if ATD use and maternal control for thyroid disease increases the likelihood of a minor birth defect to be registered, results would be biased toward a higher prevalence in exposed children. However, many of the birth defects registered after ATD use were severe and would presumably have been registered early, independent of any maternal disease. MMI is in general the most used drug for treatment of hyperthyroidism in Denmark, and the PTU-exposed group of children was smaller. We predefined exposure and outcome, and we believe misclassification would be nondifferential. We were able to adjust for a number of potential confounders, but unmeasured or residual confounding might still exist.

Perspectives

PTU treatment may in rare cases lead to severe liver failure (18). In our study population, 1 case of maternal liver failure was registered in week 9 of pregnancy among 723 PTU-exposed pregnancies (data not shown). More studies are needed to evaluate the risk of liver failure during PTU therapy in pregnancy. MMI (or CMZ) is the recommended initial drug therapy for hyperthyroidism (5), but a much discussed exception is treatment in early pregnancy, because PTU is considered less teratogenic than MMI/CMZ. In our study, early pregnancy exposure to both MMI/CMZ and PTU was associated with an increase in the prevalence of birth defects. Whereas 5.7% of the children in the control group had birth defects, this was considerably higher in ATD-exposed children, corresponding to an excess of 2 to 4 cases of birth defects per 100 live births. Many different birth defects had been registered; however, the picture of MMI/CMZ embryopathy found in MMI/CMZ-exposed children seemed to be much less common after PTU exposure.

It has been proposed that women becoming pregnant while taking MMI/CMZ should shift to PTU when pregnancy is confirmed (17). However, in the small group of women who changed to PTU after pregnancy start in the present study, we found no indication of amelioration of birth defects. This may emphasize the importance of shifting to PTU already when pregnancy is planned, but more and larger studies on this are needed.

Conclusion

Results of the present study corroborate previous findings in relation to MMI/CMZ and additionally suggest an increased prevalence of birth defects in children exposed to PTU, although this may be less than in relation to MMI/CMZ exposure. Further studies are needed to evaluate the teratogenic potential of PTU and the role of thyroid dysfunction in early pregnancy. It is imperative to treat overt hyperthyroidism in pregnant women, but the use of ATD in early pregnancy should be limited when possible. For the present, it may be optimal to shift women planning pregnancy from MMI/CMZ to PTU before pregnancy start, as previously suggested (11), and new ATDs with fewer side effects should be developed (40).

Acknowledgments

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