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Treatment of Hyperthyroidism in Pregnancy and Birth Defects

Maurizio Clementi, Elena Di Gianantonio, Matteo Cassina, Emanuele Leoncini, Lorenzo D. Botto, Pierpaolo Mastroiacovo, and the SAFE-Med Study Group*

Servizio di Informazione Teratologica (M.C., E.D.G., M.C.), Genetica Clinica, Department of Pediatrics, University of Padova, 35128 Padova, Italy; Centre of the International Clearinghouse for Birth defects Surveillance and Research (E.L., P.M.), 00195 Roma, Italy; and Division of Medical Genetics (L.D.B.), Department of Pediatrics, University of Utah Health Sciences Center, Salt Lake City, Utah 84132

Context: Clinical hyperthyroidism is not uncommon in pregnancy, with a reported prevalence of 0.1 to 0.4%. The available antithyroid drugs are propylthiouracil and methimazole/carbimazole.

Objectives: In this report we examined the association of both drugs with congenital malformations using data from the International Clearinghouse for Birth Defects Surveillance and Research.

Design: The study used a case-affected control analysis and included 18,131 cases with malformations and reported first-trimester exposure to medication. A total of 127 subjects were born to mothers with known first-trimester antithyroid drug exposure.

Results: Among the 52 groups of malformations that were analyzed, situs inversus ± dextrocardia, isolated unilateral kidney a/dysgenesis, and cardiac outflow tract defects were associated with prenatal exposure to propylthiouracil based on three, two, and five cases, respectively. Prenatal exposure to methimazole/carbimazole was significantly associated with choanal atresia, omphalocele, and total situs inversus ± dextrocardia ($P < 0.01$).

Conclusions: Further studies are required to exhaustively evaluate the associations between propylthiouracil and birth defects because of the low number, the lack of biological plausibility, and the possibility of underdiagnosis. Association between methimazole/carbimazole exposure and omphalocele and choanal atresia is consistent with previous reports and definitely suggests that these malformations could be part of a specific, even if rare, embryopathy. (***J Clin Endocrinol Metab* 95: 0000–0000, 2010**)

Clinical hyperthyroidism is not uncommon in pregnancy, with a reported prevalence of 0.1 to 0.4%, and it is caused most frequently by Graves' disease (1). Overt hyperthyroidism in pregnancy requires treatment with suppressive thyrostatic agents to ensure maternal euthyroid status (2).

The available antithyroid drugs (ATD) are propylthiouracil (PTU) and methimazole (MMI)/carbimazole (CZ). Both medications cross the human placenta with relatively similar transfer and placental clearance rates (3).

PTU and MMI are equivalent in terms of their efficacy in the treatment of clinical hyperthyroidism. Some reports suggest an association between a specific congenital malformation (MMI embryopathy) and prenatal exposure to MMI (4, 5). For PTU, the association with possible teratogenic risk is unclear, but this difference could be an artifact due to the lack of studies on PTU.

Nonetheless, in view of these reports, it is generally recommended that, when available, PTU be preferred as the initial therapy for maternal hyperthyroidism during the first trimester of pregnancy (6, 7).

In this report, we examined the association of both PTU and MMI with congenital malformations using data from

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* Members of the SAFE-Med Study Group are listed at the end of the text.

Abbreviations: ATD, Antithyroid drugs; CI, confidence interval; CZ, carbimazole; MMI, methimazole; OR, odds ratio; OTD, outflow tract defects; PTU, propylthiouracil; SI ± D, situs inversus ± dextrocardia; UK-A/D, unilateral kidney a/dysgenesis.

"Surveillance of Adverse Fetal Effects of Medications (SAFE-Med)" (8), an international ongoing project within the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) whose major goal is to monitor the birth defect risk of medications used during the first trimester of pregnancy.

Subjects and Methods

Study design

The study used a case-affected control analysis. In this "exposed case-only" design, all infants had a major birth defect and were exposed to some medication (8). Cases were those with the specific malformation being tested, and the controls were those with any other malformation; "exposed" were those with a reported exposure to the medication being tested, and "unexposed" were those exposed to any other medication. This pairwise contrast was assessed for every malformation and every medication.

Each pairwise contrast generates an odds ratio (OR) and confidence interval (CI) that estimate the strength and the direction of the association between a particular malformation and a particular medication, compared with the average clustering of medications and malformations in the entire dataset. An increased OR is considered a signal for further evaluation of a particular malformation-medication association.

Setting

The study was conducted within the framework of the International Clearinghouse for Birth Defects Surveillance and Research.

Participants

The study population consisted of liveborn infants, stillbirths, and terminations of pregnancy with a major birth defect and with a reported exposure to a medication during the first trimester, ascertained by one of the participating surveillance programs.

Data sources

Twelve surveillance programs participated in this study. The coverage, structure, methods, and sources of ascertainment, described elsewhere, varied from program to program.

Variables

Data were collected and reviewed by an international team (clinicians and epidemiologists). The malformation(s) and medication(s) were coded and classified using a standardized approach, as previously described (8). These data were reviewed for malformation classification by a clinician with expertise in genetics and dysmorphology to separate subjects of isolated major malformations from those of multiple congenital anomalies. Syndromic cases were included only in the control group. Malformations were coded using the British Pediatric Association modification of the International Classification of Diseases system. The translation of codes in the 52 selected groups for the analysis was reviewed by a single investigator (P.M.). The malformations were analyzed by 52 major groups, separately for isolated malformations and multiple congenital anomalies, and then also for total malformations.

All programs but one submitted original medication information that was coded centrally using the Anatomical Therapeutic Chemical system (ATC, http://www.whocc.no/) by a single investigator.

Statistical methods

Associations between medications and malformations were evaluated in a 2×2 table. The OR, 99% CI, and exact *P* values were computed for each association. Analyses were stratified by surveillance program. Heterogeneity among strata was evaluated using the Breslow-Day test. For associations without significant heterogeneity among strata, a Mantel-Haenzel pooled estimate and its exact *P* value were obtained. Further adjustment could include covariates such as year of birth, maternal age, and parity. Associates were tested (for each malformation) separately for isolated and multimalformed cases, to help assess associations with specific phenotypes, and for the malformation group in the aggregate (isolated and multimalformed cases together) to help detect weak associations that could be similar in isolated and multimalformed cases but could be missed in the separate analyses because of limited statistical power. The analyses were carried out using SAS 9.1 (SAS Institute, Inc., Cary, NC) and STATA (StataCorp LP, College Station, TX) software programs. A $P < 0.01$ level was considered significant.

Results

The study included 18,131 cases with malformations and reported first-trimester exposure to medication. A total of 127 subjects were born to mothers with known first-trimester ATD exposure (PTU, 47; CZ/MMI, 80) (Tables 1 and 2).

Among the 52 groups of malformations that were analyzed, situs inversus ± dextrocardia (SI ± D), unilateral kidney a/dysgenesis (UK-A/D), and cardiac outflow tract defects (OTD) were significantly associated with prenatal exposure to PTU ($P < 0.01$) based on three, two, and five cases, respectively. However, the 99% CI were not significant for total cases of UK-A/D and isolated and multimalformed cases of cardiac OTD.

Prenatal exposure to CZ/MMI was significantly associated with choanal atresia, omphalocele, and total SI ± D ($P < 0.01$). The association with choanal atresia was based on four cases, of which one had additional malformations (limb reduction defect and craniosynostosis). The 99% CI of multimalformed cases was not significant. The association with omphalocele was based on six exposed cases. Two of these six cases had additional malformations (one had hydronephrosis, the other had bladder exstrophy and anorectal atresia and could be classified as omphalocele-exstrophy-imperforate anus-spinal defects complex). The 99% CI and the *P* value of multimalformed cases were not significant. The association with SI ± D was based on one case without additional malformations, and the 99% CI was not significant.

TABLE 1. Congenital anomalies associated with PTU exposure during pregnancy (ATC code H03BA-H03B02A) and congenital anomalies found associated to CZ/MMI (ATC code H03BB-H03BB01-H03BB02), as in Table 2

Malformation	OR adj	99% CI Lower	99% CI Upper	*P* value	Case subjects exposed	Case subjects not exposed	Control subjects exposed	Control subjects not exposed
SI ± D								
Total cases	32.16	1.64	630.66	<0.00001	3	22	44	18062
Isolated cases	15.10	1.15	198.43	0.00028	1	15	40	16314
Multimalformed cases	95.49	2.35	3877.00	<0.00001	2	7	4	1748
UK-A/D								
Total cases	7.27	0.95	55.85	0.00329	2	212	45	17872
Isolated cases	9.70	1.30	72.23	0.00034	2	150	39	16179
Multimalformed cases	nc				0	62	6	1693
OTD								
Total cases	4.12	1.06	16.06	0.00364	5	731	42	17353
Isolated cases	4.01	0.85	18.84	0.01234	4	633	37	15696
Multimalformed cases	9.60	0.08	1226.78	0.14048	1	98	5	1657
Choanal atresia								
Total cases	nc				0	58	47	18026
Omphalocele								
Total cases	nc				0	154	47	17930

OR adj, OR adjusted by register; nc, not computable.

Discussion

Careful monitoring of thyroid function is critical in preventing the many potential complications that can occur in pregnancies of mothers with hyperthyroidism. Maternal complications include hypertension, thyroid storm, heart failure, preterm labor, and placental abruption. Fetal and neonatal complications include stillbirth, intrauterine growth restriction, low birth weight, heart failure, hyperthyroidism, and hypothyroidism with or without goiter (9, 10). Currently, the drugs used to control maternal hyperthyroidism are PTU, CZ, and MMI (a metabolite of carbimazole). These medications have been used for decades, and concerns about fetal risks, particularly for CZ and MMI, have been raised for many years. The first reports noted scalp defects in children whose mothers were treated with CZ during pregnancy. Additional case reports have helped define an MMI embryopathy (4, 11–13). However, case reports are subject to many potential

TABLE 2. Congenital anomalies associated with CZ/MMI exposure during pregnancy (ATC code H03BB-H03BB01-H03BB02) and congenital anomalies found associated to PTU (ATC code H03BA-H03B02A), as in Table 1

Malformation	OR adj	99% CI Lower	99% CI Upper	*P* value	Case subjects exposed	Case subjects not exposed	Control subjects exposed	Control subjects not exposed
Choanal atresia								
Total cases	36.96	6.60	207.09	0.00000	4	54	76	17997
Isolated cases	37.91	5.32	270.06	0.00000	3	36	69	16262
Multimalformed cases	16.46	0.70	387.30	0.00193	1	18	7	1735
Omphalocele								
Total cases	10.40	2.90	37.26	<0.00001	6	148	74	17903
Isolated cases	11.88	2.53	55.89	<0.00001	4	85	68	16213
Multimalformed cases	8.48	0.36	200.44	0.03653	2	63	6	1690
SI ± D								
Total cases	10.18	0.66	157.14	0.00675	1	24	79	18027
Isolated cases	15.56	0.90	269.36	0.00086	1	15	71	16283
Multimalformed cases	nc				0	9	8	1744
OTD								
Total cases	1.17	0.30	4.58	0.76203	4	732	76	17319
Isolated cases	1.36	0.35	5.36	0.55957	4	633	68	15665
Multimalformed cases	nc				0	99	8	1654
UK-A/D								
Total cases	1.12	0.28	16.48	0.91653	1	213	79	17838
Isolated cases	1.56	0.11	23.15	0.67030	1	151	71	16147
Multimalformed cases	nc				0	62	8	1691

OR adj, OR adjusted by register; nc, not computable.

biases, and need to be followed up by studies that use more robust study designs. Using prospective data from the European Teratology Information Services, Di Gianantonio *et al.* (5) concluded that there might be a higher than expected incidence of choanal and esophageal atresia in fetuses exposed to MMI between the third and seventh weeks of gestation. Further reports of congenital anomalies, specifically of choanal atresia, have suggested that MMI may be a new teratogen (14). There is also the question of whether hyperthyroidism (in addition to or instead of the medication) may contribute to the birth defect risk (15, 16). It has also been suggested that the different mechanisms of action of the two drugs could be the cause of the different teratogen risks associated with them.

Fewer data are available on PTU exposures. A recent prospective, controlled cohort study, including 115 PTU-exposed pregnancies and 1141 controls, observed comparable rates of major anomalies in the two groups (7). PTU may cause fetal/neonatal hypothyroidism with or without goiter (7). However, Momotani *et al.* (17) observed that the risk of fetal hypothyroidism is not different between women with Graves' disease taking PTU and those taking MMI.

A major challenge of such prospective cohort studies of exposed pregnancies is that they require very large sample sizes to estimate risk of rare conditions such as birth defects, particularly uncommon birth defects such as choanal atresia. Retrospective case control studies are less costly and easier to conduct but are prone to limitations such as retrospective collection of exposure data, which can be imprecise or biased (*e.g.* due to differential recall of exposures in case *vs.* control mothers). However, the two methodologies can complement one another (18, 19).

The design used in this study attempted to address recall bias by including only cases of birth defects. Multiple tests (exposed *vs.* not exposed for isolated, multiple, and total malformations stratified by year and surveillance program) were performed. A P value less than 0.01 was chosen to decrease the number of false-positive results.

The analysis identified three malformations associated with PTU exposure: SI ± D, UK-A/D, and OTD. The statistical results are, however, difficult to interpret because of the result of the 99% CI of the ORs and the low number of affected subjects. Further studies are required to exhaustively evaluate these associations. Furthermore, whereas the association with situs inversus was statistically significant, its biological plausibility is unclear. Situs viscerum inversus is associated with several genetic conditions, such as those involving primary ciliary dysgenesis or dynein mutations, and these would need to be excluded before an association can be inferred. In addition, this association has not been noted before, so replication of this finding is important in our view. A borderline association with UK-A/D was found only in the group with an isolated malformation; this result could be spurious because UK-A/D can be misdiagnosed in newborns. The cardiac OTD are not significantly associated with PTU exposure when considered as isolated and multimalformed cases. Other cardiac malformations are not associated with prenatal exposure to ATD. Further studies are needed before concluding that the observed association is true.

The exposure to CZ/MMI was found to be significantly associated with omphalocele and choanal atresia and reserves several points of interest. These associations are consistent with previous reports (4, 5, 11–13) and definitely suggest that these malformations could be part of a specific, even if rare, embryopathy. It remains unclear whether the association is driven by maternal disease, the medication, or the combination of both factors (16).

Finally, the prescription of PTU later in pregnancy and during lactation should take into account the reported risk of hepatotoxicity in both the mother and the child (20).

SAFE-Med Study Group Members

Eduardo E. Castilla—CEMIC, Buenos Aires, Argentina; and ECLAMC-FIOCRUZ, Rio de Janeiro, Brazil. Marian K. Bakker—EUROCAT Northern Netherlands, Department of Genetics, University Medical Centre Groningen, University of Groningen, The Netherlands. Sebastiano Bianca—ISMAC Registry, Genetica Medica, ARNAS Garibaldi Nesima, Catania, Italy. Guido Cocchi—IMER, Institute of Neonatology and Preventive Pediatric Health Care, Bologna University, Bologna, Italy. Caterine de Vigan—INSERM, Epidemiological Research Unit on Perinatal and Women's Health, Villejuif, France. Paul Merlob—Department of Neonatology, Rabin Medical Center, Beilinson Campus, Petah Tikva, Israel. Anna Pierini—Institute of Clinical Physiology, Unit of Epidemiology, CNR Area di Ricerca di San Cataldo, Pisa, Italy. Gioacchino Scarano—Campania Birth Defects Register, Division of Medical Genetics, General Hospital "G. Rummo" Benevento, Italy; and Regional Epidemiologic Observatory, Health Council, Benevento, Italy. Antonin Sipek—National Registry of Congenital Anomalies in the Czech Republic, Department of Medical Genetics, Thomayer's University Hospital, Prague, Czech Republic. And Michiko Yamanaka—Kanawaga Children's Medical Center, Division of Obstetrics and Gynecology, Yokohama City, Japan.

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Address all correspondence and requests for reprints to: Maurizio Clementi, Department of Pediatrics, Via Giustiniani 3, 35128 Padova, Italy. E-mail: maurizio.clementi@unipd.it.

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