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Thyroid Medication Use and Birth Defects in the National Birth Defects Prevention Study

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Abstract

Background: Thyroid disorders are common among reproductive-aged women, with hypothyroidism affecting 2 to 3% of pregnancies, and hyperthyroidism affecting an additional 0.1 to 1%. We examined associations between thyroid medications and individual birth defects using data from the National Birth Defects Prevention Study (NBDPS).

Methods: The NBDPS is a multisite, population-based, case–control study that included pregnancies with estimated delivery dates from 1997 to 2011. We analyzed self-reported thyroid medication use from mothers of 31,409 birth defect cases and 11,536 unaffected controls. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using logistic regression for birth defects with five or more exposed cases, controlling for maternal age, race/ethnicity, and study center. Crude ORs and exact 95% CIs were estimated for defects with 3 to 4 exposed cases.

Results: Thyroid hormone was used by 738 (2.3%) case and 237 (2.1%) control mothers, and was associated with anencephaly (OR = 1.68; 95% CI, 1.03–2.73), holoprosencephaly (OR = 2.48; 95% CI, 1.13–5.44), hydrocephaly (1.77; 95% CI, 1.07–2.95) and small intestinal atresia (OR = 1.81; 95% CI, 1.04–3.15). Anti-thyroid medication was used by 34 (0.1%) case and 10 (<0.1%) control mothers, and was associated with aortic valve stenosis (OR = 6.91; 95% CI, 1.21–27.0).

Conclusion: While new associations were identified, our findings are relatively consistent with previous NBDPS analyses. Our findings suggest thyroid medication use is not associated with most birth defects studied in the NBDPS, but may be associated with some specific birth defects.

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These results should not be interpreted to suggest that medications used to treat thyroid disease are teratogens, as the observed associations may reflect effects of the underlying thyroid disease.

Keywords

anti-thyroid medication; birth defects; congenital malformations; thyroid medication; thyroid hormone

Introduction

Thyroid disorders are common among women of reproductive age, with hypothyroidism affecting an estimated 2 to 3% of pregnancies, and hyperthyroidism affecting an additional 0.1 to 1% (Ecker and Musci, 1997; Stagnaro-Green et al., 2011). Current guidelines recommend that thyroid disease be treated during pregnancy to prevent both maternal and fetal complications (Alexander et al., 2017). Thyroid hormone was the most commonly reported prescription medication used among pregnant women in the United States, underlining the importance of understanding whether it is associated with birth defects (Tinker et al., 2015). Anti-thyroid medications, propylthiouracil (PTU) and methimazole (MMI), are less frequently reported during pregnancy (Bowman and Vaidya, 2011).

Studies examining thyroid medication use during pregnancy often do not distinguish between thyroid disease and the medications taken for it (Adams et al., 1989; Khoury et al., 1989; Rasmussen et al., 2007). The existing literature regarding the association between thyroid hormone use and birth defects is sparse and inconclusive. A teratogenic effect of treatment with thyroid hormone is unlikely, because it is the same as thyroid hormone that is produced endogenously. Yet, some animal studies suggest that thyroid hormone supplements may be teratogenic (Giroud et al., 1951; Miyamoto, 1967; Lavado-Autric et al., 2003), and epidemiologic studies have mixed results (Heinonen, 1977; Queisser-Luft et al., 1996; Wikner et al., 2008; Browne et al., 2009; Samadi et al., 2015). Accumulating evidence suggests anti-thyroid medications may have teratogenic effects, with MMI associated with more severe birth defects (Browne et al., 2009; Clementi et al., 2010; Bowman and Vaidya, 2011; Yoshihara et al., 2012; Andersen et al., 2013, 2014; Andersen and Laurberg, 2014; Laurberg and Andersen, 2014, 2016).

An earlier analysis of the National Birth Defects Prevention Study (NBDPS) data examined the association between thyroid medication use and birth defects (Browne et al., 2009). Analyzing births from 1997 to 2004, the authors found that thyroid hormone use was associated with hydrocephaly and hypospadias, and that anti-thyroid medication use was associated with aortic valve stenosis and anorectal atresia. That analysis, however, was limited by small numbers of exposed infants with each birth defect and lack of available data on thyroid function. We sought to update estimates of the association between thyroid medication use and the risk of major birth defects using NBDPS data on births from 1997 to 2011.

Materials and Methods

The NBDPS is a large, multisite, population-based, case–control study of birth defects that included infants with estimated delivery dates from October 1997 through December 2011 (Reefhuis et al., 2015). Infants with one or more of 30 different categories of major structural birth defects (cases), excluding those attributed to a known chromosomal or single-gene abnormality, were ascertained through birth defects surveillance programs in 10 states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah). Control infants were live births without major birth defects randomly selected from hospital records or birth certificates in the same time period and geographic area as the cases. Each study site obtained Institutional Review Board approval for the NBDPS, and case and control mothers provided informed consent.

Case inclusion criteria have been described previously (Reefhuis et al., 2015). Briefly, case information, including medical record information, was obtained from birth defects surveillance programs. Clinical geneticists reviewed each case to determine eligibility and to classify case infants as having isolated (only one defect), multiple, or complex birth defects (Rasmussen et al., 2003). Congenital heart defect (CHD) cases were further classified according to a structured protocol that took into account cardiac phenotype, complexity, and presence of noncardiac defects (Botto et al., 2007).

Muscular ventricular septal defects (VSDs) were actively ascertained during the first study year; other VSDs were actively ascertained through 2005 (Botto et al., 2007). We excluded VSDs from the remaining study years, as they were only ascertained if another eligible birth defect was present. Some defects (oral clefts, glaucoma, cataracts, and pulmonary valve stenosis) were not ascertained by all sites for all years (Rasmussen et al., 2003; Reefhuis et al., 2015). When analyzing these, cases and controls were excluded for the sites and years with incomplete data. Microtia included dysplastic ear pinna and stenosis or atresia of external auditory canal. Infants with intestinal atresia limited to the duodenum were grouped and counted as duodenal atresias; other intestinal atresias (ileal, jejunal, and multiple intestinal atresias or stenoses) were counted as small intestinal atresias. Infants with esophageal or small intestinal atresia that occurred as a component of a VATER/VACTERL association defects (vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities) were classified as having multiple defects. Only second- and third-degree hypospadias cases were included and the control group was restricted to males.

Trained interviewers conducted computer-assisted telephone interviews with mothers of case and control infants between 6 weeks to 24 months after the estimated date of delivery. The average time between the estimated delivery date and interview was 11.5 months among case mothers and 9.2 months among control mothers. Overall, 66.7% of eligible case and 63.7% of eligible control mothers participated in the interview. Mothers reported demographics, pregnancy history, health conditions, and exposures before and during pregnancy. Mothers reported medications taken during pregnancy, including timing, frequency, and duration of medication use. Reported medications were coded using the Slone Epidemiology Center Drug Dictionary.

Mothers interviewed before 2006 were asked if they had “any other disease or illnesses that we have not already talked about, such as chronic disease, infectious disease, or sexually transmitted diseases.” Mothers interviewed in or after 2006 were asked if they had “any other chronic disease or illness that we have not talked about such as asthma, thyroid disease, an autoimmune disease, or other chronic or long-term diseases.” Because the NBDPS did not have questions specifically designed to collect information on thyroid disease and its medications, we screened responses to these questions and comment fields for mention of thyroid disease. A study investigator, blinded to case–control status, manually reviewed reported thyroid disease to determine the type of thyroid disease (Graves disease, Hashimotos disease, hyperthyroidism, thyroid cancer, autoimmune thyroid disease, or unspecified thyroid disease) and to identify untreated thyroid disease. Infants were considered exposed if the mother reported thyroid medication use at any time in the month before conception through the third month of pregnancy (i.e., the periconceptional period), as this is the critical period in fetal development associated with most structural birth defects. Given that it is often hard to pinpoint the exact date of conception, we included the month before pregnancy to ensure all exposed infants were identified.

Thyroid medication use was grouped and analyzed by type: (1) thyroid hormone medications (liothyronine, levothyroxine, thyroxine, and thyroid hormone), and (2) anti-thyroid medications (PTU and MMI). Our analysis excluded infants of mothers who had incomplete information on medications, reported untreated thyroid disease, reported using unknown thyroid medications, or reported using a thyroid medication during pregnancy, but outside the periconceptional period (Fig. 1).

We used chi-square tests to compare characteristics among exposed and unexposed infants and Cochran-Armitage trend tests to explore medication trends over time. We used logistic regression to estimate associations between each type of thyroid medication and the risk of birth defects. We calculated adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for birth defects with five or more exposed cases, controlling for maternal age at delivery (a continuous variable), race/ethnicity (non-Hispanic white, Non-Hispanic black, Hispanic, other), and state of residence at the time of the infant’s birth. We explored including additional covariates in the models (maternal education, number of previous pregnancies, prepregnancy body mass index (weight in kilograms/height in meters^2), use of any treatment for infertility, smoking, and folic acid-containing supplement use), but models with these additional covariates produced similar estimates. For birth defects with three or four exposed cases, we calculated crude ORs (cOR) and Fisher’s exact CIs. Estimates were not calculated for birth defects with fewer than three exposed cases.

To reduce heterogeneity, we conducted a sub-analysis restricted to infants with isolated noncardiac defects (only one defect). Similarly, we conducted a sub-analysis restricted to cases with only one CHD or a well-recognized combination of defects that are considered a single CHD, referred to as “simple isolated” cases. We also explored differences in results between the years included in the publication by Browne et al. (1997–2004) and the remaining years of NBDPS (2005–2011). When numbers permitted, we explored associations between birth defects and PTU, the anti-thyroid medication most commonly used in NBDPS. Analyses were conducted in SAS (9.3; SAS Corporation, Cary, NC).

Results

After excluding 791 case and 293 control infants, 31,409 case and 11,536 control infants remained in the analysis (Fig. 1). Overall, 1018 mothers reported periconceptional thyroid medication use: 738 (2.3%) case and 237 (2.1%) control mothers reported using thyroid hormone, and 34 (0.1%) case and 10 (<0.1%) control mothers reported using anti-thyroid medication (Fig. 1). One control mother reported both anti-thyroid medication and thyroid hormone use. Of those reporting periconceptional anti-thyroid medication use, 30 mothers (25 case and 5 control) exclusively used PTU, 6 mothers (3 case and 3 control) used only MMI, and 8 mothers (6 case and 2 control) used both PTU and MMI. Reported thyroid hormone use increased over the study period, but anti-thyroid medication use did not (Fig. 2). Table 1 displays the distribution of selected characteristics by thyroid hormone use among controls. Because only 10 control mothers reported periconceptional anti-thyroid medication use, the distribution of characteristics by anti-thyroid medication use is not shown. Table 2 displays the reported type of thyroid disease for thyroid hormone and anti-thyroid medication users, by case/control status.

We calculated aORs for 34 birth defects, cORs for 11 birth defects, and did not calculate ORs for 10 defects with less than 3 exposed cases (Tables 3 and 4). Thyroid hormone use was significantly associated with four birth defects: anencephaly (aOR = 1.68; 95% CI, 1.03–2.73), holoprosencephaly (aOR = 2.48; 95% CI, 1.13–5.44), hydrocephaly (aOR = 1.77; 95% CI, 1.07–2.95), and small intestinal atresia (aOR = 1.81; 95% CI, 1.04–3.15). When we restricted to isolated birth defects, the aORs for anencephaly, holoprosencephaly, and hydrocephaly remained significantly elevated, and we also found significant associations for cleft palate (aOR = 1.45; 95% CI, 1.03–2.04), anorectal atresia (aOR = 1.87; 95% CI, 1.09–3.21), and longitudinal limb deficiency (aOR = 1.90; 95% CI, 1.02–3.55). While we did not find any statistically significant associations between thyroid hormone use and the individual CHDs examined, we found an association between thyroid hormone use and atrioventricular septal defects when we restricted to only simple isolated cases (aOR = 2.22; 95% CI, 1.07–4.63). We observed nonsignificantly elevated associations (defined as OR>1.50) between thyroid hormone use and eight birth defects. We found non-significant protective associations (defined as OR <0.66) between thyroid hormone use and three birth defects.

Because anti-thyroid medication use was rare, we calculated crude estimates for 6 of 55 defects included in the study (Table 5). Anti-thyroid medication was significantly associated with aortic valve stenosis (cOR = 6.91; 95% CI, 1.21–27.0). We also observed nonsignificantly elevated ORs > 1.50 for five birth defects. PTU use was significantly associated with three birth defects: anorectal atresia (cOR = 8.62; 95% CI, 1.71–40.1), coarctation of the aorta, (cOR = 7.97; 95% CI, 1.58–37.1), and aortic valve stenosis (cOR = 13.8; 95% CI, 2.13–71.2).

Results comparing the associations between each thyroid medication and birth defects by time period are presented in Supplementary Table S1 and S2, which are available online.

Discussion

In our analysis of almost 43,000 infants in the NBDPS, we did not find significant associations between thyroid hormone use and most of the 55 birth defects examined, but did find significantly increased risk of four defects: anencephaly, holoprosencephaly, hydrocephaly, and small intestinal atresia. Our findings for anencephaly, holoprosencephaly, and hydrocephaly were similar regardless of whether we examined all cases or restricted the analysis to isolated cases.

The previous NBDPS analysis of thyroid hormone use and birth defects identified three significant associations: hydrocephaly, hypospadias, and isolated anorectal atresia (Browne et al., 2009). We found elevated ORs for these defects in the current analysis of births from 1997 to 2011, but all three estimates were smaller in magnitude than previously reported, and our hypospadias OR was not statistically significant in the current analysis. We found significant associations with five birth defects previously examined in the NBDPS, but not found to be significantly associated with thyroid hormone use: anencephaly, holoprosencephaly, small intestinal atresia, isolated cleft palate, and isolated longitudinal limb deficiency (Browne et al., 2009).

For anencephaly, the number of cases exposed to thyroid hormone in the earlier analysis was small ($n = 4$), and the authors calculated a crude, nonsignificant, slightly protective OR; our estimate was significant, elevated, and based on 19 exposed case infants. The direction and magnitude of the ORs for holoprosencephaly, small intestinal atresia, isolated cleft palate, and isolated longitudinal limb deficiencies were similar in the two NBDPS analyses, but reached statistical significance only in the current analysis of births from the entire NBDPS time period. Some differences are evident when comparing the results by time period (Supplementary Table S1 and S2). We are uncertain of why some of the ORs for thyroid hormone use differed during the two time periods; however, regression to the mean, as observed for some estimates, is common with increasing sample size. For this reason, we consider the best estimate from the study to be from the data from all study years.

The birth defects we identified as significantly associated with thyroid hormone use have not been previously identified in studies outside NBDPS. Other studies often combine thyroid disease and medication use or combine birth defects, which may account for the differences between our findings and the existing literature. Thyroid hormones are essential for development of the fetal nervous system (Schroeder and Privalsky, 2014). Other studies have noted an association between maternal thyroid hormone use and central nervous system defects when analyzed in aggregate (Adamson et al., 1995; Queisser-Luft et al., 1996; Lavado-Autric et al., 2003), and with other central nervous system defects not included in the NBDPS, such as abnormal corpus callosum development (Samadi et al., 2015). A Swedish study by Wikner et al. (2008) found associations between thyroid hormone use and severe kidney malformations. We did not find an association with bilateral renal agenesis or hypoplasia, the only kidney birth defect included in the NBDPS, but the cases from the Swedish study had different subtypes of kidney malformations, which may explain the different findings (Wikner et al., 2008).

While we did not identify any associations with specific CHDs in our main analysis, two studies have found associations, but both studies reported on CHDs in aggregate (Cedergren et al., 2002; Wikner et al., 2008), and one used a combined thyroid medication exposure (Cedergren et al., 2002). Craniosynostosis has been linked to thyroid disease/medication use, a finding that has also been reported in NBDPS data (Rasmussen et al., 2007). We did not find any significant associations with craniosynostosis.

Our analysis found that 0.1% of case and control mothers reported using anti-thyroid medications during pregnancy. Based on crude ORs, anti-thyroid medication use was significantly associated with aortic valve stenosis. The previous NBDPS analysis identified two elevated crude associations with anti-thyroid medication: aortic valve stenosis and anorectal atresia (Browne et al., 2009). The previous and current NBDPS analyses included the same exposed aortic valve stenosis cases ($n = 3$) and anorectal atresia cases ($n = 4$); no additional exposed cases were identified from 2005 to 2011. Therefore, the cORs currently reported for these two birth defects are closer to the null with narrower 95% CIs than the previous NBDPS analysis.

Uncertainty persists regarding the relative safety of anti-thyroid medications during pregnancy; some studies have found no association with birth defects (Wing et al., 1994; Chen et al., 2011; Korelitz et al., 2013; Gianetti et al., 2015; Lo et al., 2015), while others have identified associations with specific anti-thyroid medications (Clementi et al., 2010; Bowman and Vaidya, 2011; Yoshihara et al., 2012; Andersen et al., 2013, 2014; Andersen and Laurberg, 2014). Among studies suggesting anti-thyroid medications have teratogenic effects, MMI is generally associated with more severe birth defects than PTU (Browne et al., 2009; Clementi et al., 2010; Bowman and Vaidya, 2011; Yoshihara et al., 2012; Andersen et al., 2013; 2014; Andersen and Laurberg, 2014; Laurberg and Andersen, 2014, 2016). Several studies have linked MMI to an increased risk of choanal atresia, aplasia cutis, and gastrointestinal atresia (Clementi et al., 2010; Bowman and Vaidya, 2011; Yoshihara et al., 2012; Andersen et al., 2013; Lo et al., 2015).

An earlier descriptive study of NBDPS choanal atresia cases noted an association between any thyroid medication use (either thyroid hormone or anti-thyroid medication) and choanal atresia (Kancherla et al., 2014). Due to the small number of exposed cases ($n = 2$), we did not calculate an OR between anti-thyroid medications and choanal atresia and did not see any association among thyroid hormone users. Small numbers prohibited us from exploring MMI users in more depth. Both exposed infants with choanal atresia had a mother who took MMI, but one infant was also exposed to PTU during the periconceptional period, and neither had aplasia cutis (not a NBDPS defect) or a gastrointestinal atresia.

We explored crude associations between PTU and birth defects, finding increased risk of anorectal atresia, coarctation of the aorta, and aortic valve stenosis. The prior NBDPS analysis did not examine specific anti-thyroid medications. Studies have linked PTU with an increased risk of face/neck malformations, but the defects associated with PTU in the current analysis have not been associated with PTU use previously (Bowman and Vaidya, 2011; Andersen et al., 2013, 2014; Laurberg and Andersen, 2015).

Some of the differences between current and previous NBDPS findings may be explained by differences in the composition of mothers with thyroid disease over the course of NBDPS (Browne et al., 2009). Several studies reported that pregnant women with subclinical hypothyroidism, particularly those with elevated thyroid-stimulating hormone (TSH) levels, may also be at increased risk for adverse outcomes (Allan et al., 2000; Casey et al., 2005, 2006; Botto et al., 2007; Casey and de Veciana, 2014). Thus, some authors suggest treating pregnant women at lower TSH levels (Carney et al., 2014; Casey and de Veciana, 2014). If mothers were being treated at lower TSH levels during the later years of NBDPS, the severity of the underlying thyroid disease may differ among our study population and the population previously analyzed (Browne et al., 2009).

Figure 2 demonstrates a significant increase in thyroid hormone use from 1997 to 2011, which is consistent with the possibility of an increase in treatment of subclinical hypothyroidism. We also found that a larger proportion of mothers reported untreated thyroid disease in the later years of the NBDPS (0.03% of controls from 1997 to 2004, 1.2% from 2005 to 2011). While this may represent an increase in nodular thyroid disease and thyroid autoimmunity, both typically untreated, it may also suggest an increase in diagnoses of subclinical hypothyroidism, with a portion of these foregoing treatment. This may be related to changes in thyroid disease screening during pregnancy. While guidelines do not recommend screening all pregnant women (Alexander et al., 2017), the debate over screening has persisted for more than a decade (Haddow et al., 1999; Lazarus, 2011; Gronowski et al., 2012; Vissenberg et al., 2012; Mannisto et al., 2013; Casey and de Veciana, 2014; Taylor et al., 2015). Given this debate, more women may have been screened and some of the self-reported “thyroid disease” may represent borderline serum TSH and not true thyroid disorders.

Because antibodies cross the placenta freely, maternal antibodies, including thyroid-stimulating immunoglobulin, transmitted to the fetus may play a role in causing birth defects by stimulating excess fetal production of thyroid hormone (Rasmussen et al., 2007). Other maternal thyroid autoantibodies (including, thyroperoxidase and thyroglobulin) have been associated with adverse pregnancy outcomes including miscarriage and preterm birth (Stagnaro-Green et al., 1990; Prummel and Wiersinga, 2004; Haddow et al., 2010; Thangaratinam et al., 2011; Mehran et al., 2013). We cannot evaluate this, because the NBDPS did not collect detailed diagnostic information or the presence and type of antibody abnormalities. A teratogenic effect of treatment with thyroid hormone is not likely because it is the same as thyroid hormone produced endogenously. Maternal thyroid disease, thyroid-related antibodies, or thyroid medications could all play a role in the development of birth defects.

The NBDPS relies on retrospective self-reports of medication use during pregnancy, making recall bias a concern. However, we expect this to be minimal, as thyroid disease and medication use is chronic and often long-term. The NBDPS did not include a specific question on thyroid disease or medication use, making us unable to assess disease independently from treatment. This also means that we do not have information on severity of thyroid disease or whether mothers achieved and maintained normal thyroid levels during pregnancy. Data on medication dose, thyroid hormone levels, and thyroid-stimulating

antibody levels would have greatly improved our ability to determine whether our effects are due to inadequately controlled disease, medication use, or both. The lack of a specific question about thyroid medication use may have resulted in underascertainment of its use. We do not think this was likely, as the prevalence of thyroid hormone (2.4%) and anti-thyroid medication (0.1%) use in our study population was similar to other reports among pregnant women (Ecker and Musci, 1997; Stagnaro-Green et al., 2011). Despite the large size of NBDPS, the number of exposed cases for some birth defects was small, limiting our ability to assess risk, especially for anti-thyroid medications. Lastly, some of our findings could be due to chance. In our main analysis of thyroid hormone, we calculated estimates for 45 birth defects. We would expect two significant findings by chance alone; we found four significantly elevated ORs.

Our study has several strengths. NBDPS clinical geneticists use strict ascertainment criteria and detailed methods to classify cases (Rasmussen et al., 2003). Given the large size of the NBDPS, we could separately evaluate the associations between individual birth defects and thyroid medications. We also separately analyzed isolated noncardiac birth defects and simple isolated CHDs.

Our findings suggest maternal thyroid hormone and anti-thyroid medication use are not associated with most of the birth defects analyzed, but may be associated with some. Our findings are mostly consistent with previous studies, but the associations that we observed for some birth defects have not been previously reported. We were not able to assess whether the treatment or the underlying thyroid disease is the true risk factor. These results should not be interpreted to suggest that medications use to treat thyroid disease are teratogens, as the associations observed may reflect effects of the underlying thyroid disease. More studies that adequately control for confounding by indication are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors have no conflicts of interest to disclose. Coding of drug information in the NBDPS used the Slone Epidemiology Center Drug Dictionary, under license from the Slone Epidemiology Center at Boston University. We thank the participating families, scientists, and staff from the NBDPS sites. We thank the California Department of Public Health Maternal Child and Adolescent Health Division for providing data. The findings and conclusions in this report are those of the authors and do not necessarily represent the official positions of the California Department of Public Health. The authors have no conflicts of interest to disclose.

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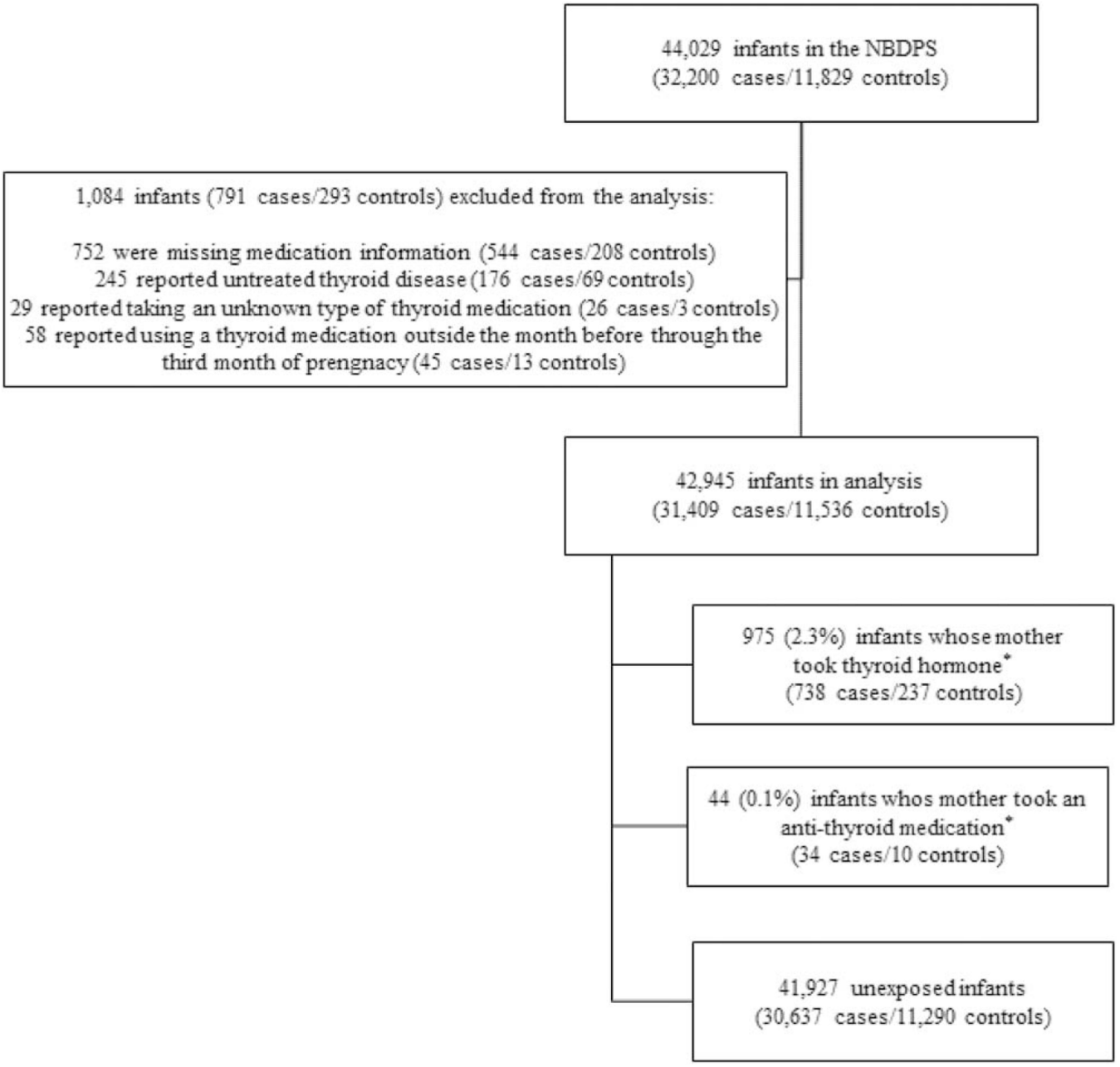

FIGURE 1.

Exclusions and thyroid medication use for cases and controls in the analysis of the National Birth Defects Prevention Study, 1997 to 2011. *One mother of a control infant reported taking an anti-thyroid medication and thyroid hormone during the month before through the third month of pregnancy.

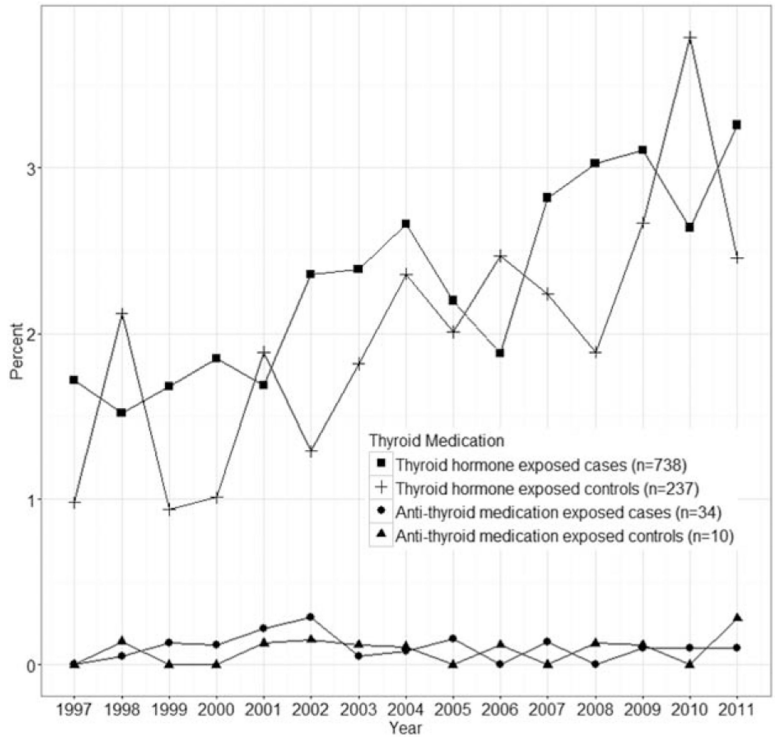

FIGURE 2.

Percentage of the National Birth Defects Prevention Study mothers reporting thyroid hormone or anti-thyroid medication use by expected year of delivery and case/control status. The change in thyroid hormone used over the study time period was statistically significant (Cochran-Armitage p-value < 0.05) among mothers of case and control infants.

TABLE 1.

Selected Characteristics of Mothers of Controls by Periconceptional Thyroid Hormone Use, National Birth Defects Prevention Study 1997 to 2011

Maternal characteristic	Thyroid hormone use (*n* = 237) Mean (SD)	No thyroid medication use (*n* = 11,290) Mean (SD)
Age (years)	31.6 (5.0)	27.6 (6.1)
	n (%)[a]	*n* (%)[a]
Race/ethnicity		
Non-Hispanic white	191 (80.6)	6,518 (57.8)
Non-Hispanic black	7 (3.0)	1,248 (11.1)
Hispanic	31 (13.1)	2,778 (24.6)
Other	8 (3.4)	740 (6.6)
Education (years)		
<12	8 (3.5)	1,880 (16.8)
12	33 (14.6)	2,676 (24.0)
12 +	185 (81.9)	6,609 (59.2)
Number of previous pregnancies		
0	51 (21.5)	3,364 (29.8)
1 or more	186 (78.5)	7,922 (70.2)
Pre-pregnancy BMI		
< 18.5	9 (3.8)	579 (5.4)
18.5–24.9	108 (45.8)	5,817 (53.8)
25–29.9	57 (24.2)	2,451 (22.7)
≥ 30	62 (26.3)	1,961 (18.1)
Periconceptional smoking		
Yes	24 (10.5)	2,031 (18.1)
No	205 (89.5)	9,171 (81.9)
Fertility treatment		
Yes	29 (12.2)	508 (4.5)
No	208 (87.8)	10,782 (95.5)
Gestational diabetes		
Yes	14 (6.4)	515 (4.7)
No	205 (93.6)	10,409 (95.3)
Pre-existing diabetes		
Yes	3 (1.3)	68 (0.6)
No	233 (98.7)	11,205 (99.4)
Folic acid-containing supplement use[b]		
Yes	173 (74.6)	5,921 (52.4)
No	59 (25.4)	5,369 (47.6)

Periconceptional means thyroid medication use in the month before through the third month of pregnancy.

[a] Numbers vary because of missing values.

[b] From 1 month before pregnancy through the first month of pregnancy.

SD, standard deviation; BMI, body mass index (weight in kilograms/height in meters^2).

TABLE 2.

Type of Thyroid Disease Reported among Periconceptional Thyroid Hormone and Anti-thyroid Medications Users, by Case–Control Status

	Thyroid hormone users		Anti-thyroid medication users	
	Cases (*n* = 738)	Controls (*n* = 237)	Cases (*n* = 34)	Controls (*n* = 10)
Type of thyroid disease	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Hashimoto disease	23 (3.1)	7 (3.0)	0	1 (10)
Graves disease	20 (2.7)	8 (3.4)	12 (35.3)	1 (10)
Hyperthyroidism	22 (3.0)	4 (1.7)	12 (35.3)	4 (40)
Thyroid cancer	15 (2.0)	5 (2.1)	0	0
Autoimmune thyroid disease	3 (0.4)	0	0	0
Thyroid disease, unspecified	655 (88.8)	213 (89.9)	10 (29.4)	4 (40)

TABLE 3.

ORs for Associations between Periconceptional Use of Maternal Thyroid Hormone and Non-cardiac Birth Defects, Overall and among Isolated Cases

	All cases		Isolated only cases	
Birth defect	**Exposed/unexposed**	**OR (95% CI)[a]**	**Exposed/unexposed**	**OR (95% CI)[a]**
Amniotic band sequence	3/330	0.43 (0.09–1.29)	3/278	0.51 (0.10–1.54)
Central nervous system				
Anencephaly	19/617	1.68 (1.03–2.73)	17/555	1.67 (1.01–2.79)
Spina bifida	25/1238	1.02 (0.67–1.56)	20/1,090	0.93 (0.58–1.49)
Encephalocele	3/220	0.65 (0.13–1.95)	3/164	0.87 (0.18–2.62)
Holoprosencephaly	7/165	2.48 (1.13–5.44)	7/117	3.28 (1.48–7.27)
Dandy-Walker malformation	6/178	2.08 (0.90–4.82)	4/109	1.75 (0.46–4.66)
Hydrocephaly	17/492	1.77 (1.07–2.95)	14/337	2.17 (1.24–3.79)
Cerebellar hypoplasia	0/61	NC	0/35	NC
Eye				
Anophthalmia/microphthalmia	4/227	0.84 (0.22–2.21)	2/137	NC
Congenital cataracts[b]	8/346	1.04 (0.50–2.13)	8/304	1.19 (0.58–2.45)
Glaucoma[b]	6/175	1.64 (0.71–3.79)	5/143	1.72 (0.69–4.30)
Anotia/microtia	9/672	0.77 (0.39–1.51)	5/465	0.65 (0.26–1.60)
Orofacial				
Choanal atresia	7/154	1.72 (0.79–3.74)	5/79	2.13 (0.84–5.40)
Cleft palate only[b]	46/1544	1.33 (0.96–1.84)	41/1,234	1.45 (1.03–2.04)
Cleft lip only[b]	31/1057	1.32 (0.90–1.94)	30/983	1.37 (0.93–2.02)
Cleft lip with cleft palate[b]	33/1967	0.88 (0.61–1.27)	28/1,678	0.85 (0.57–1.27)
Gastrointestinal				
Esophageal atresia	18/728	1.06 (0.65–1.73)	7/308	0.93 (0.43–2.01)
Duodenal atresia	1/231	NC	0/144	NC
Small intestinal atresia	14/460	1.81 (1.04–3.15)	11/393	1.66 (0.89–3.09)
Colonic atresia	0/55	NC	0/49	NC
Anorectal atresia	20/1048	1.02 (0.64–1.63)	15/448	1.87 (1.09–3.21)
Biliary atresia	4/193	0.99 (0.26–2.60)	4/164	1.16 (0.31–3.07)

Birth defect	All cases		Isolated only cases	
	Exposed/unexposed	OR (95% CI)[a]	Exposed/unexposed	OR (95% CI)[a]
Genitourinary				
Hypospadias[b]	75/2466	1.29 (0.95–1.76)	70/2,200	1.34 (0.97–1.83)
Renal agenesis	4/184	1.04 (0.28–2.73)	4/129	1.48 (0.39–3.92)
Bladder exstrophy	3/70	2.04 (0.41–6.29)	1/53	NC
Cloacal exstrophy	4/95	2.01 (0.53–5.37)	2/56	NC
Musculoskeletal				
Longitudinal limb deficiency	15/518	1.56 (0.91–2.67	11/297	1.90 (1.02–3.55)
Transverse limb deficiency	16/699	1.12 (0.67–1.88)	11/589	0.90 (0.49–1.66)
Craniosynostosis	53/1532	1.22 (0.89–1.66)	51/1,387	1.22 (0.89–1.69)
Diaphragmatic hernia	13/850	0.73 (0.42–1.29)	8/654	0.58 (0.28–1.18)
Omphalocele	12/425	1.39 (0.77–2.52)	8/249	1.52 (0.74–3.13)
Gastroschisis	13/1391	1.13 (0.63–2.03)	10/1,264	0.97 (0.51–1.87)
Sacral agenesis	1/108	NC	0/12	NC

[a]For defects with five or more exposed cases, estimates were adjusted for maternal age, maternal race/ethnicity, and state of residence at the time of birth. Counts in the adjusted analysis were slightly lower than presented due to missing values for some covariates. cORs and exact 95% CIs are presented for defects groups with three to four exposed cases. Estimates are not presented for analyses based on fewer than three exposed cases. Infants of mothers who did not report any thyroid medication use were the reference group. Analyses included 237 exposed and 11,290 unexposed control infants.

[b]Analyses for congenital cataracts and glaucoma included 213 exposed and 9,595 unexposed controls, clefts included 232 exposed and 11,162 unexposed controls, and hypospadias included 110 exposed and 5,761 unexposed male controls).

NC, not calculated.

TABLE 4.

ORs for Associations between Periconceptional Use of Maternal Thyroid Hormone and Congenital Heart Defects, Overall and among Simple Isolated Cases

	All cases		Simple isolated cases	
Birth defect	**Exposed/unexposed**	**OR (95% CI)[a]**	**Exposed/unexposed**	**OR (95% CI)[a]**
Conotruncal defects				
Truncus arteriosus	4/132	1.44 (0.38–3.83)	2/88	NC
IAA type b	1/48	NC	0/20	NC
Tetralogy of Fallot	25/1178	1.01 (0.66–1.54)	23/925	1.16 (0.75–1.80)
D-TGA	21/742	1.27 (0.80–2.00)	16/553	1.28 (0.76–2.15)
DORV-TGA	6/183	1.75 (0.76–4.03)	0/51	NC
Other DORV	2/120	NC	0/31	NC
Conoventricular VSD[b]	1/115	NC	0/53	NC
Atrioventricular septal defect	13/356	1.73 (0.97–3.07)	8/164	2.22 (1.07–4.63)
Total anomalous pulmonary venous return	9/291	1.76 (0.88–3.48)	8/245	1.79 (0.87–3.70)
LVOTO defects				
Hypoplastic heart syndrome	19/635	1.30 (0.80–2.10)	18/562	1.35 (0.82–2.21)
IAA type a	2/20	NC	2/16	NC
Coarctation of the aorta	30/1133	1.06 (0.72–1.57)	14/544	0.96 (0.55–1.67)
Aortic valve stenosis	14/490	1.08 (0.62–1.89)	8/327	0.87 (0.42–1.80)
RVOTO defects				
Pulmonary atresia	5/256	1.01 (0.41–2.48)	5/158	1.51 (0.61–3.74)
Pulmonary valve stenosis[b]	29/1514	0.85 (0.57–1.26)	21/1,019	0.90 (0.57–1.42)
Tricuspid atresia	2/177	NC	1/70	NC
Ebstein anomaly	3/177	0.81 (0.16–2.43)	2/108	NC
Septal defects				
Perimembranous VSD[b]	31/1409	1.27 (0.85–1.91)	19/880	1.28 (0.78–2.11)
Muscular VSD[b]	1/189	NC	1/143	NC
Secundum atrial septal defect	66/2991	1.11 (0.83–1.47)	39/1,506	1.38 (0.97–1.97)
Single ventricle defects	3/171	0.84 (0.17–2.51)	*c*	*c*

Birth defect	All cases		Simple isolated cases	
	Exposed/unexposed	OR (95% CI)[a]	Exposed/unexposed	OR (95% CI)[a]
Heterotaxy	3/340	0.42 (0.09–1.25)	*c*	*c*

[a]For defects with five or more exposed cases, estimates were adjusted for maternal age, race/ethnicity, and state of residence at the time of infant's birth. Counts in the adjusted analysis were slightly lower than presented due to missing values for some covariates. cORs with exact 95% CIs are presented for defects with three to four exposed cases. Estimates are not presented for analyses based on fewer than three exposed cases. Infants of mothers who did not report any thyroid medication use were the reference group. Analyses included 237 exposed and 11,290 unexposed control infants.

[b]Analyses for pulmonary valve stenosis included 232 exposed and 10,825 unexposed controls, conoventricular and perimembranous included112 exposed and 6,595 unexposed controls, and muscular VSDs included 12 exposed and 707 unexposed controls.

[c]All cases of heterotaxy and single ventricle defects were considered complex, so there are no simple isolated cases for these two birth defects.

NC, not calculated; IAA, interrupted aortic arch; TGA, transposition of the great arteries; DORV, double outlet right ventricle; LVOTO, left ventricular outflow tract obstruction; RVOTO, right ventricular outflow tract obstruction.

TABLE 5.

Crude ORs for Associations between Periconceptional Use of Anti-thyroid Medication Use and Birth Defects and Periconceptional Use of PTU Use and Birth Defects

	Use of any anti-thyroid medication in periconceptional period		Use of PTU only in periconceptional period[a]	
Birth defect	**Exposed/unexposed**	**OR (95% CI)**	**Exposed/unexposed**	**OR (95% CI)**
Non-cardiac defects				
Anorectal atresia	4/1048	4.31 (0.98–15.0)	4/1048	8.62 (1.71–40.1)
Craniosynostosis	3/1532	2.21 (0.39–8.61)	2/1532	NC
Gastroschisis	3/1391	2.43 (0.43–9.47)	2/1391	NC
Congenital heart defects				
Coarctation of the aorta	4/1133	3.99 (0.91–13.8)	4/1133	7.97 (1.58–37.1)
Aortic valve stenosis	3/490	6.91 (1.22–26.9)	3/490	13.8 (2.13–71.2)
Pulmonary valve stenosis[b]	3/1514	2.15 (0.38–8.34)	1/1514	NC

Since no defect had more than four anti-thyroid medication exposed cases, cORs with exact 95% CIs are presented. A full list of defects examined can be found in Tables 3 and 4. The reference group included infants of mothers who did not report any thyroid medication use. Analyses included 10 exposed control infants and 11,290 unexposed control infants

[a]This column includes mothers who used PTU during pregnancy, and does not include mothers who used both PTU and MMI during pregnancy.

[b]Analyses for pulmonary valve stenosis included 10 exposed and 10,825 unexposed controls.

NC, not calculated.