Maternal Thyroid Disease, Thyroid Medication Use, and Selected Birth Defects in the National Birth Defects Prevention Study

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BACKGROUND: Although thyroid disorders are present in approximately 3% of pregnant women, little is known about the association between maternal thyroid disease and birth defects. **METHODS:** We assessed the association between maternal thyroid disease, thyroid medication use, and 38 types of birth defects among 14,067 cases and 5875 controls in the National Birth Defects Prevention Study, a multisite, population-based, case-control study. Infants in this study were born between October 1997 and December 2004. Information on exposures including maternal diseases and use of medications was collected by telephone interview. **RESULTS:** We found statistically significant associations between maternal thyroid disease and left ventricular outflow tract obstruction heart defects (1.5; 95% CI, 1.0–2.3), hydrocephaly (2.9; 95% CI, 1.6–5.2), hypospadias (1.6; 95% CI, 1.0–2.5), and isolated anorectal atresia (2.4; 95% CI, 1.2–4.6). Estimates for the association between periconceptional use of thyroxine and specific types of birth defects were similar to estimates for any thyroid disease. Given that antithyroid medication use was rare, we could not adequately assess risks for their use for most case groups. **CONCLUSIONS:** Our results are consistent with the positive associations between maternal thyroid disease or thyroid medication use and both hydrocephaly and hypospadias observed in some previous studies. New associations with left ventricular outflow tract obstruction heart defects and anorectal atresia may be chance findings. *Birth Defects Research (Part A) 85:621–628, 2009.* © 2009 Wiley-Liss, Inc.

Key words: thyroid hormones; thyroxine; thyroid disease; congenital abnormalities; birth defects

INTRODUCTION

Hypothyroidism is present in approximately 2.5% of pregnancies (Becks and Burrow, 1991; Klein et al., 1991), and hyperthyroidism is present in approximately 0.2% of pregnancies (Becks and Burrow, 1991). Thyroxine (thyroid hormone) influences a variety of metabolic processes and both deficiency and excess of thyroxine have been linked to fertility problems and adverse reproductive outcomes (Karabinas and Tolis, 1998; Poppe et al., 2002).

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The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Additional Supporting Information may be found in the online version of this article.

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Information on risks to the fetus caused by abnormal thyroid function or its treatment is important in guiding prenatal monitoring and treatment of thyroid disease. The effects of overt thyroid disease may also provide clues regarding the teratogenicity of chemicals suspected of altering thyroid function, such as bisphenol A (Zoeller et al., 2005).

A recent report from the National Birth Defects Prevention Study (NBDPS) by Rasmussen et al. (2007) found an association between maternal thyroid disease and craniosynostosis (odds ratio [OR], 2.5; 95% confidence interval [CI], 1.5–9.2). Other than the association with craniosynostosis, which is supported by animal studies and human case series (Akita et al., 1994; Daneman and Howard, 1980; de Lima et al., 1999), the relatively few epidemiologic studies on this topic have not provided consistent evidence for or against an association between maternal thyroid disease and birth defects (Heinonen et al., 1977; Adams et al., 1989; Khoury et al., 1989; Ferencz et al., 1997; Queisser-Luft et al., 1996; Cedergren et al., 2002). Positive associations have been reported for thyroid disease or use of thyroid medication and selected congenital heart defects (CHDs), central nervous system defects, intestinal defects, hypospadias, and limb deficiencies (Heinonen et al., 1977; Khoury et al., 1989; Queisser-Luft et al., 1996). However, other than associations between hyperthyroidism and central nervous system defects, none of the findings were observed in more than one study.

The purpose of this study was to evaluate whether maternal thyroid disease and use of thyroid medications are associated with various birth defects. The number of cases and controls in the NBDPS allowed us to separately examine many specific types of birth defects.

MATERIALS AND METHODS

The NBDPS is an ongoing multisite, population-based, case-control study that began in 1997 (Yoon et al., 2001). Cases of 30 different categories of major structural malformations, excluding cases attributed to a known chromosomal abnormality or single-gene condition, have been ascertained through birth defects surveillance registries in 10 states. Each study site obtained institutional review board approval for the NBDPS. Controls were live births without birth defects randomly selected from hospital records in Arkansas, California, New York, and Texas; birth certificates in Iowa, Massachusetts, North Carolina, New Jersey, and Utah; and both hospital records (1997–2000) and birth certificates (2001–2004) in Georgia. Included in the present study were births with an estimated date of delivery (EDD) between October 1997 and December 2004. We excluded from analysis subjects with maternal history of type 1 or type 2 diabetes diagnosed before pregnancy, because preexisting diabetes is associated with increased risk of a variety of birth defects (Nielsen et al., 2005; Correa et al., 2008).

The association between maternal thyroid disease and craniosynostosis was investigated in a previous analysis using NBDPS data (Rasmussen et al., 2007). We examined all other types of birth defects that were included in the NBDPS and had 100 or more cases available for analysis at the time of this study including birth defects of the following organs and organ systems: cardiovascular, central nervous system, eye, ear, orofacial, gastrointestinal, genitourinary, and musculoskeletal.

Case inclusion criteria have been described by Yoon et al. (2001). Only structural heart defects confirmed by echocardiography, cardiac catheterization, or autopsy were included in the NBDPS. Patent ductus arteriosus and patent foramen ovale, which are often related to preterm birth, were not included. Oral clefts were classified into two groups that are generally recognized as having different etiology: cleft lip with or without cleft palate and cleft palate only (Cohen, Jr., 2002). Only second- and third-degree hypospadias cases were included because of concerns about incomplete ascertainment of first-degree hypospadias. The control group was restricted to male infants for the analysis of hypospadias. Clinical geneticists reviewed and classified each case as isolated or multiple (infants with two or more major unrelated defects; Rasmussen et al., 2003). To reduce etiologic heterogeneity within case groups, we separately examined isolated defects for each birth defect category. For CHDs, cases were further categorized as simple, associations, or complex (Botto et al., 2007). Most of the heart phenotypes analyzed in this study were simple CHDs (defined as a single CHD or CHD ''entity'') or common CHD associations (e.g., coarctation of the aorta + ventricular septal defect). Cases recorded as *atrial septal defect* (ASD) *not otherwise specified* were viewed as probably ASD secundum type and were counted as such in the main analysis. Certain study sites did not ascertain cases during the entire study period for pulmonary valve stenosis (California, before 2002) and muscular ventricular septal defects (after the first year of data collection for sites participating in 1997–1998). When we analyzed those birth defects, cases and controls were excluded for the study sites and years for which case ascertainment was incomplete—that is, analyses of pulmonary valve stenosis excluded California controls with EDD before 2002 and analyses of muscular ventricular septal defects were restricted to the first year of data collection for sites participating in 1997 to 1998.

A computer-assisted telephone interview was used to collect information about demographic characteristics, pregnancy history, and various health conditions and exposures before and during pregnancy from mothers of cases and controls. Study mothers were asked about all medications taken during the period from 3 months preconception through the end of pregnancy. The Slone Epidemiology Center Drug Dictionary was used to code all reported medications. Other questions addressed history of diabetes, hypertension, seizure disorder, various illnesses, and ''other diseases'' not specifically queried in the interview. Responses were screened for any reference to a thyroid disorder including hypothyroidism, hyperthyroidism, Hashimoto's thyroiditis, and Graves' disease. Women were classified as having thyroid disease if they reported taking thyroid medication or reported any thyroid disease. Thyroid medications included thyroxine-like medications (levothyroxine, liothyronine, thyroxine), antithyroid medications (propylthiouracil, methimazole), and ''unknown thyroid medicine.'' Each report of a possibly thyroid-related condition was reviewed by a clinician (S.A.R.) blinded to case-control status who determined whether it was consistent with our exposure definition.

The main analysis focused on any maternal thyroid disease including maternal reports of hypothyroidism, hyperthyroidism, unspecified thyroid disease, or any use

of thyroid medication. We also examined exposure to thyroxine or antithyroid medication during the periconceptional period, defined as 3 months before conception through the end of the first trimester. Women with thyroid disease who did not report thyroxine use were excluded from analysis of thyroxine exposure. Similarly, women with thyroid disease who did not report antithyroid medication use were excluded from the analysis of antithyroid medication exposure.

Covariates included the following maternal characteristics: age at delivery, parity, race/ethnicity, education, prepregnancy body mass index (weight in kg/height in m^2), gestational diabetes, use of fertility medications or procedures, fever during the first trimester, and mother's state of residence at the time of infant's birth. We also considered periconceptional cigarette smoking and maximum number of alcoholic drinks on one occasion as well as folic acid–containing vitamin supplement use (any during 1 month before pregnancy through month 1, any during months 2 or 3, later in pregnancy/none). The influence of family history of a defect of the same organ system and multiple gestation pregnancies were assessed by conducting a subanalysis that excluded cases and controls with these characteristics.

Logistic regression was used to estimate ORs and 95% CIs for the association between maternal thyroid disease or thyroid medication use and birth defects, while controlling for confounding variables. Separate logistic regression models were fitted for maternal thyroid disease and each birth defect phenotype. Starting with a full model including potential confounders identified in bivariate analyses, variables were dropped one-at-a-time using backward selection. Variables causing a 10% or more change in the risk estimate for thyroid disease were retained in the model. To streamline the analysis and presentation of results, three covariates in the final models of many birth defect groups were included for all analyses: maternal age, race/ethnicity, and mother's state of residence at the time of infant's birth. Other covariates were included only in analyses of birth defect groups for which they demonstrated confounding. For birth defects with three or four exposed cases, crude ORs and exact CIs are presented. Odds ratios are not presented for birth defect phenotypes with fewer than three exposed cases. All analyses were performed using SAS software, version 9.1 (SAS Corporation, Cary, North Carolina).

RESULTS

During the study period, 71.2% of eligible case mothers and 67.9% of eligible control mothers participated in the interview. A total of 14,538 cases with birth defect phenotypes evaluated in this study and 5958 controls with EDD from 1997 through 2004 were interviewed for the NBDPS. After excluding infants missing maternal medication data (124 cases, 41 controls) and those with maternal history of type 1 or type 2 diabetes diagnosed before the index pregnancy (293 cases, 29 controls), or missing information on history of diabetes (54 cases, 13 controls), 14,067 cases and 5875 controls remained. The interval between EDD and interview varied by outcome category, with average intervals ranging from 9 to 12 months among the birth defect categories included in this analysis (average=10 months for study cases) and approximately 8 months for controls. Among cases and controls included in the present analysis, 316 (2.2%) cases and 111 (1.9%) controls reported thyroid disease or thyroid medication use.

Table 1
Selected Characteristics of Controls (n = 5875) by Exposure Status, National Birth Defects Prevention Study, 1997–2004

	Nonexposed		Thyroid Disease	
	n = 5764		n = 111	
	n[a]	%	n[a]	%
Maternal age (years)				
12–19	642	11.1	2	1.8
20–34	4334	75.2	84	75.7
35+	788	13.7	25	22.5
Race/ethnicity				
White non-Hispanic	3424	59.6	87	79.1
Black non-Hispanic	668	11.6	1	0.9
Hispanic	1302	22.7	14	12.7
Other	349	6.1	8	7.3
Education (years)				
0–11	977	17.1	5	4.6
12	1446	25.3	16	14.7
12+	3298	57.6	88	80.7
Parity				
0	2319	40.3	35	31.5
1 or more	3440	59.7	76	68.5
Prepregnancy BMI				
<30	4666	84.4	88	79.3
30+ (obese)	861	15.6	23	20.7
Gestational diabetes				
No	5417	94.0	101	91.0
Yes	347	6.0	10	9.0
Smoking[b]				
No	4640	80.9	96	87.3
Yes	1097	19.1	14	12.7
Alcohol (maximum number of drinks per occasion)[b]				
0	3599	63.3	66	60.6
1–3	1397	24.6	27	24.8
4+	692	12.2	16	14.7
Folic acid supplement use[c]				
Yes, early	2972	52.6	79	73.8
Yes, later	1954	34.6	23	21.5
No	720	12.8	5	4.7

[a]Numbers vary because of missing values.
[b]During the period from 1 month prepregnancy through the 3rd month of pregnancy.
[c]*Early* is defined as any use one month prepregnancy through pregnancy month one. *Later* is defined as any use starting in pregnancy month two or three. *No* is defined as none or use starting after 3rd month of pregnancy.
BMI, body mass index (weight in kg/height in m^2).

Among control mothers, thyroid disease was more common among women who were older than 35 years, white non-Hispanic or ''other'' race/ethnicity, obese, nonsmokers, began taking folic acid before 28 days of gestation, or had a high school or greater education, one or more previous births, or gestational diabetes (Table 1).

Other than strong confounding by age observed for gastroschisis, the difference between the crude and adjusted estimate was less than 30% for all other birth defects. Table 2 summarizes results of the analysis of maternal thyroid disease and various congenital heart defects. Table 3 presents the results for the remaining

Table 2
Association of Maternal Thyroid Disease with Congenital Heart Defects,[a] National Birth Defects Prevention Study, 1997–2004

	Isolated cases		All cases[b]	
	Thyroid disease/ unexposed	OR (CI)[c]	Thyroid disease/ unexposed	OR (CI)[c]
Heterotaxy	—	—	3/172	0.9 (0.2–2.8)
Conotruncal	17/902	0.9 (0.5–1.6)	20/1059	0.9 (0.6–1.6)
Tetralogy of Fallot	10/448	1.1 (0.6–2.1)	11/560	1.0 (0.5–1.9)
d-Transposition of the great arteries	6/318	0.9 (0.4–2.1)	6/332	0.9 (0.4–2.0)
Atrioventricular septal defect	4/77	2.7 (0.7–7.4)	4/90	2.3 (0.6–6.3)
Total anomalous pulmonary venous return	3/123	1.3 (0.3–3.9)	3/133	1.2 (0.2–3.6)
LVOTO	28/863	1.4 (0.9–2.2)	32/980	1.5 (1.0–2.3)
Hypoplastic heart syndrome	8/267	1.5 (0.7–3.0)	8/289	1.4 (0.7–2.9)
Coarctation of the aorta	8/261	1.2 (0.6–2.6)	9/301	1.2 (0.6–2.5)
Aortic valve stenosis	6/148	1.7 (0.7–4.0)	7/157	1.9 (0.9–4.3)
LVOTO associations[d]	6/178	1.5 (0.6–3.5)	8/212	1.8 (0.9–3.7)
RVOTO	18/830	1.0 (0.6–1.7)	20/903	1.1 (0.6–1.7)
Pulmonary valve stenosis	9/499	0.8 (0.4–1.7)	10/525	0.9 (0.5–1.7)
RVOTO associations[d]	5/156	1.6 (0.6–4.1)	5/186	1.3 (0.5–3.4)
Septal	44/2090	1.1 (0.7–1.6)	55/2521	1.1 (0.8–1.6)
Perimembranous VSD	18/739	1.2 (0.7–2.1)	21/835	1.3 (0.8–2.1)
Muscular VSD	2/143	—	2/159	—
Secundum atrial septal defect	19/832	1.2 (0.7–2.0)	27/1046	1.4 (0.9–2.2)
Septal associations[d]	5/346	0.7 (0.3–1.7)	5/439	0.5 (0.2–1.3)

Controls: 110 maternal thyroid disease, 5743 unexposed; for crude odds ratios: 111 maternal thyroid disease, 5764 unexposed.

[a]Only simple CHDs are included with the exception of heterotaxy and common CHD associations.

[d]Both cases with isolated anomalies and those with additional defects are included in this group.

[c]For CHDs with 5+ exposed cases, estimates were adjusted for mother's state of residence at the time of infant's birth, age, and race/ethnicity and asymptotic confidence intervals were calculated. The odds ratios for LVOTO, hypoplastic left heart syndrome, and coarctation of the aorta were also adjusted for gestational diabetes. Crude odds ratios with exact 95% confidence intervals are presented for defects with 3–4 exposed cases. Estimates are not presented for analyses based on <3 exposed cases.

[d]LVOTO associations include coarctation of the aorta + aortic stenosis, coarctation of the aorta + VSD, coarctation of the aorta + VSD + ASD. RVOTO associations include PVS + VSD, PVS + ASD. Septal associations include VSD + ASD.

OR, odds ratio; CI, confidence interval; LVOTO, left ventricular outflow tract obstruction; RVOTO, right ventricular outflow tract obstruction; VSD, ventricular septal defect; CHD, congenital heart defect.

birth defects analyzed in this study. For all cases (both isolated and nonisolated defects), we found elevated ORs that were statistically significant or borderline statistically significant for associations between maternal thyroid disease and left ventricular outflow tract obstruction (1.5; 95% CI, 1.0–2.3), hydrocephaly (2.9; 95% CI, 1.6–5.2), and hypospadias (1.6; 95% CI, 1.0–2.5). For isolated birth defects, the ORs remained elevated for these three defect groups, and a statistically significant association was also observed for anorectal atresia (2.4; 95% CI, 1.2–4.6). Restriction of isolated hydrocephaly cases to those with a diagnosis of aqueductal stenosis (the largest and most well-defined subset of hydrocephaly cases) resulted in an OR of 4.3 (95% CI, 2.0–9.2). Statistically nonsignificant elevated ORs ranging from 1.5 to 3.2 were observed for maternal thyroid disease and atrioventricular septal defect, hypoplastic left heart syndrome, aortic valve stenosis, left ventricular outflow tract obstruction associations, right ventricular outflow tract obstruction associations, encephalocele, Dandy-Walker malformation, holoprosencephaly, small intestinal atresia, longitudinal limb deficiencies, omphalocele, and gastroschisis. Statistically nonsignificant reduced ORs ranging from 0.5 to 0.7 were observed for septal defect associations, anotia/microtia, esophageal atresia, duodenal atresia, and diaphragmatic hernia. Generally, the ORs were further from the null value when the analysis was restricted to isolated anomalies.

Table 4 shows the types of thyroid medications and timing of medication use during pregnancy among control and case mothers. Of 103 control mothers and 295 case mothers who reported thyroid medication use, approximately 90% used thyroxine during the periconceptional period. Only eight controls and 21 cases reported thyroid disease and did not report thyroid medication use.

Estimates for periconceptional thyroxine use were generally similar to estimates for those with any thyroid disease and are presented in Supplementary material at http://www.interscience.wiley.com. One exception was a lower risk (OR not calculated) for gastroschisis. Only two of six gastroschisis case mothers with a history of thyroid disease also reported periconceptional thyroxine use. Maternal exposure to antithyroid medication was rare; estimates could be calculated for only a few defect groups, as shown in Table 5. Elevated ORs were observed for each of the case groups and were statistically significant for aortic valve stenosis (22.0; 95% CI, 3.4–114.0) and anorectal atresia (8.6; 95% CI, 1.7–40.2), but were based on only four exposed cases for each of these birth defects.

To explore potential sources of bias, we conducted four separate subanalyses. Estimates for a subanalysis excluding multiple gestation births and subjects with a family history of the same birth defect were similar to estimates for all cases and controls. Results of a subanalysis restricted to interviews conducted within 12 months

Table 3
Association of Maternal Thyroid Disease with Selected Birth Defects, National Birth Defects Prevention Study, 1997–2004

	Isolated cases		All cases[a]	
	Thyroid disease/ unexposed	OR (CI)[b]	Thyroid disease/ unexposed	OR (CI)[b]
Central nervous system				
Anencephaly	5/263	1.0 (0.4–2.5)	6/288	1.1 (0.5–2.6)
Spina bifida	11/519	1.1 (0.6–2.1)	12/570	1.1 (0.6–2.0)
Encephalocele	3/83	1.9 (0.4–5.8)	3/112	1.4 (0.3–4.3)
Dandy-Walker	2/51	2.0 (0.2–7.9)	4/85	2.4 (0.6–6.7)
Holoprosencephaly	3/48	3.2 (0.6–10.3)	3/70	2.2 (0.4–6.9)
Hydrocephaly	11/171	3.6 (1.9–6.9)	13/247	2.9 (1.6–5.2)
Eye				
Anophthalmia/microphthalmia	0/72	—	3/124	1.3 (0.2–3.9)
Congenital cataracts	2/140	—	2/156	—
Ear				
Anotia/microtia	2/261	—	4/353	0.6 (0.2–1.7)
Orofacial clefts				
CPO	18/643	1.3 (0.8–2.2)	19/799	1.2 (0.7–1.9)
CL/P	24/1329	1.0 (0.6–1.5)	27/1500	1.0 (0.6–1.5)
Gastrointestinal				
Esophageal atresia	1/157	—	5/372	0.6 (0.2–1.5)
Small intestinal atresia	5/192	1.7 (0.7–4.2)	7/227	2.0 (0.9–4.3)
Duodenal atresia	1/65	0.9 (0.1–6.3)	1/106	0.5 (0.1–3.8)
Anorectal atresia	10/244	2.4 (1.2–4.6)	15/532	1.6 (0.9–2.7)
Genitourinary				
Hypospadias	40/989	1.6 (1.0–2.5)	43/1086	1.6 (1.0–2.5)
Renal agenesis	1/62	—	1/91	—
Musculoskeletal				
Longitudinal limb defects	5/126	2.1 (0.8–5.2)	6/228	1.5 (0.6–3.5)
Transverse limb defects	7/303	1.2 (0.6–2.7)	8/358	1.2 (0.6–2.5)
Diaphragmatic hernia	2/343	—	4/426	0.5 (0.1–1.3)
Omphalocele	5/132	1.9 (0.8–4.9)	7/218	1.7 (0.8–3.7)
Gastroschisis	6/540	1.8 (0.7–4.2)	6/593	1.6 (0.7–3.8)
Other				
Amniotic band sequence	—	—	0/150	—

Controls: 110 maternal thyroid disease/5743 unexposed; for crude odds ratios: 111 maternal thyroid disease/ 5764 unexposed.

[a]Both cases with isolated anomalies and those with additional defects are included in this group.

[b]For defects with more than five exposed cases, estimates were adjusted for mother's state of residence at the time of infant's birth, age, and race/ethnicity. Asymptotic confidence intervals were calculated. Additional covariates were included in analysis of anencephaly (plurality), spina bifida (body mass index [BMI]), hypospadias (gestational diabetes, maternal use of fertility medications or procedures), gastroschisis (BMI and smoking). Control *n*'s were slightly lower for analysis of case groups that were adjusted for BMI and smoking because of missing values for these covariates. For the analysis of hypospadias, the number of male controls was 52 and 2887 with and without maternal thyroid disease, respectively. Crude odds ratios with exact 95% confidence intervals are presented for defects with 3–4 exposed cases. Estimates are not presented for analyses based on <3 exposed cases.

CPO, cleft palate only; CL/P, cleft lip with or without cleft palate; OR, odds ratio; CI, confidence interval.

Table 4
Frequency of Maternal Thyroid Medication Use by Type of Thyroid Medication and Timing of Use among Controls (n = 5875) and Cases (n = 14,067), National Birth Defects Prevention Study, 1997–2004[a]

	Controls[b]				Cases			
	Timing of use during pregnancy[c]				Timing of use during pregnancy[c]			
	Early	Late	Unknown	Total	Early	Late	Unknown	Total
Any thyroid medications	100	2	1	103	289	5	1	295
Thyroxine	94	0	1	95	266	1	1	268
Antithyroid medication	5	2	0	7	20	3	0	23
Unknown thyroid medication	2	0	0	2	3	1	0	4

[a]Case counts are for all birth defect categories included in the present analysis. Eight control and 21 case mothers reported thyroid disease, but no thyroid medication use during the period 3 months before conception through the end of pregnancy.

[b]One control mother reported taking both thyroxine and an antithyroid medication.

[c]*Early use* is defined as any use three months before conception through the end of the first trimester. *Late use* is defined as use only during pregnancy month four through delivery. *Unknown* is defined as insufficient information to determine timing of use.

Table 5
Association of Maternal Periconceptional[a] Antithyroid Medication Use with Selected Birth Defects,[b] National Birth Defects Prevention Study, 1997–2004

	Antithyroid medication use/ unexposed	Crude OR (exact 95% CI)
Controls	5/5764	1.0
LVOTO CHDs[c]	4/972	4.7 (0.9–22.1)
Aortic valve stenosis	3/157	22.0 (3.4–114.0)
Septal CHDs[c]	3/2526	1.4 (0.2–7.0)
Anorectal atresia	4/534	8.6 (1.7–40.2)

[a]During the period one month before conception through the end of the first trimester.

[b]Among all 14,067 cases combined, 20 mothers reported periconceptional antithyroid medication use. Five of 5769 control mothers reported periconceptional antithyroid medication use. All 42 birth defect categories were examined (total cases, not restricted to isolated defects); results are presented only for birth defect categories with three or more exposed cases.

[c]Only simple congenital heart defects and common associations are included. LVOTO associations include coarctation of the aorta + aortic stenosis, coarctation of the aorta + VSD, coarctation of the aorta + VSD + ASD. Septal associations include VSD + ASD.

OR, odds ratio; CI, confidence interval; LVOTO, left ventricular outflow tract obstruction; CHD, congenital heart defect.

of the EDD were also similar to overall results. Odds ratios for the birth defect categories for which we observed positive associations in the main analysis were either the same or slightly higher in the short time-to-interview subanalysis. To examine whether there might be differences in classification accuracy within the ASD category, we conducted a subanalysis excluding ASD not otherwise specified, which yielded similar results to the analysis including both secundum-type ASDs and ASD not otherwise specified.

DISCUSSION

Our study found modest statistically significant associations between maternal report of thyroid disease and an increased risk of left ventricular outflow tract obstruction, hydrocephaly, anorectal atresia, and hypospadias. Odds ratios for these birth defects ranged from 1.5 to 3.6. Similar estimates were obtained for the analysis of maternal periconceptional thyroid hormone use. Reports of antithyroid medication use were rare. We observed positive associations for periconceptional antithyroid medication use and aortic valve stenosis and anorectal atresia.

One large prospective study (Heinonen et al., 1977) and two large retrospective studies (Khoury et al., 1989; Queisser-Luft et al., 1996) examined maternal thyroid disease or thyroid medication use and a variety of birth defects. All three studies reported positive associations between hyperthyroidism (Heinonen et al., 1977; Khoury et al., 1989) or thyroid hormone use (Queisser-Luft et al., 1996) and central nervous system defects overall with ORs ranging from 2.0 to 4.1. Khoury et al. (1989) noted increased ORs for hyperthyroidism and specific central nervous system defects, encephalocele, and hydrocephaly, with ORs of 5.26 (95% CI, 1.16–24.0) and 3.05 (95% CI, 1.23–7.59), respectively. In agreement with these studies, we observed a statistically significant elevated OR for maternal thyroid disease and hydrocephaly as well as elevated but nonsignificant ORs for encephalocele and holoprosencephaly. Khoury et al. (1989) reported significant positive findings for hypothyroidism and intestinal malrotation anomalies (OR, 3.43; 95% CI, 1.46–8.05) and limb deficiencies (OR, 1.92; 95% CI, 1.04–3.54). The NBDPS does not have a category for ''intestinal malrotation'' for comparison with the positive results from Khoury et al. Our OR for thyroid disease and isolated longitudinal limb deficiencies (OR, 2.1, 95% CI, 0.8–5.2), though not significant, was similar to the estimate by Khoury et al. for hypothyroidism and all limb deficiencies (OR, 1.92; 95%CI, 1.04–3.54). Queisser-Luft et al. (1996) noted an OR of 3.9 (95% CI, 1.9–8.0) for first-trimester thyroxine use and ''external genitourinary defects,'' the majority of which were hypospadias (personal communication, A. Queisser-Luft 2008). We observed an OR of 1.7 (1.0-2.7) for periconceptional thyroxine use and hypospadias.

Several additional studies focused on maternal thyroid disease or thyroid medication use and CHDs. Adams et al. (1989) did not report positive findings for maternal thyroid disease, but included only 83 conotruncal heart cases (one case with maternal hyperthyroidism and one case with maternal hypothyroidism). Cedergren et al. (2002) did not observe an association for thyroid medication use and all CHDs combined based on three exposed cases and two exposed controls. A larger study of CHDs by Ferencz et al. (1997) found significant positive associations between thyroid disease and both double outlet right ventricle with normally related arteries (OR, 8.5; 95% CI, 2.5–29.0) and moderate (but not severe) pulmonary valve stenosis (OR, 3.0; 95% CI, 1.2–7.6). Our study did not confirm the findings of Ferencz et al. for pulmonary valve stenosis, but we detected a positive relation for aortic valve stenosis not observed in their study. For double outlet right ventricle with normally related arteries, we observed only one exposed case and 24 nonexposed cases (data not shown).

Strengths and Weaknesses

The strengths of our study include the many subjects and the classification methods used in the NBDPS. Although it is possible that maternal thyroid disease or medication influences the risk of multiple types of birth defects or could cause more than one anomaly in a single infant, it is informative to separately evaluate etiologically homogeneous birth defect phenotypes in attempting to identify teratogenic agents. Clinical geneticists used strict ascertainment criteria and detailed methods to classify NBDPS cases (Rasmussen et al., 2003). Along with analyses that included cases with multiple congenital anomalies, we were able to analyze isolated cases separately. In this study, estimates for birth defects with statistically significant findings were generally somewhat further from the null when the analysis was restricted to isolated cases. In the analysis of hydrocephaly, additional restriction of the case group to those with a diagnosis of aqueductal stenosis (the largest and most well-defined subset of hydrocephaly cases) further increased the OR.

Several alternative explanations and study weaknesses could explain some of our findings. A limitation of our exposure assessment was reliance on self-reported medication use and responses to an open-ended question on ''other disease'' to identify maternal thyroid disease. In

addition to concerns about under-ascertainment of thyroid disease, we were not able to distinguish types of thyroid disease, such post-ablation hypothyroidism versus primary hypothyroidism, Hashimoto's thyroiditis, Graves' disease, and nonautoimmune thyroid disease. The mother's description of the thyroid condition was often limited to ''thyroid problem'' or ''thyroid disease.'' Nor could we assess whether treatment was successful in achieving or maintaining normal thyroid hormone levels during pregnancy. Our analysis focused on any maternal thyroid disease, with results also presented for periconceptional use of thyroxine and antithyroid medications. We chose not to categorize mothers with any thyroid disease as being hypothyroid or hyperthyroid, because our assessment would likely have resulted in substantial misclassification. A mother with thyroid disease could have been hypothyroid, hyperthyroid, or euthyroid during pregnancy or some combination of all three during different periods of her pregnancy, depending on the adequacy of her initial treatment and whether changes in the level of treatment were justified or implemented. Even if some of our findings represent causal associations, we cannot determine whether effects are due to inadequately controlled disease or to medication use. In addition, thyroid-stimulating antibodies may play a role in fetal effects among women with autoimmune thyroid disease (Rasmussen et al., 2007). Data on thyroid hormone levels and thyroid-stimulating antibody levels during pregnancy would have greatly improved our exposure assessment.

Recall bias is a particular concern for studies of maternal medication use and birth defects. It is somewhat reassuring that we observed positive associations between maternal thyroid disease and some birth defects and not others. If recall bias strongly influenced our findings, we would have expected elevated ORs for a wider range of birth defects. After excluding craniosynostosis (a positive association with craniosynostosis was observed in this population by Rasmussen et al. [2007]) and the four types of birth defects for which there were statistically significant positive associations in this study, the OR for all remaining birth defects combined was 1.1 (0.9–1.4). We also evaluated whether recall bias was introduced by differences in time-to-interview. An analysis restricted to interviews within 12 months of the EDD produced risk estimates similar to those for the main analysis.

It is possible that some of our findings are spurious, or conversely, that we were not able to detect true associations for some of the smaller birth defect groups and for certain types of thyroid disease or treatment. In the main analysis of any thyroid disease or thyroid medication use, 82 statistical tests were conducted (42 categories/groupings of birth defects plus 40 of the same categories restricted to isolated cases). Four statistically significant associations would be expected by chance alone. Six were observed in our study: total left ventricular outflow tract obstruction, total and isolated hydrocephaly, isolated anorectal atresia, and total and isolated hydrocephaly. Two of these associations confirm findings of other studies; two have not been reported previously. It is possible that some of the significant associations represent false-positive findings or that the effect sizes are inflated (Ioannidis, 2008). For maternal thyroid disease, we had reasonable study power to detect modest elevations in risk for a number of different birth defects. Nevertheless, because we examined individual birth defect phenotypes within organ systems, the number of exposed cases for some birth defects was relatively small despite the large size of the NBDPS. We had an 80% power to detect ORs as low as 2.0 to 2.5 for case groups with 250 to 500 cases. For the smallest case groups (100 cases) we had an 80% power to detect an OR of 3.3 or more. Maternal use of antithyroid medications was too rare to adequately assess risks associated with exposure.

CONCLUSIONS

We evaluated maternal thyroid disease, thyroid medication use, and a variety of specific birth defect phenotypes in a large population-based, case-control study and observed significant positive associations for left ventricular outflow tract obstruction, hydrocephaly, anorectal atresia, and hypospadias. Similar results were observed when exposure was limited to thyroxine use during the periconceptional period. Use of antithyroid medications was rare, and we could not adequately assess risks for maternal use of antithyroid medication for most case groups. We detected elevated ORs for periconceptional antithyroid medication and aortic valve stenosis and anorectal atresia based on small numbers of exposed cases. Our finding of a significant positive association between maternal thyroid disease and hydrocephaly and nonsignificant associations for encephalocele and holoprosencephaly are consistent with increased risk estimates observed for central nervous system defects in several previous studies and may represent true associations. Elevated risk of hypospadias following maternal thyroxine use was observed in only one other study, and our results for left ventricular outflow tract obstruction and anorectal atresia have not been reported previously and may be chance findings. Because it is possible that abnormal thyroid hormone levels (inadequate treatment) and not thyroid medication use represent a risk to the fetus, careful monitoring of thyroid function during pregnancy continues to be important (Schroeder, 2002). The findings in this study will need to be confirmed in other studies. Further studies should evaluate risk associated with antithyroid medication use as well as risk by type of thyroid disorder (e.g., Hashimoto's thyroiditis, Graves' disease, non-autoimmune thyroid disease).

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