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Maternal Autoimmune Disease and Birth Defects in the National Birth Defects Prevention Study

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Abstract

Background—Little is known about the association between maternal autoimmune disease or its treatment and the risk of birth defects. We examined these associations using data from the National Birth Defects Prevention Study, a multi-site, population-based, case–control study.

Methods—Analyses included 25,116 case and 9897 unaffected control infants with estimated delivery dates between 1997 and 2009. Information on autoimmune disease, medication use, and other pregnancy exposures was collected by means of telephone interview. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for birth defects with five or more exposed cases; crude ORs and exact 95% CIs were estimated for birth defects with three to four exposed cases.

Results—Autoimmune disease was reported by 373 mothers (279 case and 94 control mothers). The majority of birth defects evaluated were not associated with autoimmune disease; however, a statistically significant association between maternal autoimmune disease and encephalocele was observed (OR, 4.64; 95% CI, 1.95–11.04). Eighty-two mothers with autoimmune disease used an immune modifying/suppressing medication during pregnancy; this was associated with encephalocele (OR, 7.26; 95% CI, 1.37–24.61) and atrial septal defects (OR, 3.01; 95% CI, 1.16–7.80).

Conclusion—Our findings suggest maternal autoimmune disease and treatment are not associated with the majority of birth defects, but may be associated with some defects, particularly encephalocele. Given the low prevalence of individual autoimmune diseases and the rare use of

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specific medications, we were unable to examine associations of specific autoimmune diseases and medications with birth defects. Other studies are needed to confirm these findings.

Keywords

autoimmune disease; autoimmune medication; pregnancy; birth defects; congenital malformations

Introduction

Autoimmune diseases are common in the United States, and women of childbearing age are thought to be at the greatest risk (Cooper et al., 2009; Office of Women's Health, 2010). There are well-established links between autoimmune disease and infertility, recurrent miscarriage, preterm birth, pre-eclampsia, and intrauterine growth restriction (Costedoat-Chalumeau et al., 2004, 2005; Ornoy et al., 2004; Clancy et al., 2004; Carp et al., 2012; Twig et al., 2012; Tersigni et al., 2014). However, the literature is sparse in terms of the association between the presence of an autoimmune disease and the risk of birth defects.

Estimates of the association between autoimmune medications and specific birth defects are also sparse, consisting largely of case series and studies with small numbers of exposed infants. Recommendations for drug use during pregnancy vary, and limited information exists on the comparative safety during pregnancy of many immunosuppressive agents (Ostensen et al., 2006; Kim et al., 2014; Cooper et al., 2014). For example, methotrexate is used for cancer chemotherapy, as a treatment for a variety of autoimmune conditions, and as an abortifacient (Lloyd et al., 1999). It is known to have adverse fetal effects (Feldkamp and Carey, 1993; Lloyd et al., 1999; Piggott et al., 2011; Hyoun et al., 2012; Weber-Schoendorfer et al., 2014; Kim et al., 2014; Dawson et al., 2014). The Food and Drug Administration lists methotrexate as contraindicated during pregnancy for women with psoriasis or rheumatoid arthritis; however, questions remain, with some suggesting that methotrexate is not toxic when used in low doses by pregnant women (Lewden et al., 2004; Visser et al., 2009; U.S. FDA, 2011; Kim et al., 2014; Weber-Schoendorfer et al., 2014). The picture of comparative safety for the majority of medications used for autoimmune disease remains similarly unclear.

We used data from the National Birth Defects Prevention Study (NBDPS), a large, multisite, population-based, case–control study, to examine the role of autoimmune disease and its treatment on the risk of birth defects.

Materials and Methods

The NBDPS began collecting data in 1997 (Reefhuis et al., 2015). Infants with 1 or more of 30 different categories of major structural malformations (cases), excluding those attributed to a known chromosomal or single-gene abnormality, were ascertained through birth defects surveillance systems in 10 states (Arkansas, California, Georgia, Iowa, Massachusetts, North Carolina, New Jersey, New York, Texas, and Utah). Control infants were live unaffected births born in the same time period and geographic area as the cases, randomly selected from hospital records, birth certificates, or both. Each study site and the Centers for Disease

Control and Prevention obtained Institutional Review Board approval. Mothers provided informed consent.

This analysis includes births with estimated delivery dates from October 1997 through December 2009. The main analysis includes birth defects for which 100 or more cases were available for study. To avoid missing strong effects in small case groups, we conducted exploratory analyses of 15 birth defects with less than 100 infants, which included: truncus arteriosus, interrupted aortic arch (IAA) type a, IAA other/type b, double outlet right ventricle with transposition of the great arteries, conoventricular ventricular septal defects (VSD), tricuspid atresia, multiple VSD, other VSD, cerebellar hypoplasia, colonic atresia/stenosis, bladder exstrophy, intercalary limb deficiency, unspecified limb deficiencies, cloacal exstrophy, and sacral agenesis.

Trained interviewers conducted computer-assisted telephone interviews with the mothers of case and control infants to collect information on demographics, pregnancy history, health conditions, and exposures before and during pregnancy. Mothers were asked about medications taken during the period from 3 months preconception through the end of pregnancy, and information was collected on timing, frequency, and duration of medication use. The Slone Epidemiology Center Drug Dictionary was used to code all reported medications. During the study period, 67.4% of eligible case mothers and 64.8% of eligible control mothers participated in the interview. A total of 38,009 mothers (27,809 cases and 10,200 controls) completed the NBDPS interview during the study period.

Case inclusion criteria have been described previously (Reefhuis et al., 2015). Briefly, clinical geneticists reviewed and classified each case infant as having isolated, multiple, or complex birth defects (Rasmussen et al., 2003). Congenital heart defect (CHD) cases were further categorized as simple (a single CHD or CHD “entity”), association, or complex (Botto et al., 2007). CHD cases classified as atrial septal defects (ASD) not otherwise specified were likely ASD secundum type and were counted as such in the analysis (Botto et al., 2007).

In January 2006, data collection for VSD changed; the current analysis excludes VSDs diagnosed after 2005. Certain study sites did not ascertain cases during the entire study period for oral clefts and pulmonary valve stenosis, and muscular VSDs were included for the first year for sites participating from 1997 to 1998. When analyzing those defects, cases and controls were excluded for the study sites and years for which case ascertainment was incomplete. 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 stenosis) were counted as small intestinal atresias. Infants with esophageal or small intestinal atresia that occurred as a component of a VATER/VACTERL association defects were classified as having multiple defects. For hypospadias, only second- and third-degree hypospadias cases were included; the control group was restricted to males. Congenital heart block is not a structural malformation and was not collected as part of NBDPS. However, we examined the frequency of congenital heart block occurring with an

eligible NBDPS defect, given the link between maternal autoimmune antibodies and birth defects (Costedoat-Chalumeau, 2005; Yan et al., 2012).

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.” Information on autoimmune disease was also captured in comment fields throughout the interview. Maternal autoimmune disease status was compiled and manually reviewed by a study investigator, blinded to case/control status, who assigned infants to one of three mutually exclusive groups: (1) autoimmune disease, (2) possible autoimmune disease, or (3) no autoimmune disease.

Medications specifically used to treat autoimmune disease were manually reviewed for mothers classified with possible and no autoimmune disease. A vague description plus a report of a medication or procedure indicated specifically for an autoimmune condition was used to assign a more specific diagnosis in seven instances. For example, a diagnosis of ulcerative colitis was assigned for five mothers who reported “colitis,” which could have nonautoimmune etiologies, and reported taking mesalamine, which is used specifically for ulcerative colitis. Another diagnosis was confirmed for inflammatory bowel disease based on a report of an “inflammatory” disease and use of sulfasalazine. A diagnosis of rheumatoid arthritis was assigned based on a report of Bowers procedure and use of methotrexate. In two instances, the autoimmune diagnosis was made based on reported use of medication specifically used for autoimmune conditions in the absence of a reported autoimmune disease. One mother was assigned an inflammatory bowel disease diagnosis based on reported use of mesalamine. Another mother was assigned a multiple sclerosis diagnosis based on reported use of methotrexate and interferon beta-1b.

We further classified mothers with autoimmune disease as having systemic disease as opposed to organ-specific disease and conducted a sub-analysis restricted to systemic autoimmune disease and birth defects. While autoimmune diseases are broadly divided into systemic disease and not, the distinction is not always clear (Firestein et al., 2013). For this analysis, the following autoimmune diseases were considered systemic: antiphospholipid antibody syndrome; Crohn’s disease; ulcerative proctitis; ulcerative colitis; inflammatory bowel disease; psoriatic arthritis; systemic lupus erythematosus, scleroderma, Sjögren’s syndrome or another connective tissue disease; rheumatoid arthritis; and ankylosing spondylitis (Firestein et al., 2013).

To examine medications used to treat autoimmune disease, mothers with autoimmune disease were classified according to autoimmune medication use during the 3 months before through the end of pregnancy. Mutually exclusive categories were created and included: (1) mothers with any immune modifier/suppressant use (acitretin, azathioprine, cyclophosphamide, cyclosporine, hydroxychloroquine, hydroxyurea, mercaptopurine, mesalamine, methotrexate, methoxsalen, mycophenolate, rituximab, sulfasalazine, tumor necrosis factor inhibitors, or other biologic agents), (2) mothers with any glucocorticoid use

(except use of asthma medication fluticasone, beclomethasone, and mometasone) in the absence of immune modifiers/suppressants, and (3) mothers not treated with an immune modifier/suppressant, glucocorticoid, or thyroid medication. “Untreated” mothers could have taken a less specific anti-inflammatory medication for their autoimmune disease; in fact, 47% of “untreated” mothers reported taking an nonsteroidal anti-inflammatory drug.

Covariates were identified a priori by directed acyclic graphs. Adjusted analyses controlled for maternal age at delivery (≤29, 30–34, ≥35 years), parity (≤1, ≥2 previous births), race/ethnicity (non-Hispanic white, other), education (high school or less, more than high school), prepregnancy body mass index [(BMI) weight in kilograms/height in meters^2; <18.5, 18.5–24.9, 25–29.9, ≥30], state of residence at birth, folic acid-containing supplement use 1 month preconception through the first month of pregnancy, and both alcohol consumption and cigarette smoking 1 month preconception through the third month of pregnancy.

To reduce etiologic heterogeneity within case groups, we excluded infants with a birth defect that was classified either as a complex sequence (a group of defects believed to be pathogenetically related, but for which the primary defect is not apparent) or classified as an uncommon CHD association. We included infants in case groups that consist primarily of complex defects such as heterotaxia with CHD and single ventricle defect, as well as infants in case groups that are common CHD associations (e.g., coarctation of the aorta and VSD). Infants of mothers who remained in the possible autoimmune disease category were also excluded from all analyses. Lastly, infants of mothers who reported pre-existing type 1 or 2 diabetes were excluded because diabetes is a well-known risk factor for a variety of birth defects, and we wanted to separately examine other autoimmune conditions (Correa et al., 2008).

For birth defects with five or more exposed cases, multivariable logistic regression models estimated the adjusted odds ratio (ORs) and 95% confidence intervals (CIs) for the association between maternal autoimmune disease and each birth defect, while controlling for covariates. For birth defects with three or four exposed cases, crude ORs and Fisher’s exact CIs were calculated. ORs are not shown for birth defects with fewer than three exposed cases. ORs were used to estimate relative risk. To reduce etiologic heterogeneity within case groups, we separately examined isolated defects for each birth defect category.

When sample size permitted, crude and adjusted ORs and CIs were estimated for the association between autoimmune medication use and birth defects. Specifically, we examined any use of an immune modifier/suppressant, any use of a glucocorticoid in the absence of immune modifier/suppressant use, and “untreated” autoimmune disease. Infants of mothers with autoimmune disease who were taking thyroid medication, but not on an immune modifier/suppressant or a glucocorticoid were excluded from the medication analysis (45 cases, 14 controls), as were 1170 infants (925 cases, 245 controls) of mothers without autoimmune disease who reported using an immune modifier/suppressant (n = 13), glucocorticoid (n = 1149), or thyroid medication (n = 8). The reference group was infants of mothers without autoimmune disease who did not report using one of these medications.

We examined whether the association between autoimmune disease and birth defects (all cases and isolated cases only) varied by maternal BMI and folic acid-containing supplement use. Additive interaction was assessed by calculating the excess relative risk due to interaction along with the 95% CIs using a logistic regression model adjusted for the covariates (Hosmer and Leme-show, 1992). Analyses were performed using SAS software, version 9.3 (SAS Corporation, Cary, NC).

Results

After excluding 1418 infants with uncommon CHD associations or complex birth defects, 950 infants of mothers with possible autoimmune disease (710 cases, 240 controls), 280 infants of mothers with type 1 diabetes (252 cases, 28 controls), and 348 infants of mothers with type 2 diabetes (313 cases, 35 controls), 35,013 infants (25,116 cases, 9897 controls) remained in the analysis.

Overall, 373 mothers reported autoimmune disease: 279 (1.1%) case and 94 (0.9%) control infants. Table 1 outlines the distribution of covariates among controls by autoimmune disease status. Table 2 lists the number of mothers with each reported autoimmune disease. Twelve mothers reported two distinct autoimmune diseases. Systemic autoimmune disease was reported by 183 mothers (49% of all autoimmune disease; 135 mothers of case infants, 48 mothers of control infants). Six mothers reported having two systemic autoimmune conditions.

The associations between maternal autoimmune disease (irrespective of medication use) and the 28 noncardiac birth defects in the main analysis are presented in Table 3, along with the associations between systemic autoimmune disease (a subset of mothers with autoimmune disease) and noncardiac birth defects. For all cases (both isolated and not), infants of mothers with autoimmune disease had more than four times the estimated risk of encephalocele compared with infants of mothers without autoimmune disease (OR = 4.64; 95% CI, 1.95–11.04). For isolated birth defects, infants of mothers with autoimmune disease had significantly increased risk of encephalocele (OR = 6.11; 95% CI, 2.54–14.68) and hydrocephaly (OR = 2.40; 95% CI, 1.03–5.59). In the exploratory analysis, infants of mothers with autoimmune disease had an increased risk of isolated cloacal exstrophy (OR = 7.11; 95% CI, 1.39–22.80). No other defect in the exploratory analysis had more than one exposed case.

Maternal systemic autoimmune disease was associated with an increased risk of encephalocele (OR = 8.54; 95% CI, 3.25–22.38), cleft palate (OR = 1.94; 95% CI, 1.04–3.62), isolated encephalocele (OR = 11.17; 95% CI, 4.22–29.55), isolated cleft palate (OR = 2.12; 95% CI, 1.11–4.05), and isolated transverse limb deficiencies (OR = 2.55; 95% CI, 1.08–6.05). Neither autoimmune disease nor systemic autoimmune disease were significantly associated with an increased risk of a CHD (Table 4).

We examined whether the associations between maternal autoimmune disease and each birth defect differed across levels of maternal BMI and folic acid use (data not shown). We did not

find a difference in any association on the additive scale by either (relative risk due to interaction 95% CI contained 0).

Among all mothers, 95 (69 case mothers, 26 control mothers) reported taking an immune-modifying/suppressing agent any time during pregnancy and 1224 mothers (966 case mothers, 258 control mothers) reported using a glucocorticoid. Eighty-two mothers (86.3%) who used an immune modifier/suppressant had an autoimmune disease: 67 (81.7%) reported using one and 15 (18.3%) reported taking two of these medications (Table 5). Slightly less than half of these mothers reported taking an immune modifier/suppressant throughout pregnancy (39/82, 48%), while the same number reported taking an immune modifier/suppressant during the first trimester only. Mothers with autoimmune disease also reported taking anti-thyroid medication ($n = 12$), thyroid hormone ($n = 54$), nonsteroidal anti-inflammatory drug ($n = 176$), opioids ($n = 39$), and anticoagulants ($n = 11$).

Infants of mothers with autoimmune disease who reported taking an immune modifier/suppressant had over seven times the estimated risk of encephalocele (OR = 7.26; 95% CI, 1.37–24.61; Table 6) and three times the risk of ASD (OR = 3.01; 95% CI, 1.16–7.80). Glucocorticoid use among mothers with autoimmune disease and “untreated” autoimmune disease were not significantly associated with any birth defect. However, the OR for encephalocele remained elevated among the “untreated” mothers with autoimmune disease, although this was based on three “untreated” case mothers and had wide CIs (OR = 3.31; 95% CI, 0.65–10.45). The majority of transverse limb deficiencies occurred among infants whose mothers were “untreated” (8/10 infants whose mothers had autoimmune disease). We observed an increased risk that approached statistical significance for transverse limb deficiency among these “untreated” mothers with autoimmune disease compared with “untreated” mothers without autoimmune disease (OR = 2.35; 95% CI, 0.99–5.57), similar to the magnitude and direction seen in the significant transverse limb deficiency findings with systemic autoimmune disease.

Discussion

In our analysis of over 35,000 mothers in the NBDPS, 1.1% of case mothers and 0.9% of control mothers reported an autoimmune disease. We did not find increased risk associated with autoimmune disease or its treatment for the majority of birth defects examined. We found statistically significant associations between maternal autoimmune disease and encephalocele, hydrocephaly, and cloacal exstrophy, with OR estimates ranging from 2.4 to 7.1. Maternal systemic autoimmune disease was associated with encephalocele, cleft palate, and transverse limb deficiency, with OR estimates ranging from 1.9 to 11.2. We also observed statistically significant associations between immune modifier/suppressant use and encephalocele and ASD.

Our findings for encephalocele were similar regardless of how we examined the outcome (all cases vs. isolated) or the exposure (autoimmune vs. systemic disease). Estimates for encephalocele were further from the null when the analysis was restricted to isolated cases, and even further when we examined the subset with systemic disease. If the estimate represents a true increase in risk attributable to autoimmune disease, based on an estimated

prevalence of 0.84 infants with encephalocele per 10,000 live births, an OR of 4.64 would translate to a potential increase in absolute risk from 1 infant with encephalocele per 11,905 live births to 1 in 2566 live births among women with autoimmune disease. The potential increase in risk would be even greater (1 in 1394) if we considered mothers with systemic autoimmune disease (Parker et al., 2010).

Autoimmune disease has been connected to several adverse fetal outcomes, yet the literature is sparse on the association between autoimmune disease and the risk of specific birth defects. Limited information is also available about the safety of immunosuppressive agents in pregnancy, and the debate about the association of these medications with specific birth defects is ongoing (Kim et al., 2014). For many immunosuppressive agents, the recommendations for use during pregnancy differ (Ostensen et al., 2006). Often the findings of increased risk associated with specific immunosuppressive medications are based on case reports or case series, or the published findings provide contradictory estimates of the risk of birth defects.

Our analysis had to group immune modifiers/suppressants together due to small numbers, so we could not separate the effects of individual medications. We separately examined infants whose mothers took a glucocorticoid medication in the absence of an immune modifier/suppressant. While maternal use of glucocorticoids has been associated with oral clefts, a NBDPS study recently found no association (Skuladottir et al., 2014). We were only able to calculate an OR for the association between glucocorticoid use among mothers with autoimmune disease and one birth defect (ASD); the elevated OR was not statistically significant.

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 were able to separately evaluate the associations between etiologically homogenous birth defect categories and both autoimmune disease and medication use. We were also able to separately analyze isolated cases. Lastly, the NBDPS is a population-based study, and the controls represent the same base population as the cases (Cogswell et al., 2009).

Our study has several limitations. The NBDPS relies on retrospective self-reported disease status and medication use during pregnancy, making recall bias a potential concern. However, we observed positive associations between maternal autoimmune disease and some, but not all, birth defects. If recall bias strongly influenced the results, we would have expected elevated ORs for a wider range of birth defects than was found.

A few factors could have impacted our ascertainment of autoimmune disease. First, the NBDPS did not ask specifically about autoimmune disease status, instead relying on an open-ended question to identify mothers with autoimmune disease. This could have led to under-ascertainment of autoimmune disease. Second, the NBDPS questionnaire changed in 2006, so that autoimmune disease was mentioned in the question prompt. We found that mothers interviewed after this change were more likely to report autoimmune disease than mothers interviewed with the older questionnaire, but reporting of immune-modifier/

suppressant drug use did not differ. The proportions of cases and controls who reported autoimmune disease were the same in the two time periods, so any misclassification of exposure should be nondifferential.

Lastly, we excluded women with diabetes to examine the effect of other autoimmune diseases on the risk for birth defects. We found that 1.1% of NBDPS mothers (1.1% of cases, 0.9% of controls) reported autoimmune disease. Other published estimates of autoimmune disease in the general population are much higher, ranging from 3.2 to 9% (Jacobson et al., 1997; Eaton et al., 2007; Cooper et al., 2009; Sardu et al., 2012). Our findings are more in line with a Danish study of women aged 14 or older (Khashan et al., 2011). Our study and the study by Khashan et al. only included women of childbearing age. Khashan et al. reported 2.4% of women had an autoimmune disease. While this is higher than our findings, this is largely due to our exclusion of diabetics. Khashan et al. included type 1 diabetics, which was the most common autoimmune disease in their study, with a prevalence of 9.75 per 1000. If we had included infants of women with type 1 diabetes in our analysis, we would have found that 1.9% of infants (2.1% cases, 1.2% of controls) had a mother with autoimmune disease.

Despite the large size of the NBDPS, our analysis was restricted by small numbers in several ways. The number of mothers with autoimmune disease was small, and autoimmune medication use was even rarer. Thus, we analyzed a composite variable for both autoimmune disease and autoimmune medications instead of looking at risks of specific autoimmune diseases/medications. We were able to collect information on the distribution of specific autoimmune diseases and medications reported by mothers. Yet, we combined disease and treatments together to obtain a sufficient sample size. We were also limited in our ability to control for confounding by indication.

While we did not find a difference in any association on the additive scale by either BMI or folic acid use, we cannot be certain that additive interaction does not exist because small numbers and limited power may have impacted our ability to detect the presence of additive interaction. Due to small numbers of cases, we may not have been able to detect a true increase in risk for some birth defect groups. Our findings may be due to chance. The main analysis included 99 statistical tests; approximately five statistically significant associations would be expected by chance alone. We observed eight such associations and found robust associations between our exposure and encephalocele.

We examined associations between autoimmune disease and its treatment and a wide range of birth defects, finding that the majority of birth defects were not associated with autoimmune disease or its treatment. While this is reassuring, our findings do suggest an association between maternal autoimmune disease and encephalocele. However, encephalocele is rare; the increased risk we observed, if true and attributable to autoimmune disease, would translate to a risk of approximately 1 in 2500 live births compared with a risk in the general population of approximately 1 in 12,000 births. Other long-term, population-based studies are needed to confirm these findings and better evaluate the association between specific autoimmune disease and treatments and individual birth defects.

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TABLE 1

Selected Characteristics of Controls (n = 9897) with and without Autoimmune Disease, National Birth Defects Prevention Study 1997 to 2009

Select maternal characteristics	Autoimmune disease *n* = 94 *n* (%)	No autoimmune disease *n* = 9803 *n* (%)	*p* Value
Maternal age (years)			
≤29	30 (32)	6044 (62)	
30–34	37 (39)	2449 (25)	<0.001
≥35	27 (29)	1310 (13)	
Race/ethnicity			
Non-Hispanic white	83 (88)	5638 (58)	<0.001
Other	11 (12)	4155 (42)	
Education (years)			
≤12	14 (15)	3993 (42)	<0.001
>12	79 (85)	5568 (58)	
Parity			
0 or 1	78 (83)	7100 (73)	0.026
2 or more	16 (17)	2665 (27)	
Pre-pregnancy BMI			
<18.5	4 (4)	514 (6)	
18.5–24.9	51 (55)	5071 (54)	0.929
25–29.9	23 (25)	2137 (23)	
≥30	15 (16)	1612 (17)	
Smoking[b]			
Yes	14 (15)	1761 (18)	0.413
No	79 (85)	7833 (82)	
Alcohol[b]			
Yes	53 (57)	3496 (37)	<0.001
No	40 (43)	6060 (63)	
Folic acid-containing supplement use[c]			
Yes	71 (76)	5096 (53)	<0.001
No	23 (24)	4468 (47)	

[a] Numbers vary because of missing values.

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

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

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

TABLE 2

Autoimmune Conditions Reported by Mothers of Cases and Controls, National Birth Defects Prevention Study 1997 to 2009

Condition (ICD code)	All mothers (*n* = 373) *n* (%)[a]	Case mothers (*n* = 279) *n* (%)[a]	Control mothers (*n* = 94) *n* (%)[a]
Graves' disease (242)	33 (9)	25 (9)	8 (9)
Hashimoto's thyroiditis (245.2)	31 (8)	26 (9)	5 (5)
Thyroid disease, autoimmune, unspecified (246.9)	1 (< 1)	1 (< 1)	0
Addison's disease (255 .41)	1 (< 1)	1 (< 1)	0
Pernicious anemia (281)	5 (1)	3 (1)	2 (2)
Hemolytic anemia, autoimmune (283)	2 (1)	1 (<1)	1 (1)
Immune/idiopathic thrombocytopenic purpura (287.31)	13 (4)	5 (2)	8 (9)
Antiphospholipid antibody syndrome (289.81)[b]	10 (3)	9 (3)	1 (1)
Protein S deficiency (289.81)	1 (< 1)	1 (< 1)	0
Multiple sclerosis (340)	28 (8)	24 (9)	4 (4)
Guillain-Barre syndrome (357) 3	3 (1)	1 (< 1)	2 (2)
Myasthenia gravis (358)	3 (1)	3 (1)	0
Rheumatic fever (390)	2 (1)	2 (1)	0
Crohn's disease (555.9)[b]	29 (8)	20 (7)	9 (10)
Ulcerative proctitis (556.2)[b]	1 (< 1)	1 (< 1)	0
Ulcerative colitis (556.9)[b]	39 (11)	27 (10)	12 (13)
Inflammatory bowel disease (558.9)[b]	2 (1)	2 (1)	0
Hepatitis, autoimmune (571.42)	1 (< 1)	0	1 (1)
Celiac disease (579)	19 (5)	15 (5)	4 (4)
Interstitial cystitis (595.1)	15 (4)	14 (5)	1 (1)
Dermatitis herpetaformis (694)	1 (< 1)	1 (< 1)	0
Psoriatic arthritis (696)[b]	2 (1)	2 (1)	0
Psoriasis (696.1)	31 (8)	21 (8)	10 (11)
Alopecia universalis/areata (704; 704.01, 704.09)	3 (1)	2 (1)	1 (1)
Vitiligo (709.01)	3 (1)	3 (1)	0
Systemic lupus erythematosus; scleroderma; Sjögren's syndrome; connective tissue disease (710, 710.1, 710.2, 710.9)[b]	46 (12)	36 (13)	10 (11)
Rheumatoid arthritis; juvenile rheumatoid arthritis (714; 714.3)[b]	57 (15)	42 (15)	15 (16)
Ankylosing spondylitis (720)[b]	3 (1)	1 (< 1)	2 (2)

Twelve mothers reported two autoimmune conditions (10 mothers of case infants, 2 mothers of control infants).

[a]Percentages do not total 100.

[b]Considered a systemic autoimmune disease.

ICD, International Classification of Diseases (9th Revision).

TABLE 3

Associations of Maternal Autoimmune Disease and Systemic Maternal Autoimmune Disease with Non-cardiac Birth Defects, National Birth Defects Prevention Study 1997 to 2009

	Autoimmune disease[a]				Systemic autoimmune disease[a]			
	All cases[b]		Isolated cases		All cases[b]		Isolated cases	
	Exposed/ unexposed	OR (95% CI)[c]	Exposed/ unexposed	OR (95% CI)[c]	Exposed/ unexposed	OR (95% CI)[c]	Exposed/ unexposed	OR (95% CI)[c]
Amniotic band sequence	4/293	1.42 (0.38–3.81)	3/253	1.24 (0.25–3.77)	2/293	NC	1/253	NC
Central nervous system								
Anencephaly	4/515	0.81 (0.22–2.16)	4/463	0.90 (0.24–2.40)	1/515	NC	1/463	NC
Spina bifida	8/1082	0.93 (0.45–1.94)	8/960	1.02 (0.49–2.13)	2/1082	NC	2/960	NC
Encephalocele	6/190	4.64 (1.95–11.04)	6/137	6.11 (2.54–14.68)	5/190	8.54 (3.25–22.38)	5/137	11.17 (4.22–29.55)
Holoprosencephaly	1/133	NC	1/96	NC	1/133	NC	1/96	NC
Dandy-Walker	1/152	NC	1/92	NC	1/152	NC	1/92	NC
Hydrocephaly	8/411	1.99 (0.91–4.35)	7/289	2.40 (1.03–5.59)	2/411	NC	2/289	NC
Eye								
Anophthalmia/microphthalmia	4/176	2.37 (0.63–6.38)	3/103	3.04 (0.61–9.40)	3/176	3.48 (0.69–10.96)	2/103	NC
Congenital cataracts	4/275	1.44 (0.38–3.87)	4/243	1.63 (0.43–4.38)	2/275	NC	2/243	NC
Glaucoma	1/150	NC	1/126	NC	1/150	NC	1/126	NC
Anotia/microtia	5/565	1.49 (0.60–3.74)	3/402	0.78 (0.16–2.36)	4/565	1.45 (0.38–3.97)	3/402	1.52 (0.30–4.76)
Orofacial								
Choanal atresia	0/122	NC	0/65	NC	0/122	NC	0/65	NC
Cleft palate only	20/1327	1.45 (0.88–2.40)	19/1069	1.63 (0.98–2.74)	13/1327	1.94 (1.04–3.62)	12/1069	2.12 (1.11–4.05)
Cleft lip without palate	8/913	0.87 (0.42–1.80)	8/850	0.92 (0.44–1.91)	3/913	0.66 (0.13–2.06)	3/850	0.71 (0.14–2.21)

Birth Defects Res A Clin Mol Teratol. Author manuscript; available in PMC 2017 November 01.

	Autoimmune disease[a]				Systemic autoimmune disease[a]			
	All cases[b]		Isolated cases		All cases[b]		Isolated cases	
	Exposed/ unexposed	OR (95% CI)[c]	Exposed/ unexposed	OR (95% CI)[c]	Exposed/ unexposed	OR (95% CI)[c]	Exposed/ unexposed	OR (95% CI)[c]
Cleft lip with palate	15/1674	0.93 (0.51–1.67)	13/1447	0.96 (0.52–1.77)	7/1647	0.85 (0.36–2.01)	5/1447	0.79 (0.31–2.00)
Cleft lip with or without palate	23/2587	0.90 (0.56–1.46)	21/2297	0.94 (0.58–1.54)	10/2587	0.77 (0.37–1.58)	8/2297	0.74 (0.35–1.58)
Gastrointestinal								
Esophageal atresia	5/621	0.67 (0.27–1.68)	4/265	1.57 (0.42–4.21)	3/621	0.99 (0.20–3.07)	3/265	2.31 (0.46–7.25)
Duodenal atresia	2/192	NC	0/117	NC	0/192	NC	0/117	NC
Small intestinal atresia	5/411	1.85 (0.74–4.62)	4/350	1.19 (0.32–3.18)	2/411	NC	2/350	NC
Anorectal atresia	1/867	NC	0/377	NC	1/867	NC	0/377	NC
Biliary atresia	1/159	NC	1/134	NC	0/159	NC	0/134	NC
Genitourinary								
Hypospadias[d]	29/2015	1.19 (0.73–1.94)	27/1809	1.20 (0.73–1.99)	17/2015	1.19 (0.63–2.24)	15/1809	1.12 (0.58–2.18)
Renal agenesis	1/146	NC	1/107	NC	0/146	NC	0/107	NC
Musculoskeletal								
Longitudinal limb deficiency	2/380	NC	2/202	NC	1/380	NC	1/202	NC
Transverse limb deficiency	10/613	1.57 (0.76–3.28)	10/512	1.81 (0.87–3.78)	7/613	2.25 (0.95–5.32)	7/512	2.55 (1.08–6.05)
Craniosynostosis	22/1248	1.49 (0.92–2.41)	21/1129	1.57 (0.96–2.56)	6/1248	0.84 (0.35–2.00)	6/1129	0.93 (0.39–2.20)
Diaphragmatic hernia	6/689	0.82 (0.33–2.03)	6/549	1.00 (0.40–2.49)	4/689	1.19 (0.31–3.25)	4/549	1.49 (0.39–4.09)
Omphalocele	3/357	0.88 (0.18–2.66)	2/220	NC	2/357	NC	1/220	NC
Gastroschisis	5/1185	0.99 (0.38–2.56)	5/1071	1.09 (0.42–2.81)	2/1185	NC	2/1071	NC

	Autoimmune disease[a]				Systemic autoimmune disease[a]			
	All cases[b]		Isolated cases		All cases[b]		Isolated cases	
	Exposed/ unexposed	OR (95% CI)[c]	Exposed/ unexposed	OR (95% CI)[c]	Exposed/ unexposed	OR (95% CI)[c]	Exposed/ unexposed	OR (95% CI)[c]
Cloacal exstrophy[e]	3/75	4.17 (0.83–13.04)	3/44	7.11 (1.39–22.80)	0/75	NC	0/44	NC

[a]Autoimmune analysis includes 94 control infants with a mother who had autoimmune disease and 9803 control infants with a mother who had no autoimmune disease. Systemic autoimmune analysis includes 48 control infants with a mother who had a systemic autoimmune disease and 9803 control infants with a mother who did not have a systemic autoimmune disease. Women with an autoimmune disease not considered systemic were excluded from the systemic analysis.

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

[c]For defects with five or more exposed cases, estimates were adjusted for mother's state of residence at the time of infant's birth, age, race/ethnicity, education, body mass index, parity (total previous live births), folic acid-containing supplement use, smoking, and drinking. Counts included in the adjusted analysis were slightly lower than presented due to missing values for some covariates. Crude ORs with exact 95% CIs are presented for defects with three to four exposed cases. Estimates are not presented for analyses based on less than three exposed cases.

[d]For the analysis of autoimmune disease and hypospadias, the number of exposed male controls was 45 and the number of unexposed male controls was 4996. For the analysis of systemic autoimmune disease and hypospadias, the number of exposed male controls was 27 and the number of unexposed male controls was 4996.

[e]Included in the exploratory analysis (<100 in case group).

OR, odds ratio; CI, confidence interval; NC, not calculated.

TABLE 4

Associations of Maternal Autoimmune Disease and Systemic Maternal Autoimmune Disease with Congenital Heart Defects, National Birth Defects Prevention Study 1997 to 2009

	Autoimmune disease				Systemic autoimmune disease			
	All cases[b]		Isolated cases		All cases[b]		Isolated cases	
	Exposed/unexposed	OR (95% CI)[c]	Exposed/unexposed	OR (95% CI)[c]	Exposed/unexposed	OR (95% CI)[c]	Exposed/unexposed	OR (95% CI)[c]
Heterotaxy[d]	1/277	NC			1/277	NC		
Conotruncal defects								
Tetralogy of Fallot	7/978	0.72 (0.33–1.57)	6/792	0.74 (0.32–1.71)	4/978	0.84 (0.22–2.29)	4/792	1.03 (0.27–2.83)
d-Transposition of the great arteries	6/522	1.14 (0.50–2.64)	5/490	1.00 (0.40–2.48)	2/522	NC	2/490	NC
Atrioventricular septal defect	3/167	1.87 (0.38–5.74)	3/138	2.27 (0.45–6.97)	1/167	NC	1/138	NC
Total anomalous pulmonary venous return	1/229	NC	1/213	NC	1/229	NC	1/213	NC
LVOTO defects								
Hypoplastic heart syndrome	3/526	0.59 (0.12–1.80)	1/481	NC	0/526	NC	0/481	NC
Coarctation of the aorta	7/516	1.18 (0.54–2.58)	7/457	1.30 (0.60–2.85)	5/516	1.69 (0.66–4.31)	5/457	1.88 (0.74–4.80)
Aortic valve stenosis	4/298	1.40 (0.37–3.74)	3/283	1.47 (0.39–3.94)	0/298	NC	0/283	NC
LVOTO associations[e]	8/415	2.04 (0.98–4.28)	7/346	2.06 (0.94–4.52)	5/415	2.43 (0.95–6.22)	4/346	2.36 (0.61–6.50)
RVOTO defects								
Pulmonary atresia	2/144	NC	2/138	NC	0/144	NC	0/138	NC
Pulmonary valve stenosis	15/897	1.66 (0.93–2.96)	15/845	1.76 (0.99–3.14)	4/897	0.87 (0.23–2.38)	4/845	0.92 (0.24–2.52)
Ebstein anomaly	3/97	3.23 (0.64–10.00)	2/89	NC	1/97	NC	1/89	NC

	Autoimmune disease				Systemic autoimmune disease			
	All cases[b]		Isolated cases		All cases[b]		Isolated cases	
	Exposed/unexposed	OR (95% CI)[c]	Exposed/unexposed	OR (95% CI)[c]	Exposed/unexposed	OR (95% CI)[c]	Exposed/unexposed	OR (95% CI)[c]
RVOTO associations[e]	4/335	1.25 (0.33–3.33)	3/288	1.09 (0.22–3.31)	0/335	NC	0/288	NC
Septal defects								
Perimembranous VSD	7/986	0.75 (0.32–1.77)	6/870	0.70 (0.28–1.78)	3/986	0.74 (0.14–2.43)	2/870	NC
Muscular VSD	1/161	NC	1/144	NC	1/161	NC	1/144	NC
Secundum atrial septal defect	18/1580	1.54 (0.91–2.61)	16/1282	1.70 (0.98–2.98)	10/1580	1.64 (0.80–3.34)	9/1282	1.83 (0.86–3.86)
Septal associations[e]	6/658	1.03 (0.44–2.39)	5/521	1.07 (0.43–2.69)	4/658	1.24 (0.32–3.41)	3/521	1.18 (0.23–3.67)
Single ventricle defects[d]	1/139	NC			1/139	NC		

[a]Autoimmune analysis included 94 control infants of a mother with autoimmune disease and 9864 control infants of a mother with no autoimmune disease. Systemic autoimmune analysis included 48 control infants of a mother with autoimmune disease and 9864 control infants of a mother with no autoimmune disease.

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

[c]For defects with five or more exposed cases, estimates were adjusted for mother's state of residence at the time of infant's birth, age, race/ethnicity, education, body mass index, parity, folic acid-containing supplement use, smoking, and drinking. Counts included in the adjusted analysis were slightly lower than presented due to missing values for some covariates. Crude ORs with exact 95% CIs are presented for defects with three to four exposed cases. Estimates are not presented for analyses based on less than three exposed cases.

[d]All cases in birth defect group were considered complex.

[e]LVOTO associations include coarctation of the aorta + aortic stenosis, coarctation of the aorta + VSD, coarctation of the aorta + VSD + atrial septal defect (ASD). RVOTO associations include pulmonary valve stenosis + VSD, pulmonary valve stenosis + ASD. Septal associations include VSD + ASD.

OR, odds ratio; CI, confidence interval; NC, not calculated; LVOTO, left ventricular outflow tract obstruction; RVOTO, right ventricular outflow tract obstruction; VSD, ventricular septal defect.

TABLE 5

Autoimmune Medication Use[a] among Mothers with Autoimmune Disease (n = 373), National Birth Defects Prevention Study, 1997 to 2009

Medications	All mothers with autoimmune disease	Mothers of case infants	Mothers of control infants
Immune modifiers/suppressants	82[b]	61	21
Synthetic agents			
Hydroxychloroquine	17	14	3
Methotrexate	9	7	2
Cyclophosphamide	1	1	0
Azathioprine	6	3	3
Cyclosporine	1	1	0
Mycophenolate	2	2	0
Sulfasalazine	10	5	5
Mesalamine	34	24	10
Methoxsalen	1	1	0
Biologic agents			
TNF-inhibitors[c]	7	6	1
Other biologics[d]	9	7	2
Other			
Glucocorticoids[e]	73	55	18

[a]Medication use includes those who reported taking the medication at any time in the 3 months before through the end of pregnancy, as well as those who reported taking the medication in that time period, but the dates of use were unknown. No mothers reported taking acitretin, hydroxyurea mercaptopurine, or rituximab.

[b]Reported taking at least one immune modifier/suppressant; 15 mothers (10 case mothers and 5 control mothers) reported taking two of these medications.

[c]Category includes infliximab, adalimumab, and etanercept.

[d]Category includes interferon beta-1a, interferon beta-1b, and glatiramer acetate.

[e]Glucocorticoids includes all glucocorticoids except three taken only for asthma (fluticasone, beclomethasone, and mometasone). Forty of these mothers reported glucocorticoid use in the absence of an immune modifier/suppressant.

TNF, tumore necrosis factor.

TABLE 6

Associations of Immune Modifying/Suppressing Medications, Glucocorticoids, and "Untreated" Mothers with Birth Defects,[a] National Birth Defects Prevention Study 1997 to 2009

	Immune modifiers/suppressants (n = 82)[b]		Glucocorticoids (n = 40)[c]		"Untreated" with autoimmune disease (n = 192)[d]	
	Exposed/unexposed	OR (95% CI)[e]	Exposed/unexposed	OR (95% CI)[e]	Exposed/unexposed	OR (95% CI)[ij]
Non-cardiac defects						
Amniotic band sequence	1/281	NC	0/281	NC	3/281	2.22 (0.44–6.96)
Spina bifida	1/1043	NC	1/1043	NC	5/1043	1.20 (0.47–3.05)
Encephalocele	3/188	7.26 (1.37–24.61)	0/188	NC	3/188	3.31 (0.65–10.45)
Anotia/microtia	4/556	3.27 (0.81–9.74)	0/556	NC	1/556	NC
Cleft palate only	2/1293	NC	2/1293	NC	12/1293	1.79 (0.94–3.41)
Cleft lip without palate	4/886	2.03 (0.50–6.02)	0/886	NC	3/886	0.69 (0.14–2.16)
Cleft lip with palate	2/1632	NC	2/1632	NC	10/1632	1.09 (0.51–2.33)
Cleft lip with or without palate	6/2518	1.27 (0.51–3.18)	2/2518	NC	13/2518	0.90 (0.47–1.76)
Esophageal atresia	1/587	NC	0/587	NC	4/587	1.42 (0.37–3.90)
Hypospadias[f]	7/1918	1.40 (0.51–3.84)	2/1918	NC	14/1918	1.14 (0.58–2.24)
Transverse limb deficiency	1/591	NC	1/591	NC	8/591	2.35 (0.99–5.57)
Craniosynostosis	3/1205	1.13 (0.22–3.80)	2/1205	NC	11/1205	1.47 (0.75–2.87)
Gastroschisis	0/1122	NC	0/1122	NC	4/1122	0.74 (0.19–2.03)
Congenital heart defects						
Tetralogy of Fallot	1/943	NC	2/943	NC	4/943	0.88 (0.23–2.42)
d-Transposition of the great arteries	1/506	NC	1/506	NC	3/506	1.23 (0.24–3.85)

	Immune modifiers/suppressants (n = 82)[b]		Glucocorticoids (n = 40)[c]		"Untreated" with autoimmune disease (n = 192)[d]	
	Exposed/unexposed	OR (95% CI)[e]	Exposed/unexposed	OR (95% CI)[e]	Exposed/unexposed	OR (95% CI)[ij]
Hypoplastic left heart syndrome	0/506	NC	0/506	NC	3/506	1.23 (0.24–3.85)
Coarctation of the aorta	0/492	NC	1/492	NC	5/492	1.72 (0.68–4.38)
LVOTO associations[g]	3/404	3.38 (0.64–11.38)	1/404	NC	2/404	NC
Pulmonary valve stenosis	4/862	2.01 (0.50–5.97)	1/862	NC	7/862	1.69 (0.75–3.80)
Perimembranous VSD	2/952	NC	0/952	NC	4/952	1.04 (0.26–3.01)
Secundum atrial septal defect	6/1509	3.01 (1.16–7.80)	3/1509	1.46 (0.27–5.33)	6/1509	1.01 (0.42–2.43)
Septal associations[g]	2/629	NC	0/629	NC	3/629	0.99 (0.20–3.10)
Controls	21/9,554		13/9,554		46/9,554	

[a] Compared to infants of mothers without autoimmune disease who were not on an immune suppressant/modifier, a glucocorticoid, or a thyroid medication.

[b] Immune modifier/suppressant use included any use of acitretin, azathioprine, cyclophosphamide, cyclosporine, hydroxychloroquine, hydroxyurea, mercaptopurine, mesalamine, methotrexate, methoxsalen, mycophenolate, rituximab, sulfasalazine, TNF-inhibitors, or other biologic agent.

[c] Glucocorticoid use defined as any glucocorticoid use (except use of asthma medication fluticasone, beclomethasone, and mometasone) in the absence of immune suppressant/modifiers.

[d] "Untreated" with autoimmune disease defined as not treated by an immune modifier/suppressant, a glucocorticoid, or a thyroid medication. These mothers may have been on other treatments.

[e] For defects with five or more exposed cases, estimates were adjusted for mother's state of residence at the time of infant's birth, age, race/ethnicity, education, body mass index (BMI), parity (total previous live births), folic acid use, smoking, drinking. Counts included in the adjusted analysis were slightly lower than presented due to missing values for some covariates. Crude ORs with exact 95% CIs are presented for defects with three to four exposed cases. Estimates are not presented for analyses based on less than three exposed cases.

[f] The analysis of immune modifiers/suppressants and hypospadias included 11 exposed and 4865 unexposed male controls. The analysis of glucocorticoids and hypospadias included 5 exposed and 4865 unexposed male controls. The analysis of "untreated" and hypospadias included 24 exposed and 4865 unexposed male controls.

[g] 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.

ASD, atrial septal defect; OR, odds ratio; CI, confidence interval; NC, not calculated; LVOTO, left ventricular outflow tract obstruction; TNF, tumor necrosis factor; VSD, ventricular septal defect.

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