RESEARCH ARTICLE

Maternal exposure to hydroxychloroquine and birth defects

Meredith M. Howley[1] | Martha M Werler[2] | Sarah C Fisher[1] | Alissa R Van Zutphen[1,3] | Suzan L Carmichael[4,5] | Cheryl S Broussard[6] | Dominique Heinke[7] | Elizabeth C Ailes[6] | Shannon M Pruitt[6,8] | Jennita Reefhuis[6] | Allen A. Mitchell[2,9] | Marilyn L. Browne[1,3] | the National Birth Defects Prevention Study

[1]Birth Defects Registry, New York State Department of Health, Albany, New York, USA

[2]Department of Epidemiology, Boston University School of Public Health, Boston, Massachusetts, USA

[3]Department of Epidemiology and Biostatistics, School of Public Health, University at Albany, Rensselaer, New York, USA

[4]Division of Neonatal and Developmental Medicine, Department of Pediatrics, Stanford University School of Medicine, Stanford, California, USA

[5]Division of Maternal-Fetal Medicine and Obstetrics, Department of Obstetrics and Gynecology, Stanford University School of Medicine, Stanford, California, USA

[6]Division of Birth Defects and Infant Disorders, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

[7]Center for Birth Defects Research and Prevention, Massachusetts Department of Public Health, Boston, Massachusetts, USA

[8]Oak Ridge Institute for Science and Education, Oak Ridge, Tennessee, USA

[9]Slone Epidemiology Center at Boston University, Boston, Massachusetts, USA

Correspondence
Meredith M. Howley, Birth Defects Registry, New York State Department of Health, Corning Tower Room 1203, Albany, NY 12237, USA.
Email: meredith.howley@health.ny.gov

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Abstract

Background: Hydroxychloroquine is a treatment for rheumatic disease and considered safe during pregnancy. Interest in hydroxychloroquine has increased as it is being examined as a potential treatment and prophylaxis for coronavirus disease 2019. Data on the risks of specific birth defects associated with hydroxychloroquine use are sparse.

Methods: Using data from two case–control studies (National Birth Defects Prevention Study and Slone Epidemiology Center Birth Defects Study), we described women who reported hydroxychloroquine use in pregnancy and the presence of specific major birth defects in their offspring. Cases had at least one major birth defect and controls were live-born healthy infants. Women self-reported medication use information in the few months before pregnancy through delivery.

Results: In total, 0.06% (19/31,468) of case and 0.04% (5/11,614) of control mothers in National Birth Defects Prevention Study, and 0.04% (11/29,838) of case and 0.05% (7/12,868) of control mothers in Birth Defects Study reported hydroxychloroquine use. Hydroxychloroquine users had complicated medical histories and frequent medication use for a variety of conditions. The observed

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birth defects among women taking hydroxychloroquine were varied and included nine oral cleft cases; the elevated observed:expected ratios for specific oral cleft phenotypes and for oral clefts overall had 95% confidence intervals that included 1.0.

Conclusion: While teratogens typically produce a specific pattern of birth defects, the observed birth defects among the hydroxychloroquine-exposed women did not present a clear pattern, suggesting no meaningful evidence for the risk of specific birth defects. The number of exposed cases is small; results should be interpreted cautiously.

KEYWORDS

birth defects, hydroxychloroquine, lupus, rheumatoid arthritis

1 | INTRODUCTION

In patients with rheumatic diseases, hydroxychloroquine (HCQ) is a mainstay in treatment as it prevents flares, achieves remission, and reduces mortality (Clowse, Magder, Witter, & Petri, 2006; Sammaritano et al., 2020). HCQ is generally considered safe during pregnancy for treatment of rheumatic conditions, is thought to be preferable to systemic corticosteroids (Balevic et al., 2019; Eudy et al., 2018; Flint et al., 2016; Leroux et al., 2015). Professional society guidelines recommend continuation of HCQ in pregnancy for women with rheumatic diseases (Flint et al., 2016; Sammaritano et al., 2020).

Interest in HCQ has recently increased as it is being examined as potential treatment and prophylaxis for coronavirus disease 2019 (COVID-19), although many studies have failed to show benefit of HCQ for this purpose (Boulware et al., 2020; Geleris et al., 2020; Mitjà et al., 2020; Rosenberg et al., 2020). For a few months in 2020, the United States Food and Drug Administration allowed HCQ to be used for COVID-19 outside of clinical trials, including in pregnant women within a hospital setting (US Food and Drug Administration, 2000). Additionally, an ongoing clinical trial aims to assess the safety and efficacy of HCQ among COVID-positive pregnant women (https://clinicaltrials.gov/ct2/show/NCT04410562; González et al., 2020). However, concerns about its safety in pregnancy exist given that HCQ crosses the placenta and data on the risks of birth defects associated with HCQ use are sparse (Costedoat-Chalumeau et al., 2002). Though most existing studies have not identified specific signals for safety concerns, a recent cohort study using data from two pharmaceutical claims databases reported an increased risk for any birth defect among women filling prescriptions for HCQ with a daily dose ≥400 mg (Huybrechts et al., 2020). While unable to explore the risk of specific birth defects due to the small number of exposed cases, the authors found associations with large groupings of birth defects, including birth defects in the respiratory and urinary tract systems, and oral clefts (Huybrechts et al., 2020). We sought to describe all women who reported HCQ use in pregnancy and describe the presence of specific major birth defects in their offspring within two multi-site, case–control studies of birth defects, the National Birth Defects Prevention Study (NBDPS) and the Slone Epidemiology Center Birth Defects Study (BDS).

2 | METHODS

The NBDPS and BDS were both large, multisite, case–control studies designed to investigate risk factors for birth defects. Detailed methods can be found elsewhere (Parker, Van Bennekom, Anderka, & Mitchell, 2018; Reefhuis et al., 2015; Werler, Hayes, Louik, Shapiro, & Mitchell, 1999). Briefly, the NBDPS included pregnancies ending on or after October 1, 1997 with estimated delivery dates on or before December 31, 2011 (Reefhuis et al., 2015). Pregnancies affected by one or more of 30 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). Clinical geneticists reviewed cases to determine eligibility for the overall study and to classify cases as isolated (one major birth defect or organ system involved), multiple (major birth defects in more than one organ system), or complex (a group of major defects believed to be pathogenetically related, but the primary defect was not apparent) (Rasmussen et al., 2003). Congenital heart defect cases were further classified according to a protocol that

considered cardiac phenotype, complexity, and presence of noncardiac defects (Botto, Lin, Riehle-Colarusso, Malik, & Correa, 2007). Oral clefts, glaucoma, cataracts, ventricular septal defects (VSDs), and pulmonary valve stenosis were not ascertained by all sites for all years (Rasmussen et al., 2003). Only second- and third-degree hypospadias cases were included. 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.

From 1976 to 2015, the BDS identified pregnancies with any major birth defect by review of discharge records or registry data at participating hospitals or birth defect registries in greater metropolitan Boston, Massachusetts (1976–1998); areas of Massachusetts and greater metropolitan Boston (1998–2015); greater metropolitan Philadelphia, Pennsylvania (1977–2015); greater metropolitan Toronto, Ontario (1979–2006); San Diego County, California (2001–2015); parts of New York State (2004–2015); and Nashville, Tennessee (2012–2015) (Parker et al., 2018; Werler et al., 1999; Werler, Shapiro, & Mitchell, 1993). Case infants included the wide range of major birth defects. Control participants were liveborn infants without birth defects identified from study hospitals and birth certificates in the same catchment areas as case participants.

Although both studies had centers in Massachusetts, California, and New York, catchment and eligibility criteria prevented participants from being included in both studies (Parker et al., 2018). We have presented all exposed nonmalformed controls from both studies and have limited the exposed cases to specific birth defect phenotypes eligible for both studies. Cases with chromosomal abnormalities and single-gene disorders were excluded. The NBDPS and BDS obtained Institutional Review Board approval as appropriate and mothers provided informed consent.

The NBDPS and BDS collected self-reported maternal exposure information up to 24 months after delivery for NBDPS and 6 months after delivery for BDS via computer-assisted telephone interviews (entire time for NBDPS and 1998–2015 for BDS) or in-person interview (1976–1997 for BDS). In NBDPS, 66.7% of eligible case mothers and 63.7% of eligible control mothers participated in the interview; in BDS, participation rates varied over the 40-year period, ranging from approximately 65–80%. Neither study had specific questions about HCQ or autoimmune disease, including rheumatic diseases. For the NBDPS, women were asked about medications taken, as well as about "any other disease or illnesses that we have not already talked about" (pre-2006) and "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" (2006 and later). For the BDS, women were asked about their medical and medication history, with specific prompts for pain (1976 and later), joint pain (1992 and later), and arthritis (2009 and later). For both studies, women were asked about the name, timing, and frequency of any medications used, but were not asked specifically about dose or indication for each medication. We reviewed all text responses, International Classification of Diseases codes, and questionnaire comments for HCQ-exposed women to identify an indication for the HCQ use. Both studies used the Slone Epidemiology Center Drug Dictionary to code reported medications and link products to their active ingredient components.

Pregnancy timing was defined differently in the two studies. The NBDPS used the estimated date of conception as the reference date, defined pregnancy months as 30-day time periods around the estimated date of conception, and collected medication exposures in the 3 months before conception to the end of pregnancy. The BDS used the last menstrual period (LMP) date as the reference date, defined pregnancy months as 28-day time periods (lunar months) around the LMP, and collected medication exposures in the two lunar months before the LMP through the end of pregnancy (Parker et al., 2018). Given that HCQ takes about 6 months to be fully eliminated from the body, we considered a woman exposed if she reported using HCQ at any time (Stokkermans, Goyal, Bansal, & Trichonas, 2020).

For exposed women from both studies, we reviewed available clinical information on the pregnancy (birth defect[s], birth outcome, gestational age, and birth weight); HCQ use (indication, timing, and duration); and medical history (other chronic health conditions and medication use). In addition, we reviewed other possible self-reported risk factors for birth defects, including maternal age at delivery, maternal race/ethnicity, maternal educational attainment, prepregnancy body mass index, folic acid-containing supplements, and smoking status. Early pregnancy was defined as the month before through the third month of pregnancy for NBDPS and the first two lunar months of pregnancy in BDS and folic acid-containing supplement exposure was defined as use in the period before conception. Given the rarity of HCQ use, we elected to present a descriptive review of the characteristics of HCQ-exposed mothers and any birth defects in their offspring. Within each study, we calculated the observed to expected ratio (O:E) for birth defects with more than one HCQ-exposed infant and the corresponding 95% confidence intervals using the exact Poisson distribution (Daly, 1992).

3 | RESULTS

Of the 31,468 case and 11,614 control women in the NBDPS, 19 (0.06%) case and 5 (0.04%) control women reported using HCQ in the 3 months before conception through the end of pregnancy. Of the 29,838 cases and 12,868 controls in the BDS, 11 (0.04%) case women and 7 (0.05%) control women reported using HCQ in the two lunar months before LMP through the end of pregnancy. Most exposed women reported using HCQ in early pregnancy and only one woman reported starting HCQ during pregnancy (Figure 1). Reported indications included systemic lupus erythematosus ($n = 19$), rheumatoid arthritis ($n = 11$), psoriatic arthritis ($n = 1$), unspecified arthritis/joint pain ($n = 4$), unspecified autoimmune disease ($n = 1$), Sjogrens syndrome ($n = 1$), connective tissue disorder ($n = 1$), fibromyalgia ($n = 1$), and unknown indication ($n = 4$).

Several maternal and infant characteristics of exposed cases and controls were assessed (Table 1). Women who reported HCQ use also reported a wide range of other chronic conditions and medications. Ten (33%) case and two (17%) control mothers reported use of other immunosuppressive or biologic medications for the treatment of rheumatic diseases, including methotrexate (three cases, one control) and mycophenolate mofetil (one case). Seventeen (57%) case and five (41.7%) control mothers

reported concomitant use of a corticosteroid, with prednisone being the most common (Table 2). HCQ-exposed women reported taking other medications during pregnancy, including anticonvulsants, antihypertensive medications, bronchodilators, anti-depressants, anti-anxiety medications, ADHD medications, opioids, thyroid hormone, anti-migraine medications, protein pump inhibitors, and anticoagulants.

All infants exposed to HCQ in both studies were liveborn except one fetus with encephalocele electively terminated at 22 weeks gestation. Among the live-born infants, the mean gestational age was 37.0 weeks (*SD* 3.0) for cases and 38.4 weeks (*SD* 1.9) for controls. The mean birthweight was 2,844 g (*SD* 711) for live-born cases and 2,920 g (*SD* 590) for controls.

Of the more than 40 birth defect categories examined in both studies, most of the specific birth defects had no HCQ-exposed cases. The birth defects observed among HCQ users were varied and are presented in Table 2. Among the 30 exposed cases, we observed 9 oral clefts (2 with cleft lip only, 3 with cleft palate only, and 4 with cleft lip and cleft palate), 6 VSDs (2 perimembranous, 2 muscular, 1 sub-pulmonary, 1 unspecified), 4 hypospadias, and 3 atrial septal defects (ASDs). Across both studies, we observed 1 exposed infant with each of the following birth defects: encephalocele, spina bifida, glaucoma, microtia, gastroschisis, diaphragmatic hernia,
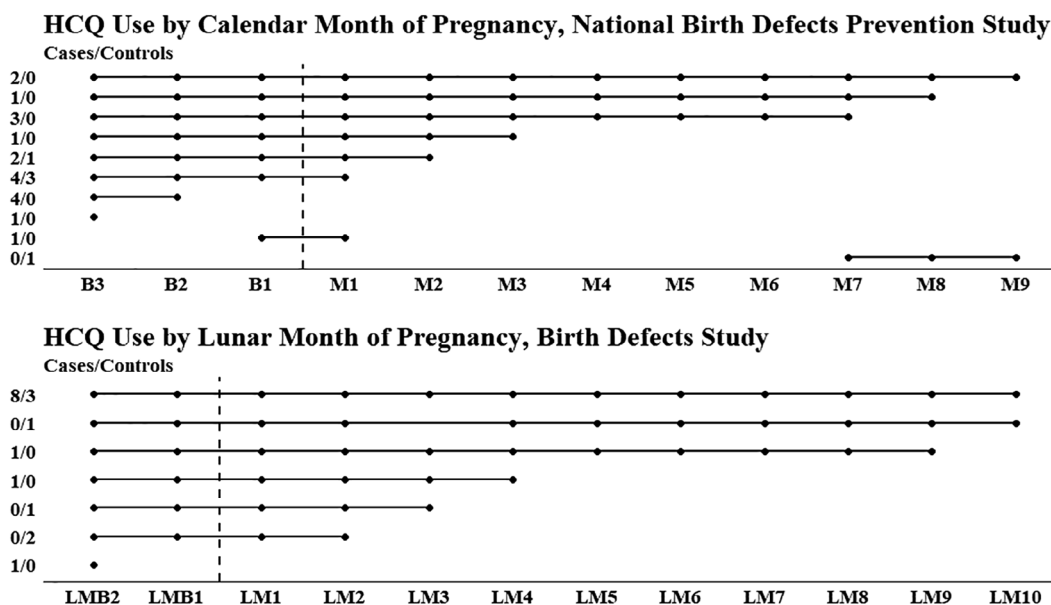

FIGURE 1 Hydroxychloroquine (HCQ) use before and during pregnancy among cases and controls by study. The National Birth Defects Prevention Study used the estimated date of conception as the interview reference date and months were defined as calendar months (30-day periods) around the estimated date of conception. B3, B2, and B1 denote months before pregnancy, whereas M1–M9 denotes months of pregnancy. The Birth Defects Study used the last menstrual period date as the interview reference date to collect information and months were defined as lunar months (28-day periods) around the last menstrual period. LMB2 and LMB1 denote lunar months before the last menstrual period, whereas LM1–LM10 denote lunar months of pregnancy

TABLE 1 Characteristics of hydroxychloroquine-exposed cases and controls, National Birth Defects Prevention Study (1997–2011), and Birth Defects Study (1976–2015)

	NBDPS		BDS	
	Cases	Controls	Cases	Controls
	(n = 19)	(n = 5)	(n = 11)	(n = 7)
Maternal age (years)				
≤24	3	0	2	2
25–29	5	2	2	2
30–34	6	2	4	2
≥35	5	1	3	1
Race/ethnicity				
Non-Hispanic White	11	4	6	5
Non-Hispanic Black	5	0	1	0
Hispanic	1	1	3	2
Other	2	0	1	0
Education (years)				
Completed high school	4	0	2	0
Completed some college	6	1	2	3
Completed college or more	9	4	7	4
Prepregnancy body mass index (kg/m²)				
<18.5	0	0	1	0
18.5–24.9	7	2	4	4
25–29.9	7	2	4	2
≥30	5	1	2	1
Parity				
0 or 1	9	4	5	3
2 or more	10	1	6	4
Folic acid-containing supplement use[a]	12	4	9	6
Yes				
No	7	1	2	1
Early pregnancy smoking				
Yes	4	1	0	0
No	15	4	11	7
Use of fertility treatments[b]				
Yes	3	0	0	0
No	16	5	10	7
Other reported chronic condition[c]				
Hypertension	9	0	3	0
Thyroid disorder	2	0	0	0
Pre-existing diabetes	1	0	0	0
Gestational diabetes	1	0	0	0
Asthma	3	0	0	0
Epilepsy	0	0	1	0
Depression	1	0	0	0
Antiphospholipid syndrome	1	0	0	0
Endometriosis	1	0	0	0

(Continues)

TABLE 1 (Continued)

	NBDPS		BDS	
	Cases	Controls	Cases	Controls
	(*n* = 19)	(*n* = 5)	(*n* = 11)	(*n* = 7)
Birth weight[d]				
Very low (<1,500 g)	1	0	0	0
Low (1500–2,499 g)	5	3	5	0
Normal (2,500+ g)	12	2	6	7
Gestational age at birth[d]				
Very preterm (<32 weeks)	3	0	0	0
Preterm (32–36 weeks)	3	3	3	0
Term (≥37 weeks)	12	2	8	7

Abbreviations: BDS, Birth Defects Study; NBDPS, National Birth Defects Prevention Study.

[a]For the NBDPS, folic acid use was defined as within the month before through the first month of pregnancy. For the BDS, folic acid use was defined as the two lunar months before through the second lunar month of pregnancy.

[b]Excludes one hydroxychloroquine-exposed BDS case with unknown fertility treatment status.

[c]Other reported chronic condition is in addition to the indication for HCQ.

[d]Excludes one HCQ-exposed case who was nonliveborn.

small intestinal atresia, anorectal atresia, esophageal atresia, conoventricular VSD (considered an outflow tract defect, unlike other VSDs), tetralogy of Fallot, aortic stenosis, pulmonary valve atresia, and interrupted aortic arch type B. The majority of exposed cases in both studies (25/30, 83%) were isolated, meaning there was one birth defect or one organ system involved. Table 3 compares the observed number of HCQ-exposed infants with one or more birth defects to the expected number by study. The O:E ratios ranged from 0.5 to 3.2, with the highest O:E ratios for any oral cleft (3.2 in NBDPS and 2.5 in BDS) and hypospadias (2.7 in NBDPS). The 95% confidence intervals for all the O:E ratios were wide and included the null value of 1.

4 | DISCUSSION

Across these two multisite, case–control studies, 30 case and 12 control women reported use of HCQ with the majority of these women exposed during early pregnancy. Three-quarters of these women reported an autoimmune condition. All of the exposed women had complicated medical histories. Their various reported conditions and use of other medications to treat those conditions may have increased the risk for birth defects (Anderson et al., 2020; Fisher et al., 2017, 2018; Howley et al., 2017, 2020; Louik, Lin, Werler, Hernández-Díaz, & Mitchell, 2007; Tinker et al., 2020; van Gelder et al., 2015). Additionally, HCQ-exposed women reported taking a variety of other medications during pregnancy for both their autoimmune diseases and other chronic conditions. As has been seen in other studies of HCQ use in pregnancy, women reporting HCQ also took other immunomodulatory agents, biologic agents, and corticosteroids for their rheumatic conditions (Bermas et al., 2018; Desai et al., 2016). Some HCQ-exposed women in our analysis reported medications thought to be teratogenic: four took methotrexate (three cases, one control) and one reported mycophenolate mofetil (one case; Götestam Skorpen et al., 2016; Kylat, 2017; Milunsky, Graef, & Gaynor Jr., 1968).

Among women with rheumatic diseases, medication use, including HCQ, during pregnancy is recommended to decrease the occurrence of flares, as disease flares have been associated with poorer pregnancy outcomes (Clowse et al., 2006; Götestam Skorpen et al., 2016; Leroux et al., 2015). A recent study by Huybrechts et al. (2020) presented a summary of existing literature surrounding HCQ and the risk of birth defects, noting that these studies have been small case series, small cohort studies of exposed pregnancies, and studies without controls. The authors used two large US claims databases to explore HCQ use and the risk of birth defects among 2,045 HCQ-exposed and 3,198,589 unexposed pregnancies. They observed a 26% increase in the risk of any major congenital malformations among HCQ-exposed patients, and the increased risk was seen only with daily doses of HCQ ≥400 mg. While Huybrechts et al. were unable to explore risks for specific birth

TABLE 2 Information on cases and controls exposed to hydroxychloroquine in the National Birth Defects Prevention Study (1997–2011) and the Birth Defects Study (1976–2015)

Birth defect	Study	Gestational age[a]	Birthweight[b]	Time of exposure[c]	Indication
Encephalocele	NBDPS	Not applicable[d]	Not applicable	B3-P2	Rheumatoid arthritis
Spina bifida, hydrocephaly, and Arnold-Chiari malformation	BDS	Term	Low	LMB2-LM10	Arthritis, unspecified
Bilateral glaucoma	NBDPS	Preterm	Low	B3-B2	Lupus
Bilateral microtia	NBDPS	Very preterm	Very low	B3-P7	Lupus
Cleft palate	NBDPS	Term	Normal	B3-B2	Psoriatic arthritis
Cleft palate	NBDPS	Term	Normal	B1-P1	Rheumatoid arthritis and lupus
Unilateral cleft palate, ASD	BDS	Term	Normal	LMB2-LM4	Arthritis, unspecified
Unilateral cleft lip	NBDPS	Term	Normal	B3-B2	Lupus
Bilateral cleft lip	NBDPS	Term	Normal	B3-P9	Lupus
Cleft lip and palate	BDS	Term	Normal	LMB2	No indication
Unilateral cleft lip and palate	NBDPS	Term	Normal	B3-P1	Rheumatoid arthritis
Unilateral cleft lip and palate	BDS	Term	Normal	LMB2-LM10	Lupus
Bilateral cleft lip and palate	NBDPS	Term	Normal	B3-P1	No indication
Second-degree hypospadias	NBDPS	Term	Normal	B3-P9	Lupus
Second-degree hypospadias	NBDPS	Preterm	Low	B3-B2	No indication
Third-degree hypospadias	NBDPS	Term	Normal	B3-P2	Lupus
Third-degree hypospadias	NBDPS	Term	Normal	B3-P3	Lupus
Gastroschisis	BDS	Term	Low	LMB2-LM10	Lupus
Diaphragmatic hernia (left), IAA type B	BDS	Preterm	Low	LMB2-LM10	Connective tissue disorder
Small intestinal (jejunal) atresia	NBDPS	Very preterm	Low	B3-P7	Rheumatoid arthritis
Anorectal atresia, unspecified VSD, VACTERL	BDS	Term	Low	LMB2-LM10	Lupus
Esophageal atresia with TEF, tetralogy of fallot	NBDPS	Preterm	Low	B3-P8	Rheumatoid arthritis
Conoventricular VSD	NBDPS	Term	Normal	B3	Rheumatoid arthritis
Aortic stenosis	NBDPS	Term	Normal	B3-P1	Rheumatoid arthritis
Pulmonary valve stenosis	NBDPS	Term	Normal	B3-P1	Rheumatoid arthritis
Subpulmonary VSD	NBDPS	Very preterm	Low	B3-P7	Sjogrens syndrome
Muscular VSD	BDS	Term	Normal	LMB2-LM10	No indication
Perimembranous VSD	BDS	Preterm	Low	LMB2-LM9	Lupus
Perimembranous VSD, ASD	BDS	Term	Normal	LMB2-LM10	Rheumatoid arthritis
Muscular VSD, ASD	BDS	Term	Normal	LMB2-LM10	Arthritis, unspecified
Control	BDS	Term	Normal	LMB2-LM10	Lupus
Control	NBDPS	Preterm	Low	B3-P1	Fibromyalgia
Control	NBDPS	Term	Normal	P7-P9	Lupus
Control	NBDPS	Preterm	Low	B3-P1	Lupus
Control	NBDPS	Term	Normal	B3-P2	Rheumatoid arthritis
Control	NBDPS	Preterm	Low	B3-P1	Rheumatoid arthritis
Control	BDS	Term	Normal	LMB2-LM2	Autoimmune disorder, unspecified
Control	BDS	Term	Normal	LMB2-LM3	Unspecified joint pain

(Continues)

T A B L E 2 (Continued)

Birth defect	Study	Gestational age[a]	Birthweight[b]	Time of exposure[c]	Indication
Control	BDS	Term	Normal	LMB2-LM10	Lupus
Control	BDS	Term	Normal	LMB2-LM2	Lupus
Control	BDS	Term	Normal	LMB2-LM2, LM4-10	Lupus
Control	BDS	Term	Normal	LMB2-LM10	Lupus

Abbreviations: ASD, atrial septal defect; BDS, Birth Defects Study; IAA, interrupted aortic arch; NBDPS, National Birth Defects Prevention Study; TEF, tracheoesophageal fistula; VACTERL, vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb deficiencies; VSD, ventricular septal defect.

[a]Gestational age categories included: Very preterm (<32 weeks), preterm (32–36 weeks), and term (37 or more weeks).

[b]Birth weight categories included: Very low (<1,500 g), low (1500–2,499 g), and normal (2,500 g or more).

[c]The NBDPS used the estimated date of conception as the interview reference date and months were defined as calendar months (30-day periods) around the estimated date of conception. B3, B2, and B1 denote months before pregnancy, whereas M1–M9 denotes months of pregnancy. The Birth Defects Study used the last menstrual period date as the interview reference date to collect information and months were defined as lunar months (28-day periods) around the last menstrual period. LMB2 and LMB1 denote lunar months before the last menstrual period, whereas LM1–LM10 denote lunar months of pregnancy.

[d]This pregnancy resulted in a non-live birth (induced abortion). All other HCQ-exposed pregnancies resulted in a live birth.

T A B L E 3 Observed to expected ratios and 95% confidence intervals for birth defects with more than 1 observed hydroxychloroquine-exposed case, National Birth Defects Prevention Study (1997–2011), and Birth Defects Study (1976–2015)

	Observed	Expected	Observed: Expected (95% CI)
National Birth Defects Prevention Study			
Any oral cleft	6	3.21	1.87 (0.69–4.07)
Cleft palate only	2	0.86	2.33 (0.28–8.42)
Cleft lip only	2	0.61	3.27 (0.40–11.82)
Cleft lip and palate	2	1.05	1.91 (0.23–6.89)
Hypospadias	4	2.72	1.47 (0.40–3.76)
Birth Defects study			
Any oral cleft	3	2.46	1.22 (0.25–3.56)
Cleft lip and palate	2	1.05	1.91 (0.23–6.89)
Ventricular septal defect, perimembranous	2	0.50	3.97 (0.48–14.32)
Ventricular septal defect, muscular	2	1.24	1.61 (0.20–5.82)
Atrial septal defect	3	1.17	2.57 (0.53–7.51)

Abbreviation: CI, confidence interval.

defects due to small numbers, the authors looked at larger groupings of birth defects, finding associations with birth defects in the urinary system, the respiratory system, and oral clefts. In a sensitivity analysis that was restricted to women with a diagnosis of rheumatic diseases, these adjusted associations persisted although they noted the confidence intervals were wide, with the relative risk for oral clefts being 3.37 with a 95% confidence interval from 1.32 to 8.56. We observed 9 oral cleft cases across our two large studies (6 in the NBDPS and 3 in the BDS), whereas 6 oral cleft cases would have been expected (3.2 in the NBDPS and 2.5 in the BDS).

However, the elevated O:E ratios for specific oral cleft phenotypes and for oral clefts overall in either study had 95% confidence intervals that were imprecise and included the null value of 1.0. Additionally, 5 out of the 9 exposed cases were also exposed to medications that could increase the risk of oral clefts (one to methotrexate and five to concomitant exposure to corticosteroids, but causal evidence for the latter is conflicting; Skuladottir et al., 2014; Xiao, Liu, Liu, Zhang, & Xue, 2017). We observed four hypospadias cases (all four in NBDPS) and would have expected 2.7, resulting in an O:E ratio of 1.47, but the 95% confidence interval was wide and

included the null value of 1.0. Huybrechts et al. (2020) did not see any observed increase in the genital anomalies group, which included hypospadias.

Diagnostic information on birth defect cases was reviewed by clinical geneticists in NBDPS and by study nurses in BDS to classify birth defects according to a standard protocol. There were some differences between the birth defects eligible for each study. While the NBDPS did not observe any ASD cases and only observed one VSD among HCQ-exposed women, there were three ASDs and five VSDs among BDS exposed cases. However, there were differences in how the NBDPS and the BDS defined septal birth defects. The NBDPS only actively ascertained isolated muscular VSDs for the first year of the study and starting in 2006 excluded all remaining isolated VSDs. Starting in 2006, the NBDPS also excluded ASD ≤4 mm or those described as "small." The BDS did not have such restrictions. We included any septal defects among exposed cases from the BDS in this analysis. In a previous NBDPS analysis of autoimmune diseases and their treatments, we observed an increased risk of encephalocele and ASD associated with use of immune modifying/suppressing medications (including HCQ) in early pregnancy (Howley et al., 2016). In the current report, no HCQ-exposed woman within NBDPS had an infant with ASD and only one mother had an infant with encephalocele, suggesting that HCQ was not a driver of the previously observed associations within NBDPS. We observed three ASD cases within HCQ-exposed women in BDS.

The case–control studies included in this report relied on large population-based and hospital- and registry-based samples and assessed a wide range of maternal characteristics and exposures. However, the NBDPS and BDS had a small number of exposed cases, which is a limitation of our study. The number of exposed women in the two case–control studies was too small to provide sufficient statistical power to test for associations between HCQ use and specific birth defects. We therefore took a descriptive approach. Given our highly imprecise confidence intervals, we cannot rule out that some of the observed birth defects with elevated O:E ratios among HCQ-exposed women were due to chance. For most specific birth defects examined, no exposed cases were observed; we did not evaluate null or potential protective effects associated with birth defects that occurred less than expected. Rather, we sought to describe HCQ-exposed cases in the NBDPS and BDS and to compare the specific birth defects observed with those that have been described in the literature to fill in some gaps of the previous studies. Studies relying on pharmaceutical claims data may miss associations with specific birth defects due to potential misclassification of the specific type of birth defect. Further, examination of birth defects at the level of organ systems may obscure association with specific birth defects within those systems.

The NBDPS and the BDS relied on maternal self-reported exposure information. Thus, there is potential for recall error and possibly biased reporting of maternal HCQ use. If recall bias strongly influenced the results, we would expect elevated O:E ratios for a wider range of birth defects than was found. Both studies lacked specific questions about HCQ, autoimmune diseases or their treatments. Thus, we may have underestimated HCQ use. We included as exposed any woman who reported HCQ at any time; six case women reported HCQ use only prior to conception and one woman reported HCQ only in the last 3 months of pregnancy. We considered them exposed since HCQ has a half-life of about 1 month and takes about half a year to achieve full elimination from the body (Stokkermans et al., 2020). Most importantly, we were unable to separate the effects of HCQ from the effects of the underlying disease or other concomitant medications. In fact, most women who reported HCQ use in both studies reported taking it for an autoimmune condition (32/42, 76%) and reported taking other medications for their autoimmune condition, including corticosteroids and immunosuppressive agents. Huybrechts et al. observed an increased risk of birth defects with daily doses of HCQ ≥400, but we were unable to explore birth defect occurrence by dose as neither NBDPS nor BDS collected dosage information. While the majority of exposed women in our analysis reported taking HCQ for lupus or rheumatoid arthritis, the dose prescribed for these conditions often varies by indication, whether it is being used initially or for maintenance, and body weight (Concordia Pharmaceuticals Inc., 2017). Generally, the recommended adult dosage for treatment of lupus is between 200 and 400 mg daily. For rheumatoid arthritis, the initial dose can be between 400 and 600 mg daily, while the dose for maintenance use is often lower (between 200 and 400 mg daily).

In our analysis of two case–control studies of birth defects, we observed that women who reported HCQ use in pregnancy had complicated medical histories and reported frequent medication use for a variety of chronic conditions. While teratogens typically produce a specific pattern of birth defects, the observed birth defects among the HCQ-exposed women did not present a clear pattern, suggesting no meaningful evidence for the risk of specific birth defects (Khoury, James, et al., 1992; Khoury, Moore, et al., 1992; Tinker et al., 2015). Our findings may be useful to clinicians as they counsel women on the risks and benefits of HCQ use during pregnancy and for future meta-analyses on this topic.

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CONFLICT OF INTEREST

Dr. Mitchell serves on the Biogen Tecfidera Pregnancy Registry Advisory Committee. The other authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data are available upon request and the process for accessing the data used in this study is described at: https://www.cdc.gov/ncbddd/birthdefects/nbdps-public-access-procedures.html.

ORCID

Meredith M. Howley https://orcid.org/0000-0002-8420-5040
Sarah C Fisher https://orcid.org/0000-0002-4702-1007
Dominique Heinke https://orcid.org/0000-0001-9217-3723

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