OBSTETRICS

Hydroxychloroquine early in pregnancy and risk of birth defects

Krista F. Huybrechts, MS, PhD; Brian T. Bateman, MD, MS; Yanmin Zhu, MS, PhD; Loreen Straub, MD, MS; Helen Mogun, MS; Seoyoung C. Kim, MD, ScD; Rishi J. Desai, PhD; Sonia Hernandez-Diaz, MD, DrPH

BACKGROUND: Hydroxychloroquine is generally considered safe in pregnancy for the treatment of rheumatic conditions, but studies have been too small to evaluate teratogenicity. Quantifying the risk of congenital malformations associated with early pregnancy exposure to hydroxychloroquine is important in both the context of its ongoing use for rheumatological disorders and its potential future use for coronavirus disease 2019 prophylaxis, for which a number of clinical trials are ongoing despite initial trials for coronavirus disease 2019 treatment having been negative.

OBJECTIVE: The study objective was to evaluate the risk of major congenital malformations associated with exposure to hydroxychloroquine during the first trimester of pregnancy, the period of organogenesis.

STUDY DESIGN: We performed a population-based cohort study nested in the Medicaid Analytic eXtract (MAX, 2000—2014) and IBM MarketScan Research Database (MarketScan, 2003—2015). The source cohort included 2045 hydroxychloroquine-exposed pregnancies and 3,198,589 pregnancies not exposed to hydroxychloroquine continuously enrolled in their respective insurance program for 3 months before the last menstrual period through at least 1 month after delivery; infants were enrolled for at least 3 months after birth. We compared the risk of congenital malformations in women using hydroxychloroquine during the first trimester of pregnancy with that of those not using hydroxychloroquine, restricting the cohort to women with rheumatic disorders and using propensity score matching to control for indication, demographics, medical comorbidities, and concomitant medications (1867 hydroxychloroquine-exposed pregnancies and 19,080 pregnancies not exposed to hydroxychloroquine). The outcomes considered included major congenital malformations diagnosed during the first 90 days after delivery and specific malformation types for which there were at least 5 exposed events: oral cleft, cardiac, respiratory, gastrointestinal, genital, urinary, musculoskeletal, and limb defects.

RESULTS: Overall, 54.8 per 1000 infants exposed to hydroxychloroquine were born with a major congenital malformation versus 35.3 per 1000 unexposed infants, corresponding to an unadjusted relative risk of 1.51 (95% confidence interval, 1.27—1.81). Patient characteristics were balanced in the restricted, propensity score—matched cohort. The adjusted relative risk was 1.26 (95% confidence interval, 1.04—1.54); it was 1.33 (95% confidence interval, 1.08—1.65) for a daily dose of $\geq$400 mg and 0.95 (95% confidence interval, 0.60—1.50) for a daily dose of $<$400 mg. Among the different malformation groups considered, more substantial increases in the risk of oral clefts, respiratory anomalies, and urinary defects were observed, although estimates were imprecise. No pattern of malformation was identified.

CONCLUSION: Our findings suggest a small increase in the risk of malformations associated with first-trimester hydroxychloroquine use. For most patients with autoimmune rheumatic disorders, the benefits of treatment during pregnancy will likely outweigh this risk. If hydroxychloroquine were shown to be effective for coronavirus disease 2019 prophylaxis in ongoing trials, the risk of malformations would need to be balanced against such benefits.

Key words: coronavirus disease 2019, hydroxychloroquine, malformations, pregnancy, rheumatic disorders, systemic lupus erythematosus

Introduction

Hydroxychloroquine (HCQ) is an antimalarial drug widely used in the treatment of systemic lupus erythematosus (SLE) and other rheumatic disorders. It is generally considered to be safe for the treatment of autoimmune rheumatic conditions during pregnancy, and the continuation of HCQ during pregnancy is commonly recommended to improve disease management and pregnancy outcomes.[1—3] However, studies have been too small to evaluate teratogenicity. Over the last several months, there has been heightened interest in HCQ because of it being a candidate drug for the treatment and/or prophylaxis of coronavirus disease 2019 (COVID-19).

Between March 30, 2020, and June 15, 2020, HCQ was granted emergency use authorization by the Food and Drug Administration, allowing it to be used for COVID-19 outside the clinical trial setting, resulting in widespread use during that time window. At some hospitals, pregnant women with moderate COVID-19 have been treated with HCQ. Although several recent studies have failed to show a clear benefit of HCQ as a postexposure prophylaxis[4—6] and the World Health Organization has discontinued the HCQ arm of the Solidarity Trial evaluating its efficacy for the treatment of patients who are hospitalized,[7] numerous randomized controlled studies are still ongoing in particular to evaluate its effects for preexposure prophylaxis,[8] including a trial in pregnant women.[9]

Most studies regarding the safety of HCQ when used for malaria and for rheumatic disorders, such as SLE, suggest no increase in the risk of common adverse obstetrical outcomes, such as spontaneous abortion, prematurity, and intrauterine growth restriction.[10—13] However, data regarding the risk of major congenital malformations associated with early pregnancy exposure are very limited, with the largest published

Cite this article as: Huybrechts KF, Bateman BT, Zhu Y, et al. Hydroxychloroquine early in pregnancy and risk of birth defects. Am J Obstet Gynecol 2020;XX:x.ex—x.ex.

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2020.09.007

Click Video under article title in Contents at **ajog.org**

AJOG at a Glance

Why was this study conducted?

Although hydroxychloroquine (HCQ) is generally considered safe for the treatment of rheumatic conditions during pregnancy, most studies have been too small to evaluate teratogenicity.

Key findings

In this cohort study including 2045 HCQ-exposed pregnancies and 3,198,589 pregnancies not exposed to HCQ (1867 and 19,080, respectively, after restriction and matching), a 26% increase in the risk of major congenital malformations among HCQ-exposed patients was observed. The risk increase was seen with daily doses of ≥400 mg. No specific pattern of malformations was identified.

What does this add to what is known?

This is the third and by far the largest study to suggest a small increased risk. This signal warrants follow-up, given that HCQ is widely used for autoimmune rheumatic disorders in women of childbearing age. Should ongoing clinical trials indicate that there is a role for HCQ in coronavirus disease 2019 prophylaxis, the benefits of HCQ for this new indication would need to be weighed against the potential risk in pregnancy.

cohort study including fewer than 200 exposed pregnancies (Supplemental Table 1).[13] Quantification of the risk of congenital malformations associated with early pregnancy exposure to HCQ is therefore important in both the context of its ongoing use for rheumatological disorders and its potential future use for COVID-19, although its usefulness in this clinical context remains highly uncertain based on the results of initial trials. Given the limited data currently available, we evaluated the risk of major congenital malformations associated with HCQ using 2 large healthcare utilization databases.

Materials and Methods

Data sources and study cohorts

We conducted a cohort study of pregnancies nested in the Medicaid Analytic eXtract (MAX, 2000−2014), composed of all patients enrolled in Medicaid, and the IBM MarketScan Research Database (MarketScan, 2003−2015), composed of a nationally representative sample of patients with employer-provided health insurance. Both data sources included demographic and insurance enrollment information, medical visits and hospitalizations, diagnoses and procedures received as an in- or outpatient, and prescriptions filled on an outpatient basis. The development of the linked mother-infant pregnancy cohorts has been described previously.[14,15] Briefly, we identified all completed pregnancies in women 12 to 55 years of age and linked these pregnancies to live-born infants by state, family identification number, and delivery and birth dates. Using a validated algorithm,[16] we estimated the date of the last menstrual period on the basis of the delivery date and diagnostic codes indicative of preterm delivery. Mothers were required to be continuously insured from 3 months before the start of pregnancy to 1 month after delivery. Infants were required to be insured from birth to 3 months thereafter, unless they died sooner. These restrictions did not affect the age or race distribution in MAX but resulted in a decrease in the proportion of who become Medicaid eligible because of the occurrence of pregnancy and a corresponding increase in the proportion of who become eligible based on other criteria.[17] Pregnancies with exposure to a known teratogenic medication (ie, warfarin, antineoplastic agents, lithium, isotretinoin, misoprostol, thalidomide) during the first trimester of pregnancy and pregnancies with chromosomal abnormalities were excluded.

Exposure

Women were considered exposed if they filled a prescription for HCQ during the first trimester of pregnancy (defined as the date of the last menstrual period to day 90 of pregnancy), the etiologically relevant exposure window for congenital malformations. To reduce the probability of exposure during early pregnancy from use of HCQ dispensed at an earlier time point, the reference group consisted of women without a prescription for HCQ for 3 months before the start of pregnancy to the end of the first trimester of pregnancy given HCQ's long half-life.

Outcomes

The outcome of interest was major congenital malformations overall. In the secondary analyses, we also evaluated the specific malformation types for which we observed at least 5 exposed events across the 2 cohorts: oral cleft, cardiac, respiratory, gastrointestinal, genital, urinary, musculoskeletal, and limb defects. The presence of malformations was defined using validated algorithms based on inpatient or outpatient diagnoses and procedures, which have been shown to identify the outcomes with high specificity (ie, more than 1 date with the respective diagnostic codes recorded or 1 diagnostic code and a code for a procedure or surgery or infant death).[18] Isolated congenital heart block was not included in the definition for cardiac malformations because its risk is increased in babies born to women with SLE.[19] Supplemental Table 2 provides the details.

Covariates

Potential confounders and proxies for confounders considered included sociodemographic information (eg, state of residence, age, race and ethnicity [MAX only]), autoimmune rheumatic disorders (eg, rheumatoid arthritis, SLE, ankylosing spondylitis, psoriatic arthritis), other maternal conditions (eg, diabetes, hypertension, psychiatric conditions, renal disease, neurologic conditions, chronic respiratory conditions, anemia, infections), concomitant medication use (eg, systemic steroids, nonbiologic and

biologic disease-modifying antirheumatic drugs [DMARDs], psychiatric medications, nonsteroidal antiinflammatory drugs [NSAIDs], suspected teratogens), and general markers of the burden of illness (eg, maternal comorbidity index, healthcare utilization measures) (Table; Supplemental Tables 3 and 4).

Analyses

Baseline characteristics were compared between women exposed to HCQ and the reference group of unexposed women. Relative risks (RRs) with their 95% confidence intervals (CIs) were estimated using generalized linear models. As a first level of adjustment, the reference group was restricted to women with a recorded diagnosis of autoimmune rheumatic disorders commonly treated with HCQ ("restricted cohort"). In fully adjusted analyses, exposed and unexposed women in the restricted cohort were matched on the basis of their propensity score (PS), using a 1:200 variable ratio matching and a 0.01 caliper ("restricted matched cohort"). The PS, which reflects the probability of being treated with HCQ, was estimated using a logistic regression model, including all (>80) prespecified covariates. When evaluating the balance in baseline characteristics in the restricted matched cohort, the counts for the unexposed group were weighted to account for the variable ratio matching. We conducted analyses stratified by dose, using the highest daily dose dispensed during the first trimester of pregnancy (<400 mg and ≥400 mg daily) and duration of exposure (≤60 days and >60 days). In a sensitivity analysis, both the exposed and the reference groups were restricted to women with a recorded diagnosis of autoimmune rheumatic disorders. Estimates from both cohorts were combined using a meta-analytic approach with random effects.

For all analyses presented, results were described as similar or different from the reference group based on the magnitude of the point estimates, taking into account the precision of each estimate as reflected in the width of its 95% CI. We focused on estimating the magnitude of effects in preference to dichotomizing the results as statistically significant or not.[20] The research was approved by the institutional review board of Brigham and Women's Hospital, which waived the need for informed consent.

Results

The combined cohort included 2045 pregnancies exposed to HCQ during the first trimester of pregnancy (686 in MAX and 1359 in MarketScan) and 3,198,589 pregnancies not exposed to HCQ (1,881,069 in MAX and 1,317,520 in MarketScan). The mean daily dose of HCQ was 371 mg (standard deviation, 379 mg), and 61% of women used a daily dose of 400 mg. Among the exposed women, 25.9% were exposed for ≤30 days, 33.6% for 31 to 60 days, and 40.5% for >60 days during the first trimester of pregnancy.

Women exposed to HCQ tended to be older, had more comorbid conditions, took more concomitant medications (especially pain medications, steroids, NSAIDs, and DMARDs), and had greater healthcare utilization. After cohort restriction and adjustment through PS matching, all covariates—including treatment indications—were well balanced (Table; Supplemental Tables 3 and 4).

The pooled risk of any congenital malformation was 54.8 per 1000 HCQ-exposed infants (n=112 events) and 35.3 per 1000 infants not exposed to HCQ in the general population (n=112,908 events), corresponding to a pooled unadjusted RR of 1.51 (95% CI, 1.27−1.81). Restricting the reference group to women with rheumatic disorders resulted in an absolute risk of 44.1 per 1000 unexposed infants (506 of 11,468 events) and an RR of 1.26 (95% CI, 1.04−1.53). Adjusting for all potential confounding variables through PS matching did not result in further attenuation of the association (RR, 1.26; 95% CI, 1.04−1.54). Estimates were consistent between the 2 cohorts. The risk of malformations among the HCQ-exposed women was the same regardless of whether women had concomitant exposure to steroids. The adjusted RR was 1.33 (95% CI, 1.08−1.65) for a daily dose of ≥400 mg and 0.95 (95% CI, 0.60−1.50) for <400 mg. The risk was not affected by the duration of exposure (Figure 1), and results were similar when restricting both the exposed and the reference group to women with a recorded diagnosis of autoimmune rheumatic disorders (Supplemental Table 5).

In the context of few events, risk estimates for the specific malformation types considered were relatively imprecise (Figure 2). The point estimates indicated an approximately 2- to 4-fold increase in the risks for oral clefts (RR, 3.70; 95% CI, 1.55−8.82), respiratory defects (RR, 1.85; 95% CI, 0.94−3.64), and urinary defects (RR, 2.21; 95% CI, 1.26−3.86), which were consistent between the 2 cohorts. None of the HCQ-exposed cases of oral clefts had concomitant exposure to steroids. The upper limit of the 95% CI for the pooled estimates suggested no more than a 2-fold increase in the risk of other specific malformation types with the exception of genital defects (upper limit 95% CI, 4.76). Among the 112 HCQ-exposed infants with malformations, 12 (10.7%) had more than 1 type of malformation recorded, with no specific pattern suggestive of a syndrome.

Discussion

Principal findings

Using data from health plans that provide coverage for large populations of both commercially and publicly insured individuals in the United States, we identified a cohort of pregnant women with chronic autoimmune rheumatic diseases and assessed the relative prevalence of major congenital malformations in their newborns following exposure to HCQ during early pregnancy. Women who filled prescriptions for HCQ during the first trimester of pregnancy had a higher risk of malformations in their newborn than the general population. On the restriction to women with the indication (mainly SLE and rheumatoid arthritis), the RR attenuated but was still elevated. In utero−exposed newborns had an adjusted risk of major congenital malformations 26% higher than unexposed newborns overall and 33% higher for daily doses of ≥400 mg (although no increased risk was observed for lower

TABLE
Selected patient characteristics for HCQ-exposed pregnancies and pregnancies not exposed to HCQ

	Original source cohort				Restricted matched cohort[a]			
	MarketScan (2003–2015)		MAX (2000–2014)		MarketScan (2003–2015)		MAX (2000–2014)	
Variable	HCQ exposed	Unexposed	HCQ exposed	Unexposed	HCQ exposed	Unexposed	HCQ exposed	Unexposed
Number of pregnancies	1359	1,317,520	686	1,881,069	1261	11,179	606	7901
Age, mean (SD)	33.0 (4.4)	31.9 (4.6)	27.8 (6.0)	24.5 (5.9)	33.1 (4.6)	33.1 (4.4)	27.9 (6.0)	28.3 (5.9)
Autoimmune rheumatic disorders[b]								
Systemic lupus erythematosus	759 (55.9)	2188 (0.2)	487 (71.0)	2707 (0.1)	675 (53.5)	6065 (54.3)	409 (67.5)	5184 (65.6)
Rheumatoid arthritis	408 (30.0)	3028 (0.2)	190 (27.7)	3056 (0.2)	392 (31.1)	3515 (31.4)	182 (30.0)	2125 (26.9)
Ankylosing spondylitis	14 (1.0)	4654 (0.4)	<11 (0.7)	2588 (0.1)	14 (1.1)	168 (1.5)	<11 (0.8)	246 (3.1)
Psoriatic arthritis	15 (1.1)	404 (0.0)	<11 (0.2)	206 (0.0)	15 (1.2)	127 (1.1)	<11 (0.2)	42 (0.5)
Sicca syndrome	134 (9.9)	647 (0.0)	60 (8.8)	183 (0.0)	122 (9.7)	1113 (10.0)	42 (6.9)	625 (7.9)
Dermatomyositis	17 (1.3)	60 (0.0)	<11 (1.2)	68 (0.0)	13 (1.0)	112 (1.0)	<11 (1.3)	90 (1.1)
Other diffuse connective tissue disease	221 (16.3)	1000 (0.1)	91 (13.3)	423 (0.0)	197 (15.6)	1774 (15.9)	73 (12.1)	1075 (13.6)
Other autoimmune disease	68 (5.0)	1295 (0.1)	<11 (1.5)	402 (0.0)	67 (5.3)	567 (5.1)	<11 (1.7)	148 (1.9)
Sarcoidosis	6 (0.4)	275 (0.0)	<11 (1.3)	455 (0.0)	6 (0.5)	50 (0.5)	<11 (1.5)	121 (1.5)
Other maternal conditions[c]								
Anemia	93 (6.8)	25,507 (1.9)	79 (11.5)	63,162 (3.4)	84 (6.7)	730 (6.5)	71 (11.7)	936 (11.9)
Diabetes	34 (2.5)	23,650 (1.8)	33 (4.8)	41,403 (2.2)	34 (2.7)	293 (2.6)	30 (5.0)	391 (4.9)
Hypertension	93 (6.8)	30,937 (2.4)	74 (10.8)	47,746 (2.5)	85 (6.7)	797 (7.1)	65 (10.7)	829 (10.5)
Neuropathic pain	68 (5.0)	27,054 (2.1)	27 (3.9)	27,145 (1.4)	66 (5.2)	577 (5.2)	24 (4.0)	351 (4.5)
Nonneuropathic pain	450 (33.1)	135,075 (10.3)	316 (46.1)	253,994 (13.5)	421 (33.4)	3773 (33.8)	279 (46.0)	3689 (46.7)
Serious infections	43 (3.2)	17,924 (1.4)	59 (8.6)	72,412 (3.9)	38 (3.0)	318 (2.8)	52 (8.6)	638 (8.1)
Renal disease	58 (4.3)	3379 (0.3)	50 (7.3)	6578 (0.4)	45 (3.6)	396 (3.5)	35 (5.8)	433 (5.5)
Concomitant medications[c]								
Systemic steroids	565 (41.6)	70,421 (5.3)	383 (55.8)	69,446 (3.7)	485 (38.5)	4262 (38.1)	309 (51.0)	4179 (52.9)
Biologic DMARDs	64 (4.7)	1303 (0.1)	16 (2.3)	459 (0.0)	64 (5.1)	575 (5.2)	16 (2.6)	227 (2.9)
Nonbiologic DMARDs	150 (11.0)	7535 (0.6)	129 (18.8)	4269 (0.2)	117 (9.3)	1021 (9.1)	93 (15.4)	872 (11.0)
Opioids	296 (21.8)	153,634 (11.7)	311 (45.3)	427,889 (22.8)	272 (21.6)	2402 (21.5)	281 (46.4)	3854 (48.8)
NSAIDs	255 (18.8)	65,980 (5.0)	290 (42.3)	317,721 (16.9)	235 (18.6)	2073 (18.5)	254 (41.9)	3361 (42.5)

Huybrechts et al. Hydroxychloroquine and birth defects. Am J Obstet Gynecol 2020.

(continued)

TABLE
Selected patient characteristics for HCQ-exposed pregnancies and pregnancies not exposed to HCQ *(continued)*

Variable	Original source cohort				Restricted matched cohort[a]			
	MarketScan (2003–2015)		MAX (2000–2014)		MarketScan (2003–2015)		MAX (2000–2014)	
	HCQ exposed	Unexposed	HCQ exposed	Unexposed	HCQ exposed	Unexposed	HCQ exposed	Unexposed
Markers of burden of illness[d]								
Maternal comorbidity index, mean (SD)	3.0 (2.4)	1.2 (1.5)	3.4 (2.5)	0.9 (1.4)	2.9 (2.3)	3.0 (2.4)	3.3 (2.5)	3.2 (2.6)
Number of distinct diagnoses, mean (SD)	4.7 (3.9)	2.1 (2.6)	6.1 (4.7)	2.8 (3.3)	4.7 (3.9)	4.8 (4.0)	6.0 (4.7)	6.2 (4.8)
Number of non-HCQ prescription drugs, mean (SD)	3.4 (3.1)	1.5 (2.2)	4.9 (3.9)	1.8 (2.5)	3.3 (3.1)	3.6 (3.5)	4.7 (3.8)	4.9 (4.0)
Number of outpatient visits, mean (SD)	4.1 (4.4)	2.1 (3.2)	4.9 (5.9)	2.1 (3.7)	4.1 (4.4)	4.4 (4.4)	4.8 (4.9)	5.0 (6.5)

Data are presented as number (percentage), unless otherwise indicated. Cell size of <11 for the MAX cohort are suppressed in accord with the CMS cell size suppression policy.

CMS, Centers for Medicare and Medicaid Services; *DMARD*, disease-modifying antirheumatic drug; *HCQ*, hydroxychloroquine; *MAX*, Medicaid Analytic eXtract; *NSAID*, nonsteroidal antiinflammatory drug; *SD*, standard deviation.

[a] Given the variable ratio matching, the counts for the unexposed group are weighted counts to demonstrate the balance in baseline covariates; [b] Autoimmune rheumatic disorders were measured from 3 months before the start to the end of pregnancy; [c] Maternal conditions and concomitant medication use were measured from 3 months before the start of pregnancy to the end of the first trimester of pregnancy; [d] General markers of the burden of illness were measured during the 3 months before but not during pregnancy, as these measures may be affected by early detection of pregnancy complications.

Huybrechts et al. Hydroxychloroquine and birth defects. Am J Obstet Gynecol 2020.

doses based on the point estimate, reflecting the estimate most consistent with the data). A more substantial increase in the risk of oral clefts, respiratory anomalies, and urinary defects was observed, although CIs for specific malformations were wide. No pattern of malformation was identified.

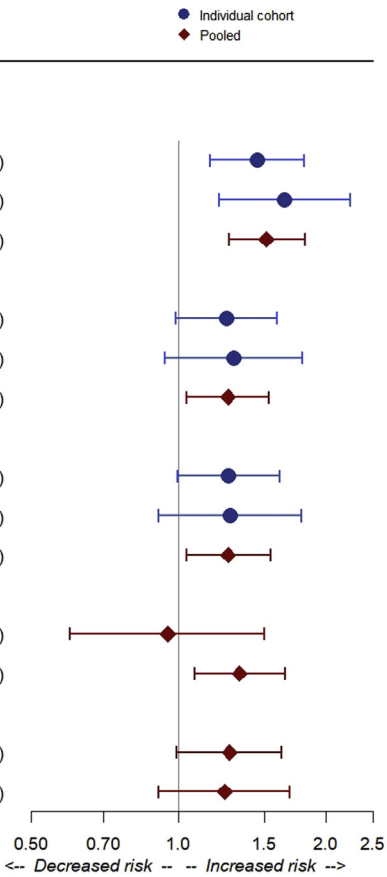
Context

Previous studies evaluating the safety of HCQ in pregnancy included between 36 and 194 women and overall suggested no increased risk of pregnancy loss, prematurity, intrauterine growth retardation, preeclampsia, fetal distress, or induction of delivery compared with the reference groups.[10,12,21–24] As flares are associated with these and other complications and HCQ is effective at controlling them, drug use in pregnancy may improve pregnancy outcomes for women with rheumatic disorders[23] and reduce the risk of congenital heart block in the neonate.[25] Moreover, HCQ use reduces the dose of prednisone needed during pregnancy.[12]

However, most of these studies were too small to assess the risk of major malformations, and many based their conclusion on the statistical significance of underpowered comparisons.[26] Given that HCQ crosses the placenta[21] and inhibits cell division and DNA synthesis[27] and that initial reports suggested an increased risk of chromosomal damage attributable to chloroquine,[28] concerns regarding effects on rapidly dividing embryonic cells remain. Specific malformations reported among exposed newborns included cleft lip and palate (1 of 79)[12] and pulmonary hypoplasia in a preterm infant (1 of 133).[21] Moreover, 2 of the largest studies found a meaningful, although not statistically significant, increased risk of malformations overall. In 1 study, malformations were more common in the 194 HCQ-exposed patients (6.7%) than in the reference (2.3%) group (adjusted RR, 3.11; 95% CI, 0.99–9.77), with no clear pattern.[13] In another study, the 114 HCQ-exposed patients had a prevalence of malformations of 7 of 97 (7.2%) and the reference group of 15 of 440 (3.4%) with a *P* value of .094,[22] again with no clear pattern.

FIGURE 1
Relative risks of any congenital malformation: main and dose-stratified analyses

Analysis for Malformations Overall	Hydroxychloroquine Events / Total N	Reference Events / Total N	Relative Risk 95% CI
Main analyses			
Unadjusted			
MarketScan	74 / 1,359	49,563 / 1,317,520	1.45 (1.16 to 1.81)
MAX	38 / 686	63,345 / 1,881,069	1.64 (1.21 to 2.24)
Pooled	112 / 2,045	112,908 / 3,198,589	1.51 (1.27 to 1.81)
Restricted to rheumatic disorders			
MarketScan	74 / 1,359	536 / 12,320	1.25 (0.99 to 1.59)
MAX	38 / 686	401 / 9,359	1.29 (0.94 to 1.79)
Pooled	112 / 2,045	937 / 21,679	1.26 (1.04 to 1.53)
Restricted to rheumatic disorders and PS matched*			
MarketScan			1.26 (0.99 to 1.61)
MAX			1.27 (0.91 to 1.79)
Pooled			1.26 (1.04 to 1.54)
Dose group analyses, pooled results*§			
Daily dose < 400 mg			0.95 (0.60 to 1.50)
Daily dose >= 400 mg			1.33 (1.08 to 1.65)
Exposure duration analyses, pooled results*§			
Duration <= 60 days			1.27 (0.99 to 1.62)
Duration > 60 days			1.24 (0.91 to 1.69)



The asterisk symbol indicates that for the variable ratio matching PS analysis after restriction to deliveries with rheumatic disorders, the number of outcome events and the total number of deliveries in both the HCQ-exposed group and group not exposed to HCQ are not meaningful for absolute risk estimation; therefore, those counts are left blank in the Figure. The section symbol indicates that data are restricted to rheumatic disorders and PS-matched estimate.

CI, confidence interval; *HCQ*, hydroxychloroquine; *MAX*, Medicaid Analytic eXtract; *PS*, propensity score.

Huybrechts et al. Hydroxychloroquine and birth defects. Am J Obstet Gynecol 2020.

Research implications

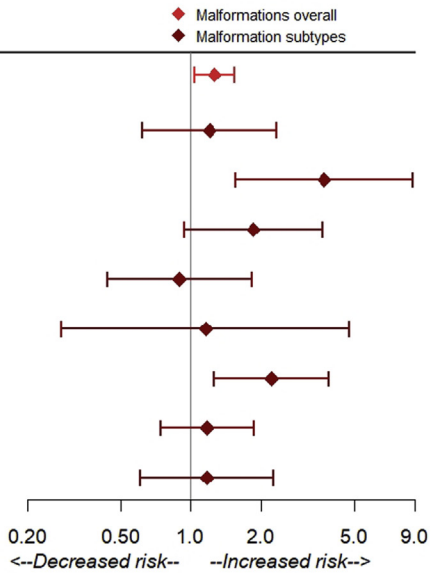
For pregnant women with malaria or rheumatic disorders, the benefits of HCQ may still outweigh the potential risk,[2] especially given that discontinuation of HCQ after conception would not necessarily prevent birth defects because the half-life is more than a month and would increase the risk of flares and their complications. Therefore, our findings of a potential small increase in the risk of malformations—although important for prescribers to be aware of—should not necessarily alter the treatment recommendation for a given woman with malaria or rheumatic disorders. For COVID-19, it will depend on whether the currently ongoing clinical trials demonstrate meaningful benefits of HCQ in reducing COVID-19 or its severity. Although initial trials using HCQ to treat COVID-19 have failed to demonstrate efficacy, trials regarding its use for preexposure prophylaxis have not yet been reported.

Strengths and limitations

In addition to several strengths (including a large and nationally representative population and a robust control for confounding through restriction and matching), our study is also subject to certain limitations, most of which would bias the results toward the null. First, we included only women with a live-born delivery because abortions and stillbirths are incompletely recorded in healthcare utilization data. This approach may have resulted in the exclusion of pregnancies with the outcome, as fetuses with malformations are more likely to experience fetal death or termination. Therefore, the incidence of major malformations reported in this study could underestimate the risk in pregnant women. If a higher proportion of women on HCQ had lethal malformations, more prenatal screening, or a higher propensity to terminate an affected pregnancy, this study would also underestimate the RR. However, differential terminations have been shown to

FIGURE 2
Pooled adjusted relative risks in the PS-matched, restricted cohorts

Malformation	Hydroxychloroquine Events / Total N*	Reference Events / Total N*	Pooled Relative Risk 95% CI
Malformations overall	112 / 2,045	937 / 21,679	1.26 (1.04 to 1.54)
Cardiac malformations	31 / 2,045	249 / 21,679	1.20 (0.62 to 2.32)
Oral clefts	<11 / 2,045	25 / 21,679	3.70 (1.55 to 8.82)
Respiratory malformations	<11 / 2,045	64 / 21,679	1.85 (0.94 to 3.64)
Gastrointestinal malformations	<11 / 2,045	118 / 21,679	0.89 (0.44 to 1.82)
Genital malformations	12 / 2,045	118 / 21,679	1.16 (0.28 to 4.76)
Urinary malformations	16 / 2,045	74 / 21,679	2.21 (1.26 to 3.86)
Musculoskeletal malformations	21 / 2,045	185 / 21,679	1.17 (0.74 to 1.86)
Limb defects	11 / 2,045	94 / 21,679	1.17 (0.61 to 2.26)



The asterisk symbol indicates that for the variable ratio matching PS analysis after restriction to deliveries with rheumatic disorders, the number of outcome events and the total number of deliveries in both the HCQ-exposed group and the group not exposed to HCQ are not meaningful for absolute risk estimation; therefore, counts after restriction to deliveries with rheumatic disorders but before the PS matching are reported in the Figure.

HCQ, hydroxychloroquine; *PS*, propensity score.

Huybrechts et al. Hydroxychloroquine and birth defects. Am J Obstet Gynecol 2020.

be an unlikely source of selection bias.[29] Second, the identification of major congenital malformations was based on the diagnosis and/or procedure codes recorded in claims. Misclassification would tend to bias RRs toward the null unless a higher proportion of malformation diagnoses were identified in women exposed to HCQ. Although others and we have shown a high positive predictive value for malformations,[13,18,30] the potential for some misclassification remains. Third, information on HCQ exposure is obtained from the claims of filled prescriptions. As some women may fill prescriptions for medications but not use them, our study may misclassify unexposed pregnancies into the HCQ group, thus underestimating any potential effect; however, a large fraction of our cohort filled prescriptions for HCQ throughout the first trimester of pregnancy. Fourth, it is possible that some women in the reference group were taking immunomodulatory agents in lieu of HCQ. If these agents were teratogenic, we would be underestimating the effect of HCQ. However, their use is negligible during pregnancy, and on restriction and PS matching, our exposed and reference groups were balanced in the use of these medications. Fifth, disease flares in women with rheumatic disorders, such as SLE, have been associated with poor pregnancy outcomes, and HCQ use during pregnancy improves disease activity and reduces the antiphospholipid syndrome.[12,23] Therefore, the reference group of women with the disease and without HCQ could have a higher risk, thus potentially underestimating the RR of flare-related adverse pregnancy outcomes, including fetal loss, fetal growth retardation, and prematurity. Alternatively, it is possible that there is a misclassification of the unexposed group with respect to the presence of underlying rheumatic disease or that women being treated with HCQ have more severe underlying disease than women without HCQ. Although neither rheumatic disorders nor flares have been associated with congenital malformations, it is conceivable that women with more severe disease receive higher doses of steroids and this may not be fully captured in our data. However, recent studies[31,32] have refuted initial reports of strong associations between steroids and oral clefts.[33] More directly, in this study, the absolute risk of malformations was the same among HCQ-exposed pregnancies with and without concomitant exposure to systemic steroids, and none of the cases of oral clefts in the HCQ-exposed pregnancies were exposed to steroids. Together, this suggests that steroid exposure is not a major threat to the validity of our analyses. Sixth, the MAX cohort included data through 2014—the most recent data available at the time of study conduct—and MarketScan included data through 2015, to avoid the use of International Classification of Diseases, 10th Revision–based algorithms for cohort creation and outcome identification that have not yet been validated. However, the biological association between HCQ

exposure and malformations should not change over time. Finally, despite being the largest exposed cohort to date, the numbers were small for specific malformation groups, and CIs were wide; specific individual defects could not be examined. However, there is enough information to suggest that the magnitude of a potential risk of malformations would not be in the order of that associated with major teratogens.

Conclusions

In this study, there was no evidence of a large increase in the prevalence of major congenital malformations in the newborn from first-trimester maternal exposure to HCQ. However, it is the third study to suggest a moderate increased risk. For most patients with autoimmune rheumatic disorders, the benefits of treatment during pregnancy will likely outweigh this risk. If proven effective for COVID-19 prophylaxis in ongoing randomized trials, the benefits of HCQ would need to be weighed against the potential risk in pregnancy.■

References

1. Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. Arthritis Care Res (Hoboken) 2020;72:461–88.
2. Flint J, Panchal S, Hurrell A, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford) 2016;55:1693–7.
3. Bermas BL, Kim SC, Huybrechts K, et al. Trends in use of hydroxychloroquine during pregnancy in systemic lupus erythematosus patients from 2001 to 2015. Lupus 2018;27:1012–7.
4. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med 2020;382:2411–8.
5. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA 2020;323:2493–502.
6. Boulware DR, Pullen MF, Bangdiwala AS, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. N Engl J Med 2020;383:517–25.
7. World Health Organization. Q&A: hydroxychloroquine and COVID-19. 2020. Available at: https://www.who.int/news-room/q-a-detail/q-a-hydroxychloroquine-and-covid-19. Accessed August 3, 2020.
8. Rome BN, Avorn J. Drug evaluation during the Covid-19 pandemic. N Engl J Med 2020;382:2282–4.
9. González R, García-Otero L, Pons-Duran C, et al. Hydroxychloroquine efficacy and safety in preventing SARS-CoV-2 infection and COVID-19 disease severity during pregnancy (COVID-Preg): a structured summary of a study protocol for a randomised placebo controlled trial. Trials 2020;21:607.
10. Buchanan NM, Toubi E, Khamashta MA, Lima F, Kerslake S, Hughes GR. Hydroxychloroquine and lupus pregnancy: review of a series of 36 cases. Ann Rheum Dis 1996;55:486–8.
11. Costedoat-Chalumeau N, Amoura Z, Duhaut P, et al. Safety of hydroxychloroquine in pregnant patients with connective tissue diseases: a study of one hundred thirty-three cases compared with a control group. Arthritis Rheum 2003;48:3207–11.
12. Clowse ME, Magder L, Witter F, Petri M. Hydroxychloroquine in lupus pregnancy. Arthritis Rheum 2006;54:3640–7.
13. Cooper WO, Cheetham TC, Li DK, et al. Brief report: risk of adverse fetal outcomes associated with immunosuppressive medications for chronic immune-mediated diseases in pregnancy. Arthritis Rheumatol 2014;66:444–50.
14. Palmsten K, Huybrechts KF, Mogun H, et al. Harnessing the Medicaid Analytic eXtract (MAX) to evaluate medications in pregnancy: design considerations. PLoS One 2013;8:e67405.
15. MacDonald SC, Cohen JM, Panchaud A, McElrath TF, Huybrechts KF, Hernández-Díaz S. Identifying pregnancies in insurance claims data: methods and application to retinoid teratogenic surveillance. Pharmacoepidemiol Drug Saf 2019;28:1211–21.
16. Margulis AV, Setoguchi S, Mittleman MA, Glynn RJ, Dormuth CR, Hernández-Díaz S. Algorithms to estimate the beginning of pregnancy in administrative databases. Pharmacoepidemiol Drug Saf 2013;22:16–24.
17. Patorno E, Huybrechts KF, Bateman BT, et al. Lithium use in pregnancy and the risk of cardiac malformations. N Engl J Med 2017;376:2245–54.
18. He M, Huybrechts KF, Dejene SZ, et al. Validation of algorithms to identify adverse perinatal outcomes in the Medicaid Analytic eXtract database. Pharmacoepidemiol Drug Saf 2020;29:419–26.
19. Friedman D, Duncanson LJ, Glickstein J, Buyon J. A review of congenital heart block. Images Paediatr Cardiol 2003;5:36–48.
20. Wasserstein RL, Lazar NA. The ASA statement on p-values: context, process, and purpose. Am Stat 2016;70:129–33.
21. Costedoat-Chalumeau N, Amoura Z, Aymard G, et al. Evidence of transplacental passage of hydroxychloroquine in humans. Arthritis Rheum 2002;46:1123–4.
22. Diav-Citrin O, Blyakhman S, Shechtman S, Ornoy A. Pregnancy outcome following in utero exposure to hydroxychloroquine: a prospective comparative observational study. Reprod Toxicol 2013;39:58–62.
23. Leroux M, Desveaux C, Parcevaux M, et al. Impact of hydroxychloroquine on preterm delivery and intrauterine growth restriction in pregnant women with systemic lupus erythematosus: a descriptive cohort study. Lupus 2015;24:1384–91.
24. Motta M, Tincani A, Faden D, et al. Follow-up of infants exposed to hydroxychloroquine given to mothers during pregnancy and lactation. J Perinatol 2005;25:86–9.
25. Izmirly PM, Costedoat-Chalumeau N, Pisoni CN, et al. Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro-antibody-associated cardiac manifestations of neonatal lupus. Circulation 2012;126:76–82.
26. Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. Nature 2019;567:305–7.
27. Gabourel JD. Effects of hydroxychloroquine on the growth of mammalian cells in vitro. J Pharmacol Exp Ther 1963;141:122–30.
28. Neill WA, Panayi GS, Duthie JJ, Prescott RJ. Action of chloroquine phosphate in rheumatoid arthritis. II. Chromosome damaging effect. Ann Rheum Dis 1973;32:547–50.
29. Heinke D, Rich-Edwards JW, Williams PL, et al. Quantification of selection bias in studies of risk factors for birth defects among livebirths. Paediatr Perinat Epidemiol 2020 [Epub ahead of print].
30. Palmsten K, Huybrechts KF, Kowal MK, Mogun H, Hernández-Díaz S. Validity of maternal and infant outcomes within nationwide Medicaid data. Pharmacoepidemiol Drug Saf 2014;23:646–55.
31. Hviid A, Mølgaard-Nielsen D. Corticosteroid use during pregnancy and risk of orofacial clefts. CMAJ 2011;183:796–804.
32. Bay Bjørn AM, Ehrenstein V, Hundborg HH, Nohr EA, Sørensen HT, Nørgaard M. Use of corticosteroids in early pregnancy is not associated with risk of oral clefts and other congenital malformations in offspring. Am J Ther 2014;21:73–80.
33. Carmichael SL, Shaw GM. Maternal corticosteroid use and risk of selected congenital anomalies. Am J Med Genet 1999;86:242–4.

Author and article information

From the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine (Drs Huybrechts, Bateman, Zhu, and Straub, Ms Mogun, and Drs Kim and Desai), Department of Anesthesiology, Perioperative and Pain Medicine (Dr Bateman), and Division of Rheumatology, Inflammation, and Immunity (Dr Kim), Brigham and Women's Hospital and Harvard Medical School, Boston, MA; and the Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA (Drs Huybrechts and Hernandez-Diaz).

Received June 26, 2020; revised Sept. 1, 2020; accepted Sept. 9, 2020.

K.F.H. reports being an investigator on grants to Brigham and Women's Hospital from Eli Lilly and Company and GlaxoSmithKline for unrelated studies. B.T.B. reports being an investigator on grants to Brigham and Women's Hospital from Eli Lilly and Company, Baxalta, GlaxoSmithKline, and Pacira Pharmaceutical Inc for unrelated studies; received personal fees from Aetion Inc and from the Alosa Foundation outside the submitted work; and served on an expert panel for a postpartum hemorrhage quality improvement project that was conducted by the Association of Women's Health, Obstetric, and Neonatal Nurses and funded by a grant from Merck for Mothers. S.C.K. reports being an investigator on grants to Brigham and Women's Hospital from Pfizer, Bristol-Myers Squibb, AbbVie Inc, and Roche Holding AG for unrelated studies. R.J.D. reports being an investigator on grants to Brigham and Women's Hospital from Bayer, Vertex, and Novartis for unrelated studies. S.H.-D. reports being an investigator on grants to her institution from Eli Lilly and Company and GlaxoSmithKline for unrelated studies; receiving personal fees from UCB outside the submitted work; and having served as an epidemiologist with the North American Antiepileptic Drug Pregnancy Registry, which is funded by multiple companies. The remaining authors report no conflict of interest.

The study was supported by internal funds of the Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School. K.F.H., B.T.B., and S.H.-D. are supported by the National Institute of Mental Health (R01 MH116194), the National Institute on Drug Abuse (R01 DA044293 and R01 DA049822), and the National Institute of Child Health and Human Development (R01 HD097778).

Corresponding author: Krista F. Huybrechts, MS, PhD. khuybrechts@bwh.harvard.edu

SUPPLEMENTAL TABLE 1
Summary of studies with information on HCQ and the risk of congenital malformations

Author	Number of patients exposed to HCQ	Number of controls not exposed to HCQ	Outcome	Risk estimates	Comments
Levy et al, 1991[1]	24 exposed pregnant women (27 pregnancies) Chloroquine=16 HCQ=8	No control	Congenital malformations	No congenital malformations were detected in 14 live births	Extremely limited sample to evaluate malformations. No control group
Buchanan et al, 1996[2]	36 pregnancies	53 unexposed pregnancies with systemic lupus erythematosus	Congenital malformations	No congenital malformations were detected in the HCQ-exposed group (1 Down syndrome); 1 case in control group (1 extra finger)	Extremely limited sample to estimate the RR of malformations
Parke et al, 1996[3]	9 pregnancies	No control	Congenital malformations	No congenital malformations were detected in 9 live births	Extremely limited sample to evaluate malformations. No control group
Levy et al, 2001[4]	10 pregnancies	10 in the placebo group	Congenital malformations	No congenital malformations were detected in 19 live births	Extremely limited sample to evaluate malformations despite being a randomized controlled study
Costedoat-Chalumeau et al, 2003[5]	133 pregnancies	70 unexposed with similar disorders	Congenital malformations	3 malformations were observed in the HCQ group (1 hypospadias, 1 craniostenosis, and 1 cardiac malformation, and 1 pulmonary hypoplasia in a preterm birth) vs 4 in the group not exposed to HCQ (1 hypospadias, 1 aplasia cutis of the scalp, 1 ulnar, and 1 severe cardiac malformation)	Modest sample to estimate the risk of malformations. Controlled study. Daily dose of 400—200 mg
Motta et al, 2005[6]	40 pregnancies	No control	Congenital malformations	No congenital malformations were detected in 39 live births	Extremely limited sample to evaluate malformations. No control group
Clowse et al, 2006[7]	56 pregnancies with continuous use of HCQ during pregnancy	163 unexposed, with lupus	Congenital malformations	Miscarriage risk was 13% in the HCQ-exposed group and 4% in the group not exposed to HCQ and stillbirth 8% and 6%, respectively. Among the 47 live-born infants exposed to HCQ, 1 had cleft lip and palate. In the 145 not exposed to HCQ, 3 fetuses had fatal congenital anomalies and 1 had an abdominal hernia	Limited sample to estimate the RR of malformations. Controlled study
Viktil et al, 2012[8]	58 pregnancies exposed between 3 months before delivery to delivery (34, first trimester of pregnancy)	Population reference	Congenital malformations and major congenital malformations	Exposed to HCQ, 4 of 58 (6.9%) Overall cohort, 5000 of 154,976 (3.2%)	Limited sample to evaluate the risk of malformations. Reference group does not consider indication or other confounders

Huybrechts et al. Hydroxychloroquine and birth defects. Am J Obstet Gynecol 2020.

(continued)

SUPPLEMENTAL TABLE 1
Summary of studies with information on HCQ and the risk of congenital malformations *(continued)*

Author	Number of patients exposed to HCQ	Number of controls not exposed to HCQ	Outcome	Risk estimates	Comments
Diav-Citrin et al, 2013[9]	114 pregnancies	455 unexposed	Congenital malformations	7 of 97 in exposed (7.2%) vs 15 of 440 (3.4%) in unexposed (malformations in the exposed: 1 spina bifida, 2 developmental dysplasia of the hip, 1 ventricular septal defect, 1 congenital hypothyroidism, 1 inguinal hernia, 1 congenital toxoplasmosis)	Modest sample to evaluate the RR of malformations; no control for indication. Daily dose of 200 to 400 mg
Cooper et al, 2014[10]	194 pregnancies exposed during the first trimester	171 women with similar indications treated before but not during, pregnancy	Congenital malformations; counts provided for specific malformations	RR, 3.11 (0.99–9.77). Malformations were more common in HCQ-exposed group (6.7%) than in the reference (2.3%) or other immunosuppressive medication (3%) group. Most common were genitourinary and cardiac but no clear pattern	Controlled study that adjusted for confounding (sociodemographic variables, chronic health diagnoses, medications used to treat chronic diseases, chronic immune-mediated diseases, geographic factors, and calendar year of pregnancy). Limited power to estimate the risk of specific congenital malformations
Gayed et al, 2014[11]	149 pregnancies during pregnancy or breastfeeding	139 unexposed with systemic lupus erythematosus	Congenital malformations	Exposed, 3 of 143 (2.1%) Unexposed 3 of 134 (2.2%)	Modest sample to estimate the RR of malformations; no control for confounding other than indication. Exposure outside relevant period possible. Only abstract, no peer review
Koh et al, 2015[12]	33 pregnancies exposed during pregnancy	No control group designed for risk estimates of congenital malformation	Goal not to assess congenital malformations, noted as remarks. Goal not to study treatments	No congenital malformations were detected in 33 HCQ-exposed pregnancies	Extremely limited sample to observe any malformation cases. No control group for malformations

HCQ, hydroxychloroquine; *RR*, relation risk.

Huybrechts et al. Hydroxychloroquine and birth defects. Am J Obstet Gynecol 2020.

SUPPLEMENTAL TABLE 2
Definition of congenital malformations

Malformation group	Malformation subgroup	ICD-9 diagnosis code
Cardiovascular anomalies[a]	Conotruncal defects	745.0x, 745.1x, 745.2x
	Single ventricle	745.3x
	Ventricular septal defect	745.4x
	Secundum atrial septal defect or patent foramen ovale	745.5x and no preterm
	Atrioventricular septal defect	745.6x
	Right-sided defects	746.00, 746.01, 746.09, 746.1x, 746.2x, 746.83, 747.3x and no preterm, 746.02 and no preterm
	Left-sided defects	747.1x, 747.2x, 746.3x, 746.5x, 746.7x, 746.81, 746.82, 746.84
	Patent ductus arteriosus	747.0x and no preterm
	Persistent pulmonary hypertension of the newborn	416.0x or 747.83 and no preterm
	Anomalous pulmonary venous return	747.4x
	Other cardiac malformation	745.7x,745.8x, 746.8 (exclude if only 746.86), 746.85–746.87, 746.89
	Cardiac malformation not otherwise specified	745, 745.9, 746, 746.9x (exclude if only 746.99), 747
Central nervous system	Overall	740.xx–742.xx
	Microcephaly	742.1x
	Hydrocephaly	742.3x
	Reduction deformities of the brain	742.2x
	Neural tube defects	741.xx, 756.17, 740.0x, 740.2x, 742.0x
Clubfoot		754.50, 754.51, 754.59, 754.60, 754.62, 754.69, 754.70, 754.71, 754.79
Gastroschisis		756.73 if coded after October 2009
		756.79 and ICD-9 procedure 54.71 if coded before October 2009
Oral cleft[a]	Cleft palate	749.0x
	Cleft lip	749.1x
	Cleft palate with cleft lip	749.2x
Eye anomalies		743.xx (exclude if only 743.6x and 743.8x)
Ear anomalies		744.xx (exclude if only 744.1x, 744.21, 744.29, and 744.4x–744.9x)

Huybrechts et al. Hydroxychloroquine and birth defects. Am J Obstet Gynecol 2020. *(continued)*

SUPPLEMENTAL TABLE 2
Definition of congenital malformations *(continued)*

Malformation group	Malformation subgroup	ICD-9 diagnosis code
Other vascular (noncardiac) anomalies		747.6x–747.9x (exclude if only 747.83)
Respiratory anomalies[a]		748.xx (exclude if only 748.1x)
Gastrointestinal anomalies[a]		750.xx–751.xx (exclude if only 750.0x, 750.1x, 750.50, 751.0x)
Genital anomalies[a]		752.xx (exclude if only 752.42, 752.52) (in addition, exclude 752.5x if preterm)
Urinary anomalies		753.xx (exclude if only 753.7x)
Musculoskeletal anomalies[a]		754.xx and 756.xx (exclude if only 754.3x, 754.81, 754.82, 756.2x)
Limb defects[a]		755.xx (exclude if only 755.65)
Other anomalies		757.xx; 759.xx (exclude if only 757.2–757.6, 759.81–759.83)

In- and outpatient claims in the infant record between DoB and DoB + 90 days and/or in the maternal record between delivery and delivery + 30 days are considered.

Subgroups of cardiovascular malformations:

- Greater than or equal to 2 dates with a code for a malformation within the group
  - Exception: codes 747.3x, 746.02, 745.5x, and 747.0x require ≥2 dates with a code for a malformation of which at least 1 code is documented at ≥6 weeks after DoB.
- Greater than or equal to 1 date with a code for a malformation within the subgroup and cardiac procedure.
  - Exception: code 746.02
- Greater than or equal to 1 date with a code for a malformation within the subgroup and infant died.
- If codes identified in the maternal record between LMP and LMP + 105 days and there are no codes in the infant record between DoB and DoB + 90 days (ie, only maternal codes between delivery and delivery + 30 days), the defect is considered a preexisting maternal defect.

Cardiovascular malformations overall:

- Any of the subgroups of cardiovascular anomalies is present.
- Greater than or equal to 2 dates with a code for any of the cardiac malformations (regardless of the subgroup[b]).
- Greater than or equal to 1 date with a code for any of the cardiac malformations[b] and cardiac procedure.
- Greater than or equal to 1 date with a code for any of the cardiac malformations[b] and infant died.
- If codes identified in the maternal record between LMP and LMP + 105 days and there are no codes in the infant record between DoB and DoB + 90 days (ie, only maternal codes between delivery and delivery + 30 days), the defect is considered a preexisting maternal defect.

Specific noncardiovascular malformations:

- Greater than or equal to 2 dates with a code for the malformation group or subgroup
  - Exception: for gastroschisis: if code 756.79 was used (before October 2009), requires ≥1 date with a code and ICD-9 procedure 54.71.
- Greater than or equal to 1 date with a code for the malformation group or subgroup and malformation-specific procedure.
- Greater than or equal to 1 date with a code for the malformation group of subgroup and infant died.
- If codes identified in the maternal record between LMP and LMP + 105 days and there are no codes in the infant record between DoB and DoB + 90 days (ie, only maternal codes between delivery and delivery + 30 days), the defect is considered a preexisting maternal defect.

Any congenital malformation:

- Any of the malformation groups or subgroups mentioned above is present.

DoB, date of birth; *ICD-9*, International Classification of Diseases, Ninth Revision; *LMP*, last menstrual period.

[a] Specific malformation types that are considered individually; [b] The following codes are not considered: 745.4x, 745.5x, 747.0x, 746.4x, 746.6x, 746.99, 747.3x if preterm, 746.02 if preterm, 747.5x, 416.0x if preterm, 747.83 if preterm, 746.08, 746.105.

Huybrechts et al. Hydroxychloroquine and birth defects. Am J Obstet Gynecol 2020.

SUPPLEMENTAL TABLE 3

Patient characteristics for HCQ-exposed pregnancies and pregnancies not exposed to HCQ: MarketScan cohort (2003–2005)

	Original source cohort					Restricted matched cohort[a]				
Variable	HCQ exposed		Unexposed		Standardized difference	HCQ exposed		Unexposed		Standardized difference
Total	1359		1,317,520		—	1261		11,179		—
Age, mean (SD)	33.0	(4.4)	31.9	(4.6)	0.234	(33.1)	4.4	(33.1)	4.6	−0.016
Region, n (%)										
Northeast	203	(14.9)	207,517	(15.8)	−0.023	199	(15.8)	1754	(15.7)	0.003
Midwest	298	(21.9)	338,554	(25.7)	−0.089	278	(22.1)	2548	(22.8)	−0.018
South	608	(44.7)	520,269	(39.5)	0.106	553	(43.9)	4796	(42.9)	0.019
West	232	(17.1)	235,923	(17.9)	−0.022	215	(17.1)	1949	(17.4)	−0.010
Unknown	18	(1.3)	15,257	(1.2)	0.015	16	(1.3)	132	(1.2)	0.008
Autoimmune rheumatic disorders[b], n (%)										
Systemic lupus erythematosus	759	(55.9)	2188	(0.2)	1.581	675	(53.5)	6065	(54.3)	−0.015
Rheumatoid arthritis	408	(30.0)	3028	(0.2)	0.914	392	(31.1)	3515	(31.4)	−0.008
Ankylosing spondylitis	14	(1.0)	4654	(0.4)	0.082	14	(1.1)	168	(1.5)	−0.035
Psoriatic arthritis	15	(1.1)	404	(0.0)	0.143	15	(1.2)	127	(1.1)	0.005
Sicca syndrome	134	(9.9)	647	(0.0)	0.464	122	(9.7)	1113	(10.0)	−0.009
Dermatomyositis	17	(1.3)	60	(0.0)	0.158	13	(1.0)	112	(1.0)	0.003
Other diffuse connective tissue disease	221	(16.3)	1000	(0.1)	0.619	197	(15.6)	1774	(15.9)	−0.007
Other autoimmune disease	68	(5.0)	1295	(0.1)	0.315	67	(5.3)	567	(5.1)	0.011
Sarcoidosis	6	(0.4)	275	(0.0)	0.087	6	(0.5)	50	(0.5)	0.004
Other maternal conditions[c], n (%)										
Attention deficit hyperactivity disorder	13	(1.0)	6198	(0.5)	0.058	12	(1.0)	109	(1.0)	−0.002
Adjustment disorder	4	(0.3)	3291	(0.3)	0.009	4	(0.3)	27	(0.3)	0.014
Alcohol abuse or dependence	2	(0.2)	1125	(0.1)	0.018	1	(0.1)	15	(0.1)	−0.016
Anxiety	63	(4.6)	40,106	(3.0)	0.083	58	(4.6)	510	(4.6)	0.002
Bipolar disorder	5	(0.4)	4030	(0.3)	0.011	4	(0.3)	41	(0.4)	−0.008
Delirium	1	(0.1)	638	(0.1)	0.010	1	(0.1)	10	(0.1)	−0.003
Depression	76	(5.6)	51,324	(3.9)	0.080	72	(5.7)	645	(5.8)	−0.003
Drug abuse or dependence	6	(0.4)	1850	(0.1)	0.056	6	(0.5)	46	(0.4)	0.010

Huybrechts et al. Hydroxychloroquine and birth defects. Am J Obstet Gynecol 2020.

(continued)

SUPPLEMENTAL TABLE 3

Patient characteristics for HCQ-exposed pregnancies and pregnancies not exposed to HCQ: MarketScan cohort (2003–2005) *(continued)*

Variable	Original source cohort					Restricted matched cohort[a]				
	HCQ exposed		Unexposed		Standardized difference	HCQ exposed		Unexposed		Standardized difference
Other psychiatric disorders	4	(0.3)	4017	(0.3)	−0.002	4	(0.3)	40	(0.4)	−0.008
Personality disorder	1	(0.1)	469	(0.0)	0.016	1	(0.1)	6	(0.1)	0.011
Psychosis	0	(0.0)	436	(0.0)	−0.026	0	(0.0)	0	(0.0)	—
Schizophrenia	2	(0.2)	126	(0.0)	0.049	1	(0.1)	5	(0.0)	0.015
Sleep disorder	35	(2.6)	11,100	(0.8)	0.134	29	(2.3)	290	(2.6)	−0.019
Tobacco use	10	(0.7)	9354	(0.7)	0.003	10	(0.8)	86	(0.8)	0.003
Anemia	93	(6.8)	25,507	(1.9)	0.241	84	(6.7)	730	(6.5)	0.005
Asthma	51	(3.8)	26,538	(2.0)	0.104	47	(3.7)	427	(3.8)	−0.005
Chronic obstructive pulmonary disease	13	(1.0)	8896	(0.7)	0.031	11	(0.9)	116	(1.0)	−0.017
Chronic fatigue syndrome	137	(10.1)	53,082	(4.0)	0.238	129	(10.2)	1187	(10.6)	−0.013
Diabetes	34	(2.5)	23,650	(1.8)	0.049	34	(2.7)	293	(2.6)	0.005
Obesity or overweight	38	(2.8)	22,882	(1.7)	0.071	34	(2.7)	319	(2.9)	−0.009
Epilepsy or convulsions	14	(1.0)	4025	(0.3)	0.089	14	(1.1)	124	(1.1)	0.000
Fibromyalgia	100	(7.4)	18,641	(1.4)	0.293	93	(7.4)	813	(7.3)	0.004
Hypertension	93	(6.8)	30,937	(2.4)	0.216	85	(6.7)	797	(7.1)	−0.015
Inflammatory myopathy	1	(0.1)	102	(0.0)	0.033	1	(0.1)	7	(0.1)	0.005
Inflammatory bowel disease	20	(1.5)	14,652	(1.1)	0.032	20	(1.6)	170	(1.5)	0.005
Irritable bowel syndrome	16	(1.2)	5366	(0.4)	0.087	14	(1.1)	129	(1.2)	−0.004
Migraine or headache	96	(7.1)	54,436	(4.1)	0.128	91	(7.2)	793	(7.1)	0.005
Nausea and vomiting	45	(3.3)	37,352	(2.8)	0.028	40	(3.2)	372	(3.3)	−0.009
Neuropathic pain	68	(5.0)	27,054	(2.1)	0.160	66	(5.2)	577	(5.2)	0.003
Nonneuropathic pain	450	(33.1)	135,075	(10.3)	0.577	421	(33.4)	3773	(33.8)	−0.008
Other pain	13	(1.0)	4290	(0.3)	0.079	12	(1.0)	108	(1.0)	−0.001
Infections	43	(3.2)	17,924	(1.4)	0.121	38	(3.0)	318	(2.8)	0.010
Renal disease	58	(4.3)	3379	(0.3)	0.272	45	(3.6)	396	(3.5)	0.001

Huybrechts et al. Hydroxychloroquine and birth defects. Am J Obstet Gynecol 2020.

(continued)

SUPPLEMENTAL TABLE 3

Patient characteristics for HCQ-exposed pregnancies and pregnancies not exposed to HCQ: MarketScan cohort (2003–2005) *(continued)*

Variable	Original source cohort					Restricted matched cohort[a]				
	HCQ exposed		Unexposed		Standardized difference	HCQ exposed		Unexposed		Standardized difference
Concomitant medications[c], n (%)										
Systemic steroids	565	(41.6)	70,421	(5.3)	0.945	485	(38.5)	4262	(38.1)	0.007
Biologic DMARDs	64	(4.7)	1303	(0.1)	0.304	64	(5.1)	575	(5.2)	−0.003
Nonbiologic DMARDs	150	(11.0)	7535	(0.6)	0.459	117	(9.3)	1021	(9.1)	0.005
Anticonvulsants	63	(4.6)	14,365	(1.1)	0.214	58	(4.6)	501	(4.5)	0.006
Antidepressants	220	(16.2)	99,633	(7.6)	0.269	187	(14.8)	1724	(15.4)	−0.017
Antipsychotics	11	(0.8)	2986	(0.2)	0.081	8	(0.6)	67	(0.6)	0.004
Anxiolytics	3	(0.2)	2917	(0.2)	0.000	3	(0.2)	30	(0.3)	−0.006
Barbiturates	40	(2.9)	14,607	(1.1)	0.130	34	(2.7)	317	(2.8)	−0.008
Benzodiazepines	116	(8.5)	49,574	(3.8)	0.200	107	(8.5)	940	(8.4)	0.003
Other hypnotics	85	(6.3)	23,721	(1.8)	0.228	70	(5.6)	631	(5.6)	−0.004
Stimulants	21	(1.6)	10,212	(0.8)	0.072	18	(1.4)	182	(1.6)	−0.017
Opioids	296	(21.8)	153,634	(11.7)	0.274	272	(21.6)	2402	(21.5)	0.002
Naloxone	2	(0.2)	575	(0.0)	0.034	2	(0.2)	19	(0.2)	−0.002
Naltrexone	0	(0.0)	97	(0.0)	−0.012	0	(0.0)	0	(0.0)	—
Buprenorphine	2	(0.2)	623	(0.1)	0.032	2	(0.2)	19	(0.2)	−0.002
Methadone	6	(0.4)	2902	(0.2)	0.039	6	(0.5)	46	(0.4)	0.010
Acetaminophen	45	(3.3)	16,027	(1.2)	0.141	38	(3.0)	352	(3.2)	−0.008
NSAIDs	255	(18.8)	65,980	(5.0)	0.435	235	(18.6)	2073	(18.5)	0.002
Antidiabetics	58	(4.3)	32,993	(2.5)	0.098	55	(4.4)	436	(3.9)	0.023
Antihypertensives	147	(10.8)	40,106	(3.0)	0.310	127	(10.1)	1074	(9.6)	0.016
Chloroquine	1	(0.1)	243	(0.0)	0.026	1	(0.1)	6	(0.1)	0.010
Insulin	54	(4.0)	13,102	(1.0)	0.192	51	(4.0)	407	(3.6)	0.021
Triptans	38	(2.8)	17,138	(1.3)	0.106	37	(2.9)	302	(2.7)	0.014
Suspected teratogens[d]	219	(16.1)	100,774	(7.7)	0.264	199	(15.8)	1785	(16.0)	−0.005

Huybrechts et al. Hydroxychloroquine and birth defects. Am J Obstet Gynecol 2020.

(continued)

SUPPLEMENTAL TABLE 3

Patient characteristics for HCQ-exposed pregnancies and pregnancies not exposed to HCQ: MarketScan cohort (2003–2005) *(continued)*

Variable	Original source cohort					Restricted matched cohort[a]				
	HCQ exposed		Unexposed		Standardized difference	HCQ exposed		Unexposed		Standardized difference
Markers of burden of illness[e]										
Maternal comorbidity index, mean (SD)	3.0	(2.4)	1.2	(1.5)	0.902	2.9	(2.3)	3.0	(2.4)	−0.018
Number of distinct diagnoses, mean (SD)	4.7	(3.9)	2.1	(2.6)	0.776	4.7	(3.9)	4.8	(4.0)	−0.042
Number of non-HCQ prescription drugs, mean (SD)	3.4	(3.1)	1.5	(2.2)	0.707	3.3	(3.1)	3.6	(3.5)	−0.073
Number of outpatient visits, mean (SD)	4.1	(4.4)	2.1	(3.2)	0.536	4.1	(4.4)	4.4	(4.4)	−0.055
Number emergency department visits, mean (SD)	0.1	(0.4)	0.1	(0.3)	0.107	0.1	(0.4)	0.1	(0.4)	−0.002
Hospitalization, n (%)	19	(1.4)	9100	(0.7)	0.070	17	(1.4)	164	(1.5)	−0.010
Number of hospitalizations, mean (SD)	0.0	(0.1)	0.0	(0.1)	0.069	0.0	(0.1)	0.0	(0.1)	−0.014
Number of d hospitalized, mean (SD)	0.1	(0.5)	0.0	(0.4)	0.058	0.0	(0.4)	0.1	(0.7)	−0.040

DMARD, disease-modifying antirheumatic drug; *HCQ*, hydroxychloroquine; *NSAID*, nonsteroidal antiinflammatory drug; *SD*, standard deviation.

[a] Given the variable ratio matching, the counts for the unexposed group are weighted counts to demonstrate the balance in baseline covariates; [b] Autoimmune rheumatic disorders were measured from 3 months before the start to the end of pregnancy; [c] Maternal conditions and concomitant medication use were measured from 3 months before the start of pregnancy to the end of the first trimester; [d] Women exposed to known teratogens have been excluded (ie, warfarin, antineoplastic agents, lithium, isotretinoin, misoprostol, thalidomide). Suspected teratogens considered include danazol, methimazole, propylthiouracil, aminoglycosides, trimethoprim, triamterene, sulfasalazine, spasmofen, cholestyramine, potassium iodide, tetracycline, and fluconazole; [e] General markers of the burden of illness were measured during the 3 months before but not during pregnancy, as these measures may be affected by early detection of pregnancy complications

Huybrechts et al. Hydroxychloroquine and birth defects. Am J Obstet Gynecol 2020.

SUPPLEMENTAL TABLE 4

Patient characteristics for HCQ-exposed and pregnancies not exposed to HCQ: MAX cohort (2000–2014)

	Original source cohort					Restricted matched cohort[a]				
Variable	HCQ exposed		Unexposed		Standardized difference	HCQ exposed		Unexposed		Standardized difference
Total	686		1,881,069			606		7901		
Age, mean (SD)	27.8	(6.0)	24.5	(5.9)	0.568	27.9	(6.0)	28.3	(5.9)	−0.068
Race, n (%)										
White	219	(31.9)	763,706	(40.6)	−0.181	209	(34.5)	2861	(36.2)	−0.036
Black or African American	236	(34.4)	609,802	(32.4)	0.042	204	(33.7)	2599	(32.9)	0.016
Hispanic or Latino	109	(15.9)	271,736	(14.5)	0.040	97	(16.0)	1183	(15.0)	0.029
Other or unknown	122	(17.8)	235,825	(12.5)	0.147	96	(15.8)	1258	(15.9)	−0.002
Region, n (%)										
Northeast	171	(24.9)	330,760	(17.6)	0.180	146	(24.1)	1953	(24.7)	−0.014
Midwest	200	(29.2)	592,663	(31.5)	−0.051	180	(29.7)	2395	(30.3)	−0.013
South	164	(23.9)	535,503	(28.5)	−0.104	147	(24.3)	1926	(24.4)	−0.003
West	151	(22.0)	422,143	(22.4)	−0.010	133	(22.0)	1628	(20.6)	0.033
Autoimmune rheumatic disorders[b], n (%)										
Systemic lupus erythematosus	487	(71.0)	2707	(0.1)	2.200	409	(67.5)	5184	(65.6)	0.040
Rheumatoid arthritis	190	(27.7)	3056	(0.2)	0.867	182	(30.0)	2125	(26.9)	0.070
Ankylosing spondylitis	<11	(0.7)	2588	(0.1)	0.090	<11	(0.8)	246	(3.1)	−0.165
Psoriatic arthritis	<11	(0.2)	206	(0.0)	0.049	<11	(0.2)	42	(0.5)	−0.063
Sicca syndrome	60	(8.8)	183	(0.0)	0.437	42	(6.9)	625	(7.9)	−0.038
Dermatomyositis	<11	(1.2)	68	(0.0)	0.153	<11	(1.3)	90	(1.1)	0.016
Other diffuse connective tissue disease	91	(13.3)	423	(0.0)	0.552	73	(12.1)	1075	(13.6)	−0.047
Other autoimmune disease	<11	(1.5)	402	(0.0)	0.168	<11	(1.7)	148	(1.9)	−0.017
Sarcoidosis	<11	(1.3)	455	(0.0)	0.158	<11	(1.5)	121	(1.5)	−0.004

Huybrechts et al. Hydroxychloroquine and birth defects. Am J Obstet Gynecol 2020.

(continued)

SUPPLEMENTAL TABLE 4

Patient characteristics for HCQ-exposed and pregnancies not exposed to HCQ: MAX cohort (2000–2014) *(continued)*

Variable	Original source cohort					Restricted matched cohort[a]				
	HCQ exposed		Unexposed		Standardized difference	HCQ exposed		Unexposed		Standardized difference
Other maternal conditions[c], n (%)										
Attention deficit hyperactivity disorder	<11	(0.9)	19,977	(1.1)	−0.019	<11	(0.7)	60	(0.8)	−0.012
Adjustment disorder	<11	(0.7)	10,427	(0.6)	0.022	<11	(0.7)	53	(0.7)	−0.001
Alcohol abuse or dependence	<11	(0.7)	13,958	(0.7)	−0.002	<11	(0.7)	73	(0.9)	−0.029
Anxiety	40	(5.8)	76,887	(4.1)	0.080	38	(6.3)	500	(6.3)	−0.002
Bipolar disorder	11	(1.6)	25,851	(1.4)	0.019	11	(1.8)	172	(2.2)	−0.026
Delirium	<11	(0.7)	1701	(0.1)	0.100	<11	(0.7)	33	(0.4)	0.034
Depression	75	(10.9)	120,954	(6.4)	0.160	66	(10.9)	873	(11.1)	−0.005
Drug abuse or dependence	24	(3.5)	37,945	(2.0)	0.091	21	(3.5)	291	(3.7)	−0.012
Other psychiatric disorders	14	(2.0)	22,868	(1.2)	0.065	<11	(1.7)	104	(1.3)	0.027
Personality disorder	<11	(0.2)	4345	(0.2)	−0.020	<11	(0.2)	17	(0.2)	−0.011
Psychosis	<11	(0.4)	4149	(0.2)	0.038	<11	(0.3)	38	(0.5)	−0.024
Schizophrenia	<11	(0.3)	3133	(0.2)	0.026	<11	(0.3)	32	(0.4)	−0.012
Sleep disorder	18	(2.6)	14,869	(0.8)	0.142	18	(3.0)	211	(2.7)	0.018
Tobacco use	29	(4.2)	77,232	(4.1)	0.006	27	(4.5)	377	(4.8)	−0.015
Anemia	79	(11.5)	63,162	(3.4)	0.315	71	(11.7)	936	(11.9)	−0.004
Asthma	38	(5.5)	79,108	(4.2)	0.062	34	(5.6)	494	(6.3)	−0.027
Chronic obstructive pulmonary disease	15	(2.2)	35,194	(1.9)	0.022	13	(2.2)	194	(2.5)	−0.021
Chronic fatigue syndrome	63	(9.2)	60,757	(3.2)	0.249	57	(9.4)	764	(9.7)	−0.009
Diabetes	33	(4.8)	41,403	(2.2)	0.142	30	(5.0)	391	(4.9)	0.000
Obesity or overweight	33	(4.8)	48,447	(2.6)	0.119	31	(5.1)	408	(5.2)	−0.002
Epilepsy or convulsions	19	(2.8)	13,534	(0.7)	0.157	15	(2.5)	179	(2.3)	0.014
Fibromyalgia	73	(10.6)	19,343	(1.0)	0.419	62	(10.2)	906	(11.5)	−0.040
Hypertension	74	(10.8)	47,746	(2.5)	0.335	65	(10.7)	829	(10.5)	0.007
Inflammatory myopathy	<11	(0.6)	91	(0.0)	0.107	<11	(0.5)	36	(0.5)	0.006
Inflammatory bowel disease	20	(2.9)	39,963	(2.1)	0.050	19	(3.1)	293	(3.7)	−0.032
Irritable bowel syndrome	<11	(0.9)	4722	(0.3)	0.083	<11	(0.8)	76	(1.0)	−0.015
Migraine or headache	98	(14.3)	141,233	(7.5)	0.219	86	(14.2)	1160	(14.7)	−0.014

Huybrechts et al. Hydroxychloroquine and birth defects. Am J Obstet Gynecol 2020.

(continued)

SUPPLEMENTAL TABLE 4

Patient characteristics for HCQ-exposed and pregnancies not exposed to HCQ: MAX cohort (2000–2014) *(continued)*

Variable	Original source cohort					Restricted matched cohort[a]				
	HCQ exposed		Unexposed		Standardized difference	HCQ exposed		Unexposed		Standardized difference
Nausea and vomiting	55	(8.0)	133,447	(7.1)	0.035	50	(8.3)	694	(8.8)	−0.019
Neuropathic pain	27	(3.9)	27,145	(1.4)	0.154	24	(4.0)	351	(4.5)	−0.024
Nonneuropathic pain	316	(46.1)	253,994	(13.5)	0.762	279	(46.0)	3689	(46.7)	−0.013
Other pain	25	(3.6)	18,050	(1.0)	0.180	21	(3.5)	341	(4.3)	−0.044
Infections	59	(8.6)	72,412	(3.9)	0.198	52	(8.6)	638	(8.1)	0.018
Renal disease	50	(7.3)	6578	(0.4)	0.368	35	(5.8)	433	(5.5)	0.013
Concomitant medications[c], n (%)										
Systemic steroids	383	(55.8)	69,446	(3.7)	1.387	309	(51.0)	4179	(52.9)	−0.038
Biologic DMARDs, n (%)	16	(2.3)	459	(0.0)	0.215	16	(2.6)	227	(2.9)	−0.014
Nonbiologic DMARDs	129	(18.8)	4269	(0.2)	0.667	93	(15.4)	872	(11.0)	0.128
Anticonvulsants	67	(9.8)	42,724	(2.3)	0.319	61	(10.1)	848	(10.7)	−0.022
Antidepressants	161	(23.5)	174,161	(9.3)	0.391	140	(23.1)	1960	(24.8)	−0.040
Antipsychotics	<11	(1.3)	27,612	(1.5)	−0.013	<11	(1.3)	129	(1.6)	−0.026
Anxiolytics	<11	(1.5)	8696	(0.5)	0.102	<11	(1.3)	143	(1.8)	−0.040
Barbiturates	30	(4.4)	22,716	(1.2)	0.193	25	(4.1)	393	(5.0)	−0.040
Benzodiazepines	49	(7.1)	64,984	(3.5)	0.165	46	(7.6)	617	(7.8)	−0.008
Other hypnotics	65	(9.5)	68,885	(3.7)	0.236	55	(9.1)	820	(10.4)	−0.044
Stimulants	<11	(1.3)	15,280	(0.8)	0.049	<11	(1.3)	117	(1.5)	−0.014
Opioids	311	(45.3)	427,889	(22.8)	0.491	281	(46.4)	3854	(48.8)	−0.048
Naloxone	<11	(0.4)	4270	(0.2)	0.037	<11	(0.5)	34	(0.4)	0.010
Naltrexone	<11	(0.2)	237	(0.0)	0.047	<11	(0.0)	<11	(0.0)	−0.010
Buprenorphine	<11	(0.4)	4646	(0.3)	0.033	<11	(0.5)	33	(0.4)	0.012
Methadone	<11	(0.3)	6084	(0.3)	−0.006	<11	(0.3)	53	(0.7)	−0.049
Acetaminophen	74	(10.8)	78,658	(4.2)	0.253	63	(10.4)	909	(11.5)	−0.035
NSAIDs	290	(42.3)	317,721	(16.9)	0.579	254	(41.9)	3361	(42.5)	−0.013
Antidiabetics	12	(1.8)	17,424	(0.9)	0.072	<11	(1.3)	153	(1.9)	−0.049
Antihypertensives	140	(20.4)	56,587	(3.0)	0.562	113	(18.7)	1548	(19.6)	−0.024

Huybrechts et al. Hydroxychloroquine and birth defects. Am J Obstet Gynecol 2020.

(continued)

SUPPLEMENTAL TABLE 4

Patient characteristics for HCQ-exposed and pregnancies not exposed to HCQ: MAX cohort (2000–2014) *(continued)*

Variable	Original source cohort					Restricted matched cohort[a]				
	HCQ exposed		Unexposed		Standardized difference	HCQ exposed		Unexposed		Standardized difference
Chloroquine	<11	(0.2)	20	(0.0)	0.053	<11	(0.2)	13	(0.2)	0.000
Insulin	17	(2.5)	16,250	(0.9)	0.126	14	(2.3)	181	(2.3)	0.001
Triptans	20	(2.9)	21,062	(1.1)	0.128	18	(3.0)	231	(2.9)	0.003
Suspected teratogens[d]	152	(22.2)	218,185	(11.6)	0.285	134	(22.1)	1918	(24.3)	−0.051
Markers of burden of illness[e]										
Maternal comorbidity index, mean (SD)	3.4	(2.5)	0.9	(1.4)	1.203	3.3	(2.5)	3.2	(2.6)	0.016
Number of distinct diagnoses, mean (SD)	6.1	(4.7)	2.8	(3.3)	0.815	6.0	(4.7)	6.2	(4.8)	−0.037
Number of non-HCQ prescription drugs, mean (SD)	4.9	(3.9)	1.8	(2.5)	0.959	4.7	(3.8)	4.9	(4.0)	−0.053
Number of outpatient visits, mean (SD)	4.9	(5.9)	2.1	(3.7)	0.580	4.8	(4.9)	5.0	(6.5)	−0.050
Number of emergency department visits, mean (SD)	0.5	(1.1)	0.3	(0.9)	0.195	0.5	(1.0)	0.6	(1.3)	−0.040
Hospitalization, n (%)	51	(7.4)	67,486	(3.6)	0.169	42	(6.9)	525	(6.7)	0.011
Number of hospitalizations, mean (SD)	0.1	(0.3)	0.0	(0.2)	0.168	0.1	(0.3)	0.1	(0.3)	0.007
Number of d hospitalized, mean (SD)	0.4	(2.5)	0.1	(1.2)	0.128	0.4	(2.4)	0.3	(1.7)	0.025

Cell size of <11 for the MAX cohort are suppressed in accord with the CMS cell size suppression policy.

CMS, Centers for Medicare and Medicaid Services; *DMARD*, disease-modifying antirheumatic drug; *HCQ*, hydroxychloroquine; *MAX*, Medicaid Analytic eXtract; *NSAID*, nonsteroidal antiinflammatory drug; *SD*, standard deviation.

[a] Given the variable ratio matching, the counts for the unexposed group are weighted counts to demonstrate the balance in baseline covariates; [b] Autoimmune rheumatic disorders were measured from 3 months before the start to the end of pregnancy; [c] Maternal conditions and concomitant medication use were measured from 3 months before the start of pregnancy to the end of the first trimester; [d] Women exposed to known teratogens have been excluded (ie, warfarin, antineoplastic agents, lithium, isotretinoin, misoprostol, thalidomide). Suspected teratogens considered include danazol, methimazole, propylthiouracil, aminoglycosides, trimethoprim, triamterene, sulfasalazine, spasmofen, cholestyramine, potassium iodide, tetracycline, and fluconazole; [e] General markers of the burden of illness were measured during the 3 months before but not during pregnancy, as these measures may be affected by early detection of pregnancy complications.

Huybrechts et al. Hydroxychloroquine and birth defects. Am J Obstet Gynecol 2020.

SUPPLEMENTAL TABLE 5

Sensitivity analyses: adjusted RRs restricting the cohort to women with a recorded diagnosis of autoimmune rheumatic disorders

Outcome	Fully adjusted pooled RR (95% CI)	
	Restricting the reference group to women with recorded diagnosis of autoimmune rheumatic disorders (original estimate)	Restricting both the HCQ and reference groups to women with recorded diagnosis of autoimmune rheumatic disorders (sensitivity analysis)
Malformations overall	1.26 (1.04–1.54)	1.27 (1.03–1.57)
Cardiac malformations	1.20 (0.62–2.32)	1.36 (0.68–2.72)
Oral clefts	3.70 (1.55–8.82)	3.37 (1.32–8.56)
Respiratory malformations	1.85 (0.94–3.64)	1.63 (0.63–4.26)
Gastrointestinal malformations	0.89 (0.44–1.82)	0.86 (0.35–2.14)
Genital malformations	1.16 (0.28–4.76)	1.01 (0.26–3.90)
Urinary malformations	2.21 (1.26–3.86)	2.26 (1.27–4.02)
Musculoskeletal malformations	1.17 (0.74–1.86)	1.09 (0.65–1.83)
Limb defects	1.17 (0.61–2.26)	1.18 (0.60–2.35)

CI, confidence interval; *HCQ*, hydroxychloroquine; *RR*, relative risk.

Huybrechts et al. Hydroxychloroquine and birth defects. Am J Obstet Gynecol 2020.

Supplemental References

1. Levy M, Buskila D, Gladman DD, Urowitz MB, Koren G. Pregnancy outcome following first trimester exposure to chloroquine. Am J Perinatol 1991;8:174–8.

2. Buchanan NM, Toubi E, Khamashta MA, Lima F, Kerslake S, Hughes GR. Hydroxychloroquine and lupus pregnancy: review of a series of 36 cases. Ann Rheum Dis 1996;55:486–8.

3. Parke A, West B. Hydroxychloroquine in pregnant patients with systemic lupus erythematosus. J Rheumatol 1996;23:1715–8.

4. Levy RA, Vilela VS, Cataldo MJ, et al. Hydroxychloroquine (HCQ) in lupus pregnancy: double-blind and placebo-controlled study. Lupus 2001;10:401–4.

5. Costedoat-Chalumeau N, Amoura Z, Duhaut P, et al. Safety of hydroxychloroquine in pregnant patients with connective tissue diseases: a study of one hundred thirty-three cases compared with a control group. Arthritis Rheum 2003;48:3207–11.

6. Motta M, Tincani A, Faden D, et al. Follow-up of infants exposed to hydroxychloroquine given to mothers during pregnancy and lactation. J Perinatol 2005;25:86–9.

7. Clowse ME, Magder L, Witter F, Petri M. Hydroxychloroquine in lupus pregnancy. Arthritis Rheum 2006;54:3640–7.

8. Viktil KK, Engeland A, Furu K. Outcomes after anti-rheumatic drug use before and during pregnancy: a cohort study among 150,000 pregnant women and expectant fathers. Scand J Rheumatol 2012;41:196–201.

9. Diav-Citrin O, Blyakhman S, Shechtman S, Ornoy A. Pregnancy outcome following in utero exposure to hydroxychloroquine: a prospective comparative observational study. Reprod Toxicol 2013;39:58–62.

10. Cooper WO, Cheetham TC, Li DK, et al. Brief report: risk of adverse fetal outcomes associated with immunosuppressive medications for chronic immune-mediated diseases in pregnancy. Arthritis Rheumatol 2014;66:444–50.

11. Gayed M, Khamashta M, Culliford D, et al. O58. Longterm outcomes of children born to mothers with SLE exposed to hydroxychloroquine in pregnancy. Rheumatology 2014;53(Suppl 1):i55.

12. Koh JH, Ko HS, Kwok SK, Ju JH, Park SH. Hydroxychloroquine and pregnancy on lupus flares in Korean patients with systemic lupus erythematosus. Lupus 2015;24:210–7.