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Maternal Use of Hydroxychloroquine is Associated with a Reduced Risk of Recurrent Anti-SSA/Ro Associated Cardiac Manifestations of Neonatal Lupus

Peter M. Izmirly, MD[1], **Nathalie Costedoat-Chalumeau, MD**[2], **Cecilia Pisoni, MD**[3], **Munther A. Khamashta, MD**[4], **Mimi Y. Kim, ScD**[5], **Amit Saxena, MD**[1], **Deborah Friedman, MD**[6], **Carolina Llanos, MD**[7], **Jean-Charles Piette, MD**[2], and **Jill P. Buyon, MD**[1]

[1]Division of Rheumatology, Dept of Medicine, NYU School of Medicine, New York, NY

[2]UPMC, Université Paris 6 & AP-HP, Internal Medicine Dept, SLE & APS National Referral Center, Pitié-Salpêtrière Hospital; Paris, France

[3]Hospital in Argentina, Division of Rheumatology & Immunology, CEMIC, Buenos Aires, Argentina

[4]Lupus Research Unit, St Thomas' Hospital, King's College School of Medicine, London, United Kingdom

[5]Dept of Epidemiology & Population Health, Albert Einstein College of Medicine, Bronx, NY

[6]Division of Pediatric Cardiology, New York Medical College, Valhalla, NY

[7]Division of Rheumatology, Pontificia Universidad Catolica de Chile, Santiago, Chile

Abstract

Background—A recent case control study suggested a benefit of hydroxychloroquine (HCQ) in lowering the risk of cardiac manifestations of neonatal lupus (cardiac-NL) in pregnancies of anti-SSA/Ro positive patients with Systemic Lupus Erythematosus (SLE). A historical cohort assembled from three international databases was used to evaluate whether HCQ reduces the nearly tenfold increase in risk of recurrence of cardiac-NL, independent of maternal health status.

Methods and Results—Two hundred fifty seven pregnancies of anti-SSA/Ro positive mothers (40 exposed and 217 unexposed to HCQ) subsequent to the birth of a child with cardiac-NL were identified from three databases (U.S., England, and France). Exposure was defined as the sustained use of HCQ throughout pregnancy with initiation prior to ten weeks of gestation. The recurrence rate of cardiac-NL in fetuses exposed to HCQ was 7.5% (3/40) compared to 21.2% (46/217) in the unexposed group (p=0.050). While there were no deaths in the exposed group, the overall case fatality rate of the cardiac-NL fetuses in the unexposed group was 22%. In a multivariable analysis which adjusted for database source, maternal race/ethnicity, and anti-SSB/La status, HCQ use remained significantly associated with a decreased risk of cardiac-NL (Odds Ratio=0.23; 95% CI: 0.06–0.92; p=0.037). Similar results were obtained with propensity score analysis, an alternative approach to adjust for possible confounding by indication.

Conclusions—Based on aggregate data from a multinational effort, in mothers at high risk of having a child with cardiac-NL, the use of HCQ may protect against recurrence of disease in a subsequent pregnancy.

Correspondence: Peter M. Izmirly, MD, NYU School of Medicine, TH-407, New York, NY 10016, Tel: 212-263-0745, Fax: 212-263-0759, Peter.Izmirly@nyumc.org.

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Keywords

heart block; antibodies; cardiomyopathy; prevention; hydroxychloroquine

Introduction

Neonatal lupus (NL) represents a pathologic readout of passively acquired autoimmunity associated with anti-SSA/Ro-SSB/La antibodies. The cardiac and cutaneous manifestations are now well characterized; the former are associated with a significant mortality (17.5%, primarily fetal/neonatal) and morbidity (70% require permanent pacing).[1] Prospective studies of women with the candidate autoantibodies have estimated the risk of cardiac-NL at approximately 2% if the mother has had no previously affected pregnancies.[2–4] Recurrence rates in a subsequent pregnancy are approximately six to tenfold this risk[5–11] and the occurrence rate after a previous child born with cutaneous-NL ranges from 13–18%.[12] Despite intense efforts to prospectively monitor fetuses at risk and treat heart block immediately upon identification, sustained reversal of 3rd degree block has never been achieved.

The high mortality rate in cardiac-NL and absence of data to suggest fluorinated steroids can prevent mortality[1,13,14] or reverse 3rd degree block[15] support the need for prevention. Based on the potential involvement of Toll-like receptor (TLR) signaling in the pathogenesis of cardiac-NL[16,17] a recently published case control study suggested a benefit of hydroxychloroquine (HCQ), an inhibitor of TLR ligation[18], in lowering the risk of cardiac-NL in pregnancies of anti-SSA/Ro positive patients with Systemic Lupus Erythematosus (SLE).[19] The restriction of this study to mothers with SLE, in an attempt to minimize confounding by indication, limited the number of cases available to address whether HCQ prevents recurrent cardiac-NL.

Given the higher rate of cardiac-NL in mothers with previously affected children, a decrease in recurrence rate across all anti-SSA/Ro positive pregnancies, irrespective of maternal health, would provide more robust support for the efficacy of HCQ. Accordingly, this study was initiated to determine whether HCQ prevents cardiac-NL in pregnancies subsequent to the birth of a child with cardiac-NL. The approach leveraged three international registries of neonatal lupus, from the United States, United Kingdom, and France.

Methods

Study Population

Patients were identified from three databases 1) United States (U.S), The Research Registry for Neonatal Lupus (RRNL), 2) United Kingdom (U.K), and 3) France (FR). Each of these databases has IRB approval for evaluation of de-identified information. In all registries, the enrolled women by definition must have at least anti-SSA/Ro antibodies and have at least one child with NL. The U.S. Registry was established in 1994 to collect information on children with various manifestations of NL and their families. The U.K. Registry was established in 2004 in anticipation of addressing the prevention of recurrent cardiac-NL.[10] The FR Registry was established in 2000 with goals identical to that of the U.S. Registry.

Inclusion Criteria

Pregnancies were included if the mother met each of the following criteria: a) gave birth to a previous child with cardiac-NL (defined below), b) had documented anti–SSA/Ro and/or SSB/La antibodies at the time of, or prior to pregnancy (based on results from a commercial laboratory or performed in the research laboratory of JPB), irrespective of maternal health

status. In addition to meeting the maternal inclusion criteria, the following were also required: a) confirmation of the children's outcomes based on review of medical records, b) information on medications used during pregnancy based on questionnaires and review of medical records, and c) birth of subsequent pregnancy by October 31, 2011. Ten pregnancies were excluded from the analysis (all from U.S.) because of inability to confirm pregnancy outcome and/or medications taken during pregnancy. Two hundred and fifty seven pregnancies (N = 181 U.S., N = 24 U.K., N = 52 FR) were included in the final analyses, 33 (U.S.) of which had been previously included in the initial case control evaluation of HCQ.[19]

Study Design, Outcome Measure, and Data Collection

This was a historical cohort study to determine whether exposure to HCQ reduced the risk of recurrent cardiac-NL. Cardiac-NL was defined equivalently for both inclusion in the study (first affected child) and outcome of the study (subsequent pregnancies) as follows: a) 2nd/3rd degree heart block in utero or at birth, or b) isolated cardiomyopathy, including endocardial fibroelastosis (EFE), in utero or at birth. These outcomes were documented by electrocardiogram, echocardiogram, history of pacemaker, or statement in the medical record; and/or presence of cardiac injury which specifically included autopsy evidence of a mononuclear infiltrate in the endocardium, myocardium and/or pericardium, and/or EFE with or without cardiac dysfunction on echocardiogram. Noncardiac-anti-SSA/Ro exposed (noncardiac) was defined as either being healthy or having a noncardiac manifestation of NL (cutaneous, hepatic, hematologic). Given the uncertainty regarding the clinical significance of sinus bradycardia and isolated 1st degree block and their absence of progression in most cases, they were categorized as noncardiac.[20] A pregnancy was considered exposed to HCQ if the mother took at least 200 mg per day by 10 weeks of gestation and continued throughout pregnancy. A pregnancy was considered unexposed to HCQ if the drug was never taken or was discontinued before 10 weeks of gestation. Additional data assessed included mother's age at time of birth, mother's race/ethnicity, maternal diagnosis at the time of subsequent pregnancy, and anti-SSA/Ro-SSB/La antibody status. Other therapies assessed included plasmapheresis, azathioprine, IVIG, and steroids (fluorinated or non-fluorinated). With regard to fluorinated steroids, its use as prophylaxis versus treatment of an identified block was distinguished.

Statistical Analysis

Generalized linear models (GLM) with a logit link were fit to the data to evaluate the effects of HCQ use and other patient and clinical characteristics on risk of cardiac-NL. Because multiple children from the same family were included in the analysis, generalized estimating equations (GEE) were used to account for within-family correlation in the data. Variables which were predictive of cardiac-NL in bivariate analyses ($p < 0.20$) as well as those deemed to be associated with the outcome a priori based on clinical factors, were considered for inclusion in a multivariable model. The final model was determined using a backward selection approach and included only those covariates which remained significant at the $p< 0.05$ level or changed the regression coefficient for HCQ use by more than 15%. A propensity score analysis was also performed as an alternative approach to control for confounding of the primary association between HCQ and cardiac-NL by other clinical factors. Following the approach of Brookhart[21] and Rubin and Thomas,[22] the propensity score model included all variables which were potentially related to the outcome (maternal age at time of birth, study source, maternal diagnosis, race/ethnicity, non-fluorinated steroids, IVIG, antibody status, sex of child, and birth year). The effect of HCQ on cardiac-NL adjusted for propensity score was then estimated in two ways: stratifying according to quintiles of the estimated propensity score, and including the score as a covariate in the GLM model. Two-sided p-values less than 0.05 were considered statistically significant.

Results

Patient Demographics, Maternal Autoantibody Status, Medication Use

Two hundred fifty seven pregnancies met the inclusion criteria, 40 exposed to HCQ and 217 unexposed. The demographic characteristics, maternal diagnosis at time of pregnancy, antibody status, and use of immunosuppressive medications for each group are shown in Table 1. There were no differences in age, anti-SSB/La status, prophylactic use of fluorinated steroids, IVIG exposure or plasmapheresis with regard to the use of HCQ. As expected, a greater percentage of mothers taking HCQ had been diagnosed with a rheumatic disease compared to those not taking HCQ. In addition, mothers taking HCQ were more likely to be part of the FR Registry, to have given birth more recently than those not exposed to HCQ, to be on non-fluorinated steroids, or to be non-white.

Evaluation of Hydroxychloroquine and Other Predictors in the Reduction of Recurrent Cardiac-NL

The overall recurrence rate in this study was 19.1% (49/257). The recurrence rate of cardiac-NL was 64% lower in pregnancies exposed to HCQ compared to those unexposed. Specifically, of the 40 fetuses exposed to HCQ, only 3 (7.5%) developed cardiac-NL compared to 46 (21.2%) of 217 fetuses not exposed to HCQ, p=0.050 (Table 1). There was no difference in the dosage of HCQ between the 3 cases who developed cardiac-NL and those 37 who did not.

Table 2 displays the outcome of the cardiac-NL cases. Of the three cases exposed to HCQ in utero, one had EFE which had largely resolved two years after birth, one had 2nd degree congenital heart block which reversed after exposure to dexamethasone and one had sustained 3rd degree heart block without any signs of an associated cardiomyopathy. There were no deaths. In the non HCQ exposed group the manifestations of the 46 cases with cardiac-NL were as follows: three had isolated 2nd degree block, one of which reversed with dexamethasone; 32 had isolated advanced block which included 2nd degree block with periods of 3rd degree or stable 3rd degree block, six had advanced block with a concomitant dilated cardiomyopathy (DCM) and/or EFE, and five had DCM and/or EFE in the absence of block. The overall fatality rate was 22% in the unexposed group.

For the other potential predictors of recurrent cardiac-NL, bivariate results in Table 3 indicate that being positive for both SSA/Ro and SSB/La antibodies was the only variable which was significantly associated with risk of cardiac-NL (p = 0.052). Use of non-fluorinated steroids, prophylactic fluorinated steroids, maternal race/ethnicity, and maternal diagnosis were not associated with a reduction of recurrent cardiac-NL.

Given the spectrum of cardiac disease associated with maternal anti-SSA/Ro antibodies, inclusion of milder cases might dilute those considered more clinically worrisome. Accordingly, a subsequent analysis was done in which the following subsequent cardiac-NL cases were excluded (highlighted by an asterisk, Table 2): a) any child with 2nd degree block (N=4), including two which remained in 2nd degree block at birth and two which completely reversed following in utero treatment with maternal dexamethasone and b) mild CM and or EFE treated in utero with steroids and in one case also exposed to maternal IVIG, but at birth and thereafter did not require treatment for heart failure (N=4). In this analysis restricted to the more severe cases, the protective effect of HCQ was even more significant. Specifically, the recurrence rate on HCQ was 2.6% (1/38) and HCQ - unexposed was 19.0% (40/211), p = 0.036 (Table 1).

Multivariable and Propensity Analyses

Results of the multivariable GEE analysis to adjust for potential confounders are shown in Table 3. The final model indicates that the adjusted odds ratio for cardiac-NL associated with HCQ was 0.23 (95% CI: 0.06–0.92; p = 0.037). Similar results were obtained when the less severe cases of cardiac-NL were removed from the analysis (p = 0.020), Table 3. In addition, propensity score analyses were performed as an alternative approach to adjust for possible confounding by indication. Results were very similar to those of the multivariable GEE model: the odds ratio associated with HCQ was 0.18 (95% CI: 0.05 – 0.58; p = 0.011) when the data were stratified by quintile of propensity score, and 0.19 (95% CI: 0.05 – 0.80; p = 0.023) when propensity score was included as a covariate in the model.

Discussion

Recent data suggesting a role of TLRs in the pathogenesis of cardiac-NL[16,17] raised the translational question of whether HCQ, which inhibits the acidification required for optimal ligation of Toll-like receptors,[18] might be effective in preventing cardiac tissue injury. A previous case control study restricted to anti-SSA/Ro positive mothers with SLE attempted to address this hypothesis and the results supported a decreased risk of cardiac-NL in fetuses exposed to HCQ.[19] The study presented herein significantly extends these findings in a high risk group of pregnancies in which mothers had a previous child with cardiac-NL. HCQ reduced the recurrence rate by 64% in this cohort. Since the nature of the study precluded randomization, several potential confounders, including the presence of a rheumatic disease in the mother, use of non-fluorinated steroids, year of birth, and race/ethnicity, which had potential to impact outcome, were statistically different between the HCQ exposed and unexposed groups. However, HCQ remained protective in both multivariable (OR 0.23) and propensity analyses (OR 0.18).

The overall use of HCQ in this study was about 16%. This relatively low use in mothers, most of whom had a known rheumatic disease, may be due to case reports of adverse outcome resulting in the treating physician's reluctance to prescribe HCQ and/or the patients' reluctance to take HCQ during pregnancy. Specifically, auditory toxicity was reported in two children from the same mother on chloroquine (CQ)[23] and retinal toxicity in two children from the same mother on quinine.[24] The current FDA designation of CQ and HCQ is pregnancy category risk C (safety in human pregnancy has not been determined). However, recent reviews of the literature suggest that, in particular, HCQ is safe to use during pregnancy.[25–27] No study to date (inclusive of over 300 children) has reported an increased frequency of congenital malformation.[25–27] Moreover, maternal use of HCQ was not associated with either hearing or visual abnormalities in the offspring.[26] Available ECGs revealed no differences with regard to duration of the PR or QTC intervals between unexposed or exposed children.[26] The retrospective nature of our study precludes systematic evaluation of adverse fetal effects of HCQ.

Antimalarials, including HCQ and chloroquine (CQ), are among the most frequently prescribed medications in patients with a rheumatic disease, especially SLE patients. The use of antimalarials to prevent SLE flares during pregnancy has been addressed by several studies.[28–30] In a limited placebo randomized double-blind controlled trial of 10 SLE patients receiving HCQ (dose not stated) and 10 receiving placebo, the drug was administered at 8–18 gestational weeks.[28] In the active drug group, there were no flares of disease activity compared to 3 of 10 in the placebo group. Neither congenital abnormalities nor ophthalmologic or auditory abnormalities were detected up to a minimum follow up of 1.5 years.[28] A second study, non-randomized, compared three groups of pregnant patients: those continuously exposed to HCQ before and throughout pregnancy (N = 56), those with no exposure (N = 163), and those in whom HCQ was discontinued prior to or during the first

trimester (N = 38).[29] The patients discontinuing HCQ were reported to have a higher degree of SLE activity and an increased frequency of flares. The patients taking HCQ were maintained on a lower dose of prednisone.[29] The doses of HCQ were not provided. A third study showed that discontinuation of CQ at the onset of pregnancy was associated with increased lupus activity.[30] Furthermore, the use of HCQ may have a beneficial effect on survival of patients with SLE,[31] and specifically provide protection against renal damage.[32]

The prophylactic treatment of pregnancies at risk for cardiac-NL, prior to any evidence of cardiac dysfunction, with maternal steroids has been previously advocated.[33] The study by Shinohara et al. reported a decrease in the risk of congenital heart block in 87 offspring from 40 anti-SSA/Ro positive mothers who received steroids prior to 16 weeks as compared to those who received steroids after 16 weeks or did not receive steroids. In this study the authors combined non-fluorinated (which are not active in the fetus[34]) and fluorinated steroids.

In the study reported herein, the use of non-fluorinated steroids was considered distinct from fluorinated steroids. Although there was a significantly higher concomitant use of non-fluorinated steroids in mothers taking HCQ, which likely reflects the treatment of an associated rheumatic disease, there was no significant association with use of non-fluorinated steroids and a reduction in the recurrence of cardiac-NL. Moreover, the prophylactic use of fluorinated steroids did not associate with a reduction in recurrent cardiac-NL. This supports the general discouragement of fluorinated steroids as prophylaxis due to higher adverse events in both mother and fetus and the absence of proven efficacy.[35]

Two recent studies have also evaluated the use of prophylactic IVIG at 400mg/kg for five doses in the second trimester to prevent recurrent cardiac-NL.[9,10] In these multicenter, prospective, open-label studies (one U.S. and one European) based on Simon's 2-stage optimal design,[36] there were 6 (18%) recurrences despite treatment with IVIG in 33 women who had previous pregnancies complicated by cardiac-NL. The aggregate result suggested inefficacy of IVIG at this low dose since each study was originally designed to conclude inefficacy of IVIG if 6 cases of 54 were identified. In the studyreported herein, there was no significant difference in the use of IVIG between the HCQ exposed and unexposed groups, nor was IVIG associated with a reduction of cardiac-NL.

This study has several limitations. Although the major risk factor for developing cardiac-NL is the presence of anti-SSA/Ro antibodies irrespective of overall maternal health status, the use of HCQ is influenced by diagnosis which could result in confounding by indication. We attempted to account for this by performing a propensity analysis which showed HCQ remained significantly associated with reduced recurrence rate. However, in the absence of a double blinded placebo controlled prospective trial, the possibility of confounding by indication cannot be completely eliminated. The recurrence rate of the overall group was on the higher end of the published recurrence rates available in the literature,[5–11] although previously reported rates included those taking HCQ during pregnancy. Most studies on the recurrence rate of cardiac-NL do not consider the potential influence of maternal race/ethnicity, maternal health status, or concomitant medications. However, it is readily acknowledged that the recurrence rate could be an over estimation due to bias of enrollment in a Registry of mothers who have had more than one affected child. Even if the recurrence rate is closer to the 16.7% (7/42) reported in the recently published prospective IVIG studies including the European control arm, the recurrence rate on HCQ, 7.5% is still a greater than 50% reduction. While, the extension of these data to occurrence of cardiac-NL following a child with cutaneous-NL is of interest, limited numbers of mothers on HCQ precluded meaningful analysis.

In conclusion, the data from this multinational historical cohort study suggest that HCQ use in a mother with anti-SSA/Ro antibodies and a previous child with cardiac-NL may reduce the risk of cardiac-NL recurrence in a subsequent offspring. However, further prospective studies in larger study populations are needed to confirm these findings.

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Table 1

Clinical and Demographic Characteristics

	HCQ (N=40)	No HCQ (N=217)	P Value
Age at time of birth (Mean±SD)	32.5 ±3.8	31.4 ± 4.6	0.23
Cardiac-NL	3 (7.5%)	46 (21.2%)	0.050
3rd degree and/or severe DCM/EFE	1 (2.5%)	40 (18.4%)	0.036$
2nd degree or mild DCM/EFE	2 (5.0%)	6 (2.8%)	
Registry			
U.S.	15 (37.5%)	166 (76.5%)	
FR	20 (50.0%)	32 (14.7%)	<0.001*
U.K.	5 (12.5%)	19 (8.8%)	0.070*
Race/Ethnicity			0.029 **
White	23 (57.5%)	171 (78.8%)	
Black	3 (7.5%)	14 (6.5%)	
Hispanic	3 (7.5%)	9 (4.5%)	
Asian	5 (12.5%)	8 (4.0%)	
Other/NA	6 (15.0%)	15 (6.9%)	
Maternal Diagnosis			0.0051 ***
Asym/UAS	9 (22.5%)	105 (48.4%)	
SS	10 (25.0%)	64 (29.5%)	
SLE	16 (40.0%)	28 (12.9%)	
SLE/SS	4 (10.0%)	18 (8.3%)	
MCTD	1 (2.5%)	1 (.5%)	
NA	0 (0%)	1 (0.5%)	
Antibody Status			0.65
Anti-Ro+/La +	25 (62.5 %)	144 (67.0%)	
Anti-Ro+/La−	15 (37.5%)	71 (32.7%)	
Anti-Ro+/La NA	0 (0.0%)	2 (0.92%)	
Sex of Child			0.13
Male	14 (35.0%)	101 (46.5%)	
Female	24 (60.0%)	103 (47.5%)	
NA	2 (5.0%)	13 (6.0%)	
Medications			
Fluorinated Steroids			
Total patients taking	3 (7.5%)	36 (16.6%)	0.15
Patients taking prior to cardiac-NL or 30 weeks gestation	0 (0%)	14 (38.8%)	0.54
Non-fluorinated steroids			
Total patients taking	19 (52.8%)	38 (18.8%)	<0.0001

	HCQ (N=40)	No HCQ (N=217)	P Value
IVIG	8 (20.0%)	28 (12.9%)	0.28
Plasmapheresis	0	3	1.00
Average Date of Birth	8/2007	7/1999	<0.0001

Age and hydroxychloroquine dosage are presented as mean with standard deviation. All other data are reported as N (%).

$ P value represents the comparison between HCQ and no HCQ eliminating the 2nd degree or mild DCM/EFE

* P value represents comparison of FR and UK Registries to the US

** P value represents the comparison of white to non white

*** P value represents the comparison of Asym/UAS to all others maternal diagnoses combined

Asym=Asymptomatic, UAS=Undifferentiated Autoimmune Syndrome, SLE=Systemic Lupus Erythematosus, SS=Sjogren's Syndrome, MCTD=Mixed Connective Tissue Disease, DCM = Dilated Cardiomyopathy, EFE = Endocardial Fibroelastosis, NA=Not Available

Table 2

Outcome of Children

HCQ Exposure (N=40)	
Noncardiac	N=37 (92.5%)
Normal	35
Cutaneous-NL	1
1st Degree Heart Block (resolved after a few months; child also had cutaneous NL)	1
Cardiac-NL	N=3 (7.5%)
EFE * (near complete resolution at 2 years)	1
2nd Degree Heart Block * (reversed with dexamethasone in utero)	1
3rd Degree Heart Block	1

Non HCQ Exposure (N=217)		
Noncardiac	N=171(78.8%)	
Normal	149	
Isolated Hepatic/Hematologic NL	2	
Cutaneous NL	17	
1st Degree Heart Block	3	
Cardiac-NL	N=46 (21.2%)	Deaths
Advanced Block (2nd/3rd)	32	4
2nd Degree Block *(never 3rd) (1 reversed with dexamethasone)	3	0
Advanced Block with Cardiomyopathy/EFE	6	5
Isolated Cardiomyopathy/EFE (3 had mild EFE requiring no cardiac meds at birth *)	5	1

NL=Neonatal Lupus

EFE= Endocardial Fibroelastosis

*Considered less severe cases of cardiac –NL

Table 3

Unadjusted and Adjusted Odds Ratios for Risk Factors of Recurrent Cardiac-NL

Variable	OR (95% CI)*	P-value	OR_{adj} (95% CI)**	P-value	OR_{adj} (95% CI)***	P-value
HCQ						
No	1 (ref)		1 (ref)		1(ref)	
Yes	0.30(0.09–1.00)	0.050	0.23(0.06–0.92)	0.037	0.10(0.014–0.70)	0.020
Maternal Age at Time of Birth	1.01(0.93–1.09)	0.91				
Maternal Race						
Non-White	1		1		1	
White	0.67 (0.29–1.56)	0.35	0.47(0.19–1.15)	0.099	0.55(0.21–1.45)	0.22
Maternal Diagnosis						
Asym/UAS	1					
SLE/SS/MCTD	1.33 (0.69–2.59)	0.38				
Anti-SSB/La+						
No	1		1		1	
Yes	2.02(0.99–4.10)	0.052	2.06(0.98–4.37)	0.058	1.82(0.82–4.03)	0.14
Registry Source						
U.S.	1		1		1	
U.K.	0.97(0.30–3.10)	0.96	1.23(0.38–3.94)	0.73	1.41(0.43–4.61)	0.57
FR	1.78(0.84–3.80)	0.13	2.68(1.08–6.67)	0.03	2.06(0.79–5.32)	0.14
Sex of Child						
Male	1					
Female	0.64(0.33–1.22)	0.18				
Prophylactic Fluorinated Steroid Use						
No	1					
Yes	0.64(0.13–3.15)	0.58				
Non-Fluorinated Steroid Use						
No	1					
Yes	0.83(0.40–1.72)	0.61				

Variable	OR (95% CI)*	P-value	OR_{adj} (95% CI)**	P-value	OR_{adj} (95% CI)***	P-value
IVIG						
No	1					
Yes	0.80(0.35–1.80)	0.59				
Year of Birth	1.01(0.97–1.06)	0.51				

*estimates of unadjusted Odds Ratios (OR) based on bivariate analyses with the 95% Confidence Intervals (CI) and corresponding p values.

**estimates of adjusted OR with 95% CI and corresponding p value from a multivariable GEE model including hydroxychloroquine (HCQ) use, maternal race, the presence of anti-SSB/La antibody, and Registry source

***estimates of adjusted OR with 95% CI and corresponding p value from a multivariable GEE model including hydroxychloroquine (HCQ) use, maternal race, the presence of anti-SSB/La antibody, and Registry source, excluding 2nd degree block and mild EFE cases

Asym=Asymptomatic, UAS=Undifferentiated Autoimmune Syndrome, SLE=Systemic Lupus Erythematosus, SS=Sjogren's Syndrome, MCTD=Mixed Connective Tissue Disease