# Maternal Use of Hydroxychloroquine Is Associated With a Reduced Risk of Recurrent Anti-SSA/Ro-Antibody–Associated Cardiac Manifestations of Neonatal Lupus

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***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. A historical cohort assembled from 3 international databases was used to evaluate whether HCQ reduces the nearly 10-fold increase in risk of recurrence of cardiac-NL independently 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 3 databases (United States, England, and France). Exposure was defined as the sustained use of HCQ throughout pregnancy with initiation before 10 weeks of gestation. The recurrence rate of cardiac-NL in fetuses exposed to HCQ was 7.5% (3 of 40) compared with 21.2% (46 of 217) in the unexposed group ($P=0.050$). Although there were no deaths in the exposed group, the overall case fatality rate of the cardiac-NL fetuses in the unexposed group was 21.7%. In a multivariable analysis that 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% confidence interval, 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.

***Conclusion***—Aggregate data from a multinational effort show that 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. **(*Circulation*. 2012; 126:76-82.)**

**Key Words:** anti-SSA/Ro antibody ■ cardiomyopathies ■ congenital heart block ■ hydroxychloroquine ■ neonatal lupus ■ prevention and control



Neonatal lupus (NL) represents a pathological readout of passively acquired autoimmunity associated with anti-SSA/Ro-SSB/La antibodies. The cardiac (cardiac-NL) 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 ≈2% if the mother has had no previously affected pregnancies.[2–4] Recurrence rates in a subsequent pregnancy are ≈6- to 10-fold this risk,[5–11,] and the occurrence rate after a previous child born with cutaneous-NL ranges from 13% to 18%.[12] Despite intense efforts to prospectively monitor fetuses at risk and to treat heart block immediately on identification, sustained reversal of third-degree block has never been achieved.

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The high mortality rate in cardiac-NL and the absence of data to suggest that fluorinated steroids can prevent mortality[1,13,14] or reverse third-degree block[15] support the need for prevention. Based on the potential involvement of Toll-like receptor signaling in the pathogenesis of cardiac-NL,[16,17] a recently published case-control study suggested a benefit of hydroxychloroquine (HCQ), an inhibitor of Toll-like receptor ligation,[18] in lowering the risk of cardiac-NL in pregnancies

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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, regardless 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 3 international registries of neonatal lupus from the United States, United Kingdom, and France.

## Methods

### Study Population

Patients were identified from 3 databases: the US Research Registry for Neonatal Lupus, a UK registry, and a French registry. Each of these databases has Institutional Review Board approval for the evaluation of deidentified information. In all registries, the enrolled women by definition must have at least anti-SSA/Ro antibodies and have at least 1 child with NL. The US registry was established in 1994 to collect information on children with various manifestations of NL and their families. The UK registry was established in 2004 in anticipation of addressing the prevention of recurrent cardiac-NL.[10] The French registry was established in 2000 with a goal identical to that of the US registry.

### Inclusion Criteria

Pregnancies were included if the mother met each of the following criteria: gave birth to a previous child with cardiac-NL (defined below) and had documented anti–SSA/Ro and/or SSB/La antibodies at the time of or before pregnancy (based on results from a commercial laboratory or performed in the research laboratory of J.P.B.), regardless of maternal health status. In addition to meeting the maternal inclusion criteria, the following were also required: confirmation of the children's outcomes by review of medical records, information on medications used during pregnancy assessed with questionnaires and review of medical records, and the birth of subsequent child by October 31, 2011. Ten pregnancies were excluded from the analysis (all from the United States) because of an inability to confirm pregnancy outcome and/or medications taken during pregnancy. Two hundred fifty-seven pregnancies (n=181 in the United States, n=24 in the United Kingdom, n=52 in France) were included in the final analyses, 33 (from the United States) of which had previously been 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: second- or third-degree heart block in utero or at birth or isolated cardiomyopathy, including endocardial fibroelastosis (EFE), in utero or at birth. These outcomes were documented by ECG, echocardiogram, history of pacemaker, or statement in the medical record; and/or the presence of cardiac injury that 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 about the clinical significance of sinus bradycardia and isolated first-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/d 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 the mother's age at the 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, intravenous immunoglobulin (IVIG), and steroids (fluorinated or nonfluorinated). With regard to fluorinated steroids, its use as prophylaxis was distinguished from treatment of an identified block.

### Statistical Analysis

Generalized linear models with a logit link were fit to the data to evaluate the effects of HCQ use and other patient and clinical characteristics on the risk of cardiac-NL. Because multiple children from the same family were included in the analysis, generalized estimating equations were used to account for within-family correlation in the data. Variables that were predictive of cardiac-NL in bivariate analyses ($P<0.20$) and those deemed to be associated with the outcome a priori on the basis of clinical factors were considered for inclusion in a multivariable model. The final model was determined with a backward selection approach and included only those covariates that remained significant at the $P<0.05$ level or changed the regression coefficient for HCQ use by >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 et al[21] and Rubin and Thomas,[22] the propensity-score model included all variables that were potentially related to the outcome (maternal age at time of birth, study source, maternal diagnosis, race/ethnicity, nonfluorinated steroids, IVIG, antibody status, sex of the child, and birth year). The effect of HCQ on cardiac-NL adjusted for propensity score was then estimated in 2 ways: stratifying according to quintiles of the estimated propensity score and including the score as a covariate in the generalized linear model. Two-sided values of $P<0.05$ were considered statistically significant.

## Results

### Patient Demographics, Maternal Autoantibody Status, and 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 with those not taking HCQ. In addition, mothers taking HCQ were more likely to be part of the French registry, to have given birth more recently than those not exposed to HCQ, to be on nonfluorinated steroids, and to be nonwhite.

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

The overall recurrence rate in this study was 19.1% (49 of 257). The recurrence rate of cardiac-NL was 64.6% lower in pregnancies exposed to HCQ compared with those unexposed. Specifically, of the 40 fetuses exposed to HCQ, only 3

**Table 1. Clinical and Demographic Characteristics**

| | HCQ (n=40) | No HCQ (n=217) | *P* |
|---|---|---|---|
| Age at time of birth (mean±SD), y | 32.5±3.8 | 31.4±4.6 | 0.23 |
| Cardiac-NL, n (%) | 3 (7.5) | 46 (21.2) | 0.050 |
| Third-degree and/or severe DCM/EFE | 1 (2.5) | 40 (18.4) | 0.036* |
| Second-degree or mild DCM/EFE | 2 (5.0) | 6 (2.8) | |
| Registry, n (%) | | | |
| United States | 15 (37.5) | 166 (76.5) | |
| France | 20 (50.0) | 32 (14.7) | <0.001† |
| United Kingdom | 5 (12.5) | 19 (8.8) | 0.070† |
| Race/ethnicity, n (%) | | | 0.029‡ |
| White | 23 (57.5) | 171 (78.8) | |
| Black | 3 (7.5) | 14 (6.5) | |
| Hispanic | 3 (7.5) | 9 (4.1) | |
| Asian | 5 (12.5) | 8 (3.7) | |
| Other/NA | 6 (15.0) | 15 (6.9) | |
| Maternal diagnosis, n (%) | | | 0.0051§ |
| Asymptomatic/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 (0.5) | |
| NA | 0 (0) | 1 (0.5) | |
| Antibody status, n (%) | | | 0.65 |
| Anti-Ro$^+$/La$^+$ | 25 (62.5) | 144 (66.4) | |
| Anti-Ro$^+$/La$^-$ | 15 (37.5) | 71 (32.7) | |
| Anti-Ro+/La NA | 0 (0.0) | 2 (0.92) | |
| Sex of child, n (%) | | | 0.13 |
| Male | 14 (35.0) | 101 (46.5) | |
| Female | 24 (60.0) | 103 (47.5) | |
| NA | 2 (5.0) | 13 (6.0) | |
| Medications, n (%) | | | |
| Fluorinated steroids | | | |
| Total patients taking | 3 (7.5) | 36 (16.6) | 0.15 |
| Patients taking before cardiac-NL or 30 wk gestation | 0 (0) | 14 (38.8) | 0.54 |
| Nonfluorinated steroids | | | |
| Total patients taking | 21 (52.5) | 44 (20.3) | <0.0001 |
| IVIG | 8 (20.0) | 28 (12.9) | 0.28 |
| Plasmapheresis | 0 | 3 | 1.00 |
| Average date of birth | August 2007 | July 1999 | <0.0001 |

HCQ indicates hydroxychloroquine; NL, neonatal lupus; DCM, dilated cardiomyopathy; EFE, endocardial fibroelastosis; UAS, undifferentiated autoimmune syndrome; SS, Sjögren's syndrome; SLE, systemic lupus erythematosus; MCTD, mixed connective tissue disease; NA, not available; and IVIG, intravenous immunoglobulin.

*A comparison between HCQ and no HCQ eliminating the second-degree block or mild DCM/EFE.

†A comparison of French and UK registries with the US registry.

‡A comparison of white and nonwhite.

§A comparison of asymptomatic/UAS and all other maternal diagnoses combined.

**Table 2. Outcome of Children**

| | | Deaths |
|---|---|---|
| HCQ exposure (n=40), n (%) | | |
| Noncardiac | 37 (92.5) | |
| Normal | 35 | |
| Cutaneous-NL | 1 | |
| First-degree heart block (resolved after a few months; child also had cutaneous-NL) | 1 | |
| Cardiac-NL | 3 (7.5) | |
| EFE* (nearly complete resolution at 2 y) | 1 | |
| Second-degree heart block* (reversed with dexamethasone in utero) | 1 | |
| Third-degree heart block | 1 | |
| HCQ nonexposure (n=217), n (%) | | |
| Noncardiac | 171 (78.8) | |
| Normal | 149 | |
| Isolated hepatic/hematologic NL | 2 | |
| Cutaneous-NL | 17 | |
| First-degree heart block | 3 | |
| Cardiac-NL | 46 (21.2) | |
| Advanced block (second/third) | 32 | 4 |
| Second-degree block* (never third) (1 reversed with dexamethasone) | 3 | 0 |
| Advanced block with cardiomyopathy/EFE | 6 | 5 |
| Isolated cardiomyopathy/EFE (3 had mild EFE requiring no cardiac medications at birth*) | 5 | 1 |

HCQ indicates hydroxychloroquine; NL, neonatal lupus; and EFE, endocardial fibroelastosis.

*Considered less severe cases of cardiac-NL.

(7.5%) developed cardiac-NL compared with 46 of 217 fetuses (21.2%) 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 gives the outcomes of the cardiac-NL cases. Of the 3 cases exposed to HCQ in utero, 1 had EFE that had largely resolved 2 years after birth, 1 had second-degree congenital heart block that reversed after exposure to dexamethasone, and 1 had sustained third-degree heart block without any signs of an associated cardiomyopathy. There were no deaths. In the nonexposed group, the manifestations of the 46 cases with cardiac-NL were as follows: 3 had isolated second-degree block, one of which reversed with dexamethasone; 32 had isolated advanced block, which included second-degree block with periods of third-degree or stable third-degree block; 6 had advanced block with a concomitant dilated cardiomyopathy and/or EFE; and 5 had dilated cardiomyopathy and/or EFE in the absence of block. The overall fatality rate was 21.7% 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 that was significantly associated with risk of cardiac-NL ($P$=0.052). Use of nonfluorinated steroids, prophylactic fluorinated steroids, maternal race/ethnicity, and maternal diagnosis were not associated with a reduction of recurrent cardiac-NL.

**Table 3. Unadjusted and Adjusted Odds Ratios for Risk Factors of Recurrent Cardiac Manifestations of Neonatal Lupus**

| Variable | OR (95% CI)* | *P* | $OR_{adj}$ (95% CI)† | *P* | $OR_{adj}$ (95% CI)‡ | *P* |
|---|---|---|---|---|---|---|
| HCQ | | | | | | |
| No | 1 (Referent) | | 1 (Referent) | | 1 (Referent) | |
| 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 | | | | | | |
| Nonwhite | 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 | | | | | | |
| Asymptomatic/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 | | | | | | |
| United States | 1 | | 1 | | 1 | |
| United Kingdom | 0.97 (0.30–3.10) | 0.96 | 1.23 (0.38–3.94) | 0.73 | 1.41 (0.43–4.61) | 0.57 |
| France | 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 | | | | |
| Nonfluorinated steroid use | | | | | | |
| No | 1 | | | | | |
| Yes | 0.83 (0.40–1.72) | 0.61 | | | | |
| IVIG | | | | | | |
| No | 1 | | | | | |
| Yes | 0.80 (0.35–1.80) | 0.59 | | | | |
| Year of Birth | 1.01 (0.97–1.06) | 0.51 | | | | |

OR indicates odds ratio; CI, confidence interval; HCQ, hydroxychloroquine; UAS, undifferentiated autoimmune syndrome; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; MCTD, mixed connective tissue disease; and IVIG, intravenous immunoglobulin.

*Estimates of unadjusted OR based on bivariate analyses with 95% CI and corresponding *P* values.

†Estimates of adjusted OR with 95% CI and corresponding *P* value from a multivariable generalized estimating equation model including 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 generalized estimating equation model including HCQ use, maternal race, the presence of anti-SSB/La antibody, and registry source, excluding second-degree block and mild endocardial fibroelastosis cases.



Given the spectrum of cardiac disease associated with maternal anti-SSA/Ro antibodies, the 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 in Table 2): (1) any child with second-degree block (n=4), including 2 who remained in second-degree block at birth and 2 who completely reversed after in utero treatment with maternal dexamethasone, and (2) children with mild cardiomyopathy and/or EFE treated in utero with steroids and, in 1 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 of 38) and in the unexposed group was 19.0% (40 of 211; $P=0.036$; Table 1).

## Multivariable and Propensity Analyses

Results of the multivariable generalized estimating equation 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% confidence interval, 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 generalized estimating equation model; the odds ratio associated with HCQ was 0.18 (95% confidence interval, 0.05–0.58; $P=0.011$) when the data were stratified by quintile of propensity score and 0.19 (95% confidence interval, 0.05–0.80; $P=0.023$) when propensity score was included as a covariate in the model.

## Discussion

Recent data suggesting a role for Toll-like receptors 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 here 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 64.6% in this cohort. Several potential confounders, including the presence of a rheumatic disease in the mother, maternal use of nonfluorinated steroids, year of birth, and maternal race/ethnicity, were statistically different between the HCQ exposed and unexposed groups and thus may have accounted for the protective effect of HCQ. However, after accounting for those variables, HCQ remained protective in both multivariable (odds ratio, 0.23) and propensity (odds ratio, 0.18) analyses.

The overall use of HCQ in this study was ≈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 physicians' reluctance to prescribe HCQ and/or the patients' reluctance to take HCQ during pregnancy. Specifically, auditory toxicity was reported in 2 children from the same mother on chloroquine[23] and retinal toxicity in 2 children from the same mother on quinine.[24] The current Food and Drug Administration designation of chloroquine and HCQ is pregnancy category risk C (safety in human pregnancy has not been determined). However, recent reviews of the literature suggest that HCQ in particular is safe to use during pregnancy.[25–27] No study to date (inclusive of >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 precluded systematic evaluation of adverse fetal effects of HCQ.

Antimalarials, including HCQ and chloroquine, 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 to 18 gestational weeks.[28] In the active drug group, there were no flares of disease activity compared with 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, nonrandomized, compared 3 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 before 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 chloroquine at the onset of pregnancy was associated with increased lupus activity.[30] Furthermore, the use of HCQ may have a beneficial effect on the survival of patients with SLE[31] and specifically provide protection against renal damage.[32]

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

In the study reported here, the use of nonfluorinated steroids was considered distinct from the use of fluorinated steroids. Although there was a significantly higher concomitant use of nonfluorinated steroids in mothers taking HCQ, which likely reflects the treatment of an associated rheumatic disease, there was no significant association with use of nonfluorinated 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 because of 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 400 mg/kg for 5 doses in the second trimester to prevent recurrent cardiac-NL.[9,10] In these multicenter, prospective, open-label studies (one in the United States and one in Europe) based on Simon's 2-stage optimal design,[36] there were 6 recurrences (18%) despite treatment with IVIG in 33 women who had previous pregnancies complicated by cardiac-NL. The aggregate result suggested the inefficacy of IVIG at this low dose because each study was originally designed to conclude inefficacy of IVIG if 6 cases of 54 were identified. In the study reported here, there was no significant difference in the use of IVIG between the HCQ-exposed and -unexposed groups, nor was IVIG associated with a reduction in cardiac-NL.

This study has several limitations. Although the major risk factor for developing cardiac-NL is the presence of anti-SSA/Ro antibodies regardless 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 that showed that HCQ remained significantly associated with reduced recurrence rate. However, in the absence of a double-blind 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 subjects 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 overestimation resulting from bias of enrollment in a registry of mothers who have had >1 affected child. Even if the recurrence rate is closer to the 16.7% (7 of 42) reported in the recently published prospective IVIG studies including the European control arm, the 7.5% recurrence rate on HCQ is still a >50% reduction. Although the extension of these data to the occurrence of cardiac-NL after a child with cutaneous-NL is of interest, the limited number of mothers on HCQ precluded meaningful analysis.

## Conclusions

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 are needed to confirm these findings.

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## Disclosures

None.

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## CLINICAL PERSPECTIVE

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. In this study, we examined whether HCQ reduces the ≈10-fold higher recurrence rate in cardiac-NL by identifying 257 pregnancies of anti-SSA/Ro–positive mothers (40 exposed and 217 unexposed to HCQ) after the birth of a child with cardiac-NL from 3 international databases. Exposure was defined as the sustained use of HCQ throughout pregnancy with initiation before 10 weeks of gestation. The recurrence rate of cardiac-NL in fetuses exposed to HCQ was 7.5% (3 of 40) compared with 21.2% (46 of 217) in the unexposed group ($P=0.050$). There were no deaths in the HCQ-exposed group, whereas the overall case fatality rate of the cardiac-NL fetuses in the unexposed group was 21.7%. In a multivariable analysis, HCQ use remained significantly associated with a decreased risk of cardiac-NL (odds ratio, 0.23; $P=0.037$). Similar results (odds ratio, 0.18; $P=0.011$) were obtained with propensity score analysis, an alternative approach to adjust for possible confounding by indication. Data obtained 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. Further prospective studies are needed to confirm these findings.