OBSTETRICS

Maternal autoantibody levels in congenital heart block and potential prophylaxis with antiinflammatory agents

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OBJECTIVE: The importance of maternal autoantibody levels in congenital heart block and elucidation of maternal factors that may reduce disease burden require further clarification.

STUDY DESIGN: Pregnancies complicated by maternal anti-Ro antibodies from 2007 through 2011 were retrospectively reviewed.

RESULTS: In all, 33 women were followed up throughout pregnancy. Semiquantitative maternal anti-La levels were significantly higher in pregnancies complicated by fetal heart block of any degree (median difference, 227.5; $P = .04$), but there was no difference in maternal anti-Ro levels. In all, 94% of fetuses maintained normal conduction when the mother was treated with hydroxychloroquine or daily prednisone therapy throughout pregnancy, compared to 59% in the untreated group (odds ratio, 0.1; $P = .04$).

CONCLUSION: Pregnancies complicated by fetal heart block did not have higher levels of maternal anti-Ro antibodies. Maternal anti-La level may be a useful predictor of fetal heart block. Maternal treatment with either hydroxychloroquine or daily low-dose prednisone throughout pregnancy may provide a protective effect.

Key words: autoantibodies, congenital heart block, fetal echocardiography, prevention

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Pregnant women who are positive for anti-Ro/SSA antibodies have approximately a 2% risk for the fetus developing congenital complete heart block.[1,2] This risk increases to 16% when a previous child has had heart block and approaches 55% when maternal hypothyroidism is present in combination with anti-Ro antibodies.[2,3] It has been demonstrated that mothers with antibodies against the 52-kd Ro protein have longer atrioventricular (AV) conduction times and are at greater risk.[4-7] A recent prospective cohort study suggests that the amount of anti-Ro antibody, rather than simply its presence, is associated with damage to the fetal conduction tissue.[5]

Despite this improved understanding, clinical management of these mothers and fetuses remains challenging. Two prior studies have shown that PR prolongation does not necessarily precede more advanced heart block.[8,9] With no surrogate markers for fetal heart block known, frequent screening via fetal echocardiography of fetuses exposed to maternal anti-Ro antibodies to trend the mechanical PR interval remains a common clinical practice. The mechanical PR interval, obtained by using pulsed-wave Doppler to measure the time from the onset of atrial systole to the onset of ventricular systole, is a validated approach for fetal rhythm assessment.[10] While routine use of dexamethasone for prophylaxis is not recommended due to its association with significant adverse events, several anecdotal reports demonstrate regression or stabilization of first- or second-degree fetal heart block after maternal steroid therapy.[11] Recent work by Izmirly et al[12,13] suggests that women with systemic lupus erythematosus who are treated with hydroxychloroquine throughout pregnancy have a lower risk of having a child affected by cardiac neonatal lupus and that hydroxychloroquine use may protect against the recurrence of cardiac manifestations in subsequent pregnancies. Additionally, beneficial effects of maternal antiinflammatory treatment have not been firmly established by prospective studies and routine use of these medications is not currently standard of care.

Given these continued challenges, the goals of this study were to determine the rate of congenital heart block in fetuses exposed to maternal Anti-Ro/SSA antibodies at our institution, determine the correlation between fetal heart block and maternal autoantibody levels, and investigate the efficacy of maternal therapy with antiinflammatory medications. We hypothesized that pregnancies complicated by congenital heart block would be associated with higher maternal levels of anti-Ro antibody. We also hypothesized that mothers treated with a daily antiinflammatory medication throughout pregnancy would be less likely to have a fetus with congenital heart block. To test these hypotheses, we conducted a retro-

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spective review of appropriate patients managed at our institution.

Materials and Methods

This study was approved by the Duke University Hospital Institutional Review Board. Subjects were identified by reviewing the outpatient schedule and records from our fetal cardiology clinic and affiliated community pediatric cardiology clinics from 2007 through 2011. Records from our rheumatology and maternal-fetal medicine clinics were also reviewed for supplemental information. All pregnant women who were positive for anti-Ro/SSA antibodies and serially screened via fetal echocardiography throughout the pregnancy were included in the study. One subject with only 1 clinical assessment performed at our institution was excluded. Maternal information including age, parity, primary rheumatologic diagnosis, significant medical and family history, medications taken during the pregnancy, and their dosages were collected by reviewing the electronic medical record from our institution. No patients were directly contacted for data collection. Two subjects were concurrently enrolled in the 2010 Preventive IVIG Therapy for Congenital Heart Block (PITCH) trial, assessing the efficacy of maternal therapy with low-dose intravenous immunoglobulin (IVIG) as a preventive therapy for fetal heart block.[14] Semiquantitative levels of anti-Ro, anti-La, anti-Smith, and anti-RNP antibodies were collected from immunology laboratory records from our institution, as well as via direct communication with referring providers and laboratories. Antibody levels analyzed at our institution were obtained using the AtheNA Multi-Lyte ANA-II Plus test system (Zeus Scientific Inc, Raritan, NJ) on 1 of 2 instruments, with a value of >120 arbitrary units considered positive. Our immunology laboratory performs biannual carryover and precision testing on these instruments, maintaining that each pipetting probe must have an average carryover of <3% and a coefficient of variation ≤5% to meet acceptance criteria. Results of maternal antibody levels drawn by referring physicians were obtained by direct communication with these providers and were included in the analysis only if the same methodology was used for sample processing. Each fetal echocardiogram performed during the pregnancy was independently reviewed. Analysis of the fetal echocardiograms included measurement of the mechanical PR interval, qualitative assessment of systolic function, assessment for the presence of pericardial or pleural effusions, endomyocardial fibroelastosis or other evidence suggestive of hydrops fetalis, and a careful assessment for structural heart disease. The mechanical PR interval was measured using simultaneous left ventricular inflow-outflow pulsed-wave Doppler aligned parallel to direction of blood flow.[10] Gestational age and interval between fetal echocardiograms expressed in weeks was recorded. Infant status immediately following birth, as well as at follow-up evaluations, was also noted.

Descriptive statistics, including calculations of the mean, median, SD, and interquartile range for anti-Ro, anti-La, anti-Smith, and anti-RNP antibody levels were calculated. The distribution of the maternal autoantibody levels were assessed by standard numeric and graphic assessments. Patients with missing antibody level data or those with results available in different units of measure that could not be converted to units used for the majority of the sample were excluded from this portion of the analysis. Antibody levels in patients with fetal heart block of any degree vs those with normal conduction were compared. Differences between these groups were assessed by the Wilcoxon rank sum test. Data tables were also created demonstrating the proportion of mothers treated with daily hydroxychloroquine or prednisone who had fetuses affected by congenital heart block of any degree. Odds ratios (ORs), 95% confidence intervals (CIs), and *P* values for these proportional data were calculated by the Fisher exact test. Two-sided *P* values were used for all analyses. A level of statistical significance was set at .05 prior to data analysis. All data analysis was performed using R statistical software, version 2.13.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

In all, 33 subjects were followed up at our institution during the study period. Maternal information is summarized in Table 1. Average subject age was 29.2 years. In all, 61% (n = 20) had a diagnosis of systemic lupus erythematosus. Other rheumatologic diagnoses included unspecified rheumatologic disease (n = 8, 24%), Sjögren syndrome (n = 3, 9%), spondyloarthritis with associated Crohn's disease and autoimmune neutropenia (n = 1, 3%), and rheumatoid arthritis (n = 1, 3%). An average of 9 screening fetal echocardiograms was performed throughout each pregnancy. Twenty-three subjects had fetal echocardiograms performed every 2 weeks from 17-34 weeks' gestation. Nine subjects were screened on a weekly basis for a portion of the pregnancy due to elevated concern for fetal heart block in the current pregnancy (n = 7), history of a pregnancy with fetal conduction abnormality (n = 3), history of fetal demise of unknown etiology (n = 1), or concomitant maternal hypothyroidism (n = 1). One subject whose fetus maintained normal conduction was screened every 4 weeks from 19-27 weeks' gestation. All of the fetuses had structurally normal hearts. In all, 42% of subjects (n = 14) were treated with 200-400 mg/d of hydroxychloroquine throughout the pregnancy. Additionally, 2 patients were treated only with low-dose daily prednisone (1-20 mg once daily) and 6 subjects treated with both medications concurrently.

Fetal outcomes

Six fetuses (18%) developed congenital AV block of any degree during the pregnancy. Two fetuses rapidly progressed to complete fetal heart block at 19 and 22 weeks' gestation, respectively. In the first case, the fetus had a normal mechanical PR interval at 18 weeks' gestation and complete heart block by repeat assessment at 19 weeks. In the second case, the fetus developed first-degree AV block at 22 weeks at which time oral dexamethasone was prescribed. The mother developed significant nausea and vomiting

TABLE 1
Summary of maternal information

Patient No.	Age, y	Gravida status	Rheumatologic diagnosis	Adverse obstetrical outcomes in prior pregnancies	Autoantibody assessment timing (relative to gestation)	No. of fetal echocardiograms	Fetal rhythm diagnosis	Hydroxychloroquine therapy	Prednisone therapy
1	18	1	SLE	None	+3 d	7	CHB[a]	N	N
2	36	3	Sjögren	CHB s/p pacer × 2	10 wk	18	CHB[b]	N	N
3	24	2	SLE	CHB, hydrops, intrauterine demise	9 wk	25	CHB[b]	N	N
4	28	2	SLE	Prematurity	16 wk	12	First-degree AVB	200 mg BID	N
5	31	2	Unspecified	None	+1 mo	15	First-degree AVB	N	N
6	36	2	Sjögren, autoimmune hypothyroidism	SA × 1	+7 mo	23	First-degree AVB; resolved second-degree AVB	N	N
7	24	2	SLE	Chondrodysplasia punctata	9 wk	7	Normal	400 mg qd	15 mg qd
8	25	1	SLE	None	20 wk	6	CHB[a]	N	N
9	31	2	SLE	SA × 1	4 wk	7	Normal	N	N
10	32	1	SLE	None	13 wk	7	Normal	200 mg qd	N
11	27	1	SLE	None	8 wk	8	Normal	200 mg BID	5 mg qd
12	26	2	SLE	SA × 1	6 wk	6	Normal	N	N
13	24	1	SLE	None	−1 mo	10	Normal	200 mg qd	N
14	29	1	SLE	None	12 wk	6	Normal	200 mg BID	N
15	29	1	Unspecified	None	15 wk	7	Normal	N	N
16	21	1	SLE	None	29 wk	3	Normal	200 mg BID	7.5 mg qd
17	22	3	SLE	None	20 wk	8	Normal	N	N
18	38	3	? Antiphospholipid syndrome	SA × 1	6 wk	9	Normal	N	N
19	26	2	Unspecified	None	7 wk	20	First-degree AVB	N	N
20	40	3	Sjögren	None	9 wk	9	Normal	N	N
21	32	1	Unspecified	None	6 wk	8	Normal	N	N
22	37	1	SLE	None	−3 y	9	Normal	400 mg qd	1 mg qd
23	29	1	Spondyloarthritis, Crohn's, autoimmune neutropenia	None	9 wk	10	Normal	N	5 mg qd
24	39	2	SLE	Stillbirth of twins	14 wk	6	Normal	N	20 mg qd
25	22	1	SLE	None	9 wk	7	Normal	200 mg BID	5-10 mg qd
26	27	1	Unspecified	None	17 wk	11	Normal	400 mg qd	N
27	32	5	SLE	None	14 wk	2	Normal	400 mg qd	15 mg qd
28	40	3	Unspecified	SA × 1; intrauterine demise × 1	−1 y	11	Normal	N	N
29	20	2	SLE	None	12 wk	4	Normal	200 mg BID	N
30	27	3	Unspecified	None	NA	3	Normal	N	N
31	30	2	SLE	None	25 wk	9	Normal	Y	N
32	27	3	RA	Intrauterine demise × 2	NA	6	Normal	200 mg qd	N
33	37	2	SLE	None	NA	6	Normal	N	N

Timing of maternal autoantibody assessment expressed as weeks of gestation or ±time interval relative to current pregnancy (+postpartum; –prior to pregnancy).
AVB, atrioventricular block; *BID*, twice daily; *CHB*, complete heart block; *N*, no therapy provided; *NA*, not available; *qd*, every day; *RA*, rheumatoid arthritis; *SA*, spontaneous abortion; *SLE*, systemic lupus erythematosus; *s/p*, status post; *Y*, therapy given, but dose unknown; *?*, disease felt likely by clinical evaluation but not confirmed.

[a] Referred to our institution in CHB; [b] Rapid progression to CHB.

Tunks. Predictors and prophylaxis for fetal heart block. Am J Obstet Gynecol 2013.

TABLE 2
Semiquantitative levels of maternal anti-Ro and anti-La antibodies by degree of fetal heart block

Degree of heart block	Mean anti-Ro (SD, median)	Mean anti-La (SD, median)	Mean anti-Smith (SD, median)	Mean anti-RNP (SD, median)	No. of patients
Normal	495.8 (286.2, 482)	108.7 (164.5, 29.5)	79.5 (109, 41.5)	98.7 (95.2, 73)	25
First-degree AVB	443 (143.1, 468)	334.7 (252.3, 364)	40.3 (52.8, 15)	57 (53.6, 40)	3
Second-degree AVB	520 (NA, 520)	128 (NA, 128)	12 (NA, 12)	26 (NA, 26)	1
Third-degree AVB	520 (381.9, 739)	267.3 (254.7, 257)	24 (12.7, 24)	64.5 (61.5, 64.5)	4

All antibody levels are expressed as AU. Differences in semiquantitative maternal antibody levels in pregnancies complicated by congenital heart block of any degree vs normal fetal conduction were assessed by Wilcoxon rank sum test.
AU, arbitrary unit; *AVB*, atrioventricular block; *NA*, not available.
Tunks. Predictors and prophylaxis for fetal heart block. Am J Obstet Gynecol 2013.

and did not report this intolerance to her physicians; unfortunately, complete heart block was detected 2 days later. An additional 2 subjects were referred to our institution for evaluation with a diagnosis of complete fetal heart block that developed at 20 weeks' gestation in both fetuses. There were no cases of intrauterine demise, endomyocardial fibroelastosis, or hydrops fetalis. All of the subjects carrying fetuses with complete heart block were treated with dexamethasone at a dose of 4 mg orally once daily. All of these fetuses remained in complete heart block at birth and 3 required insertion of a pacemaker in the neonatal period. All of these infants were still alive at the time of this report.

Three fetuses (9%) developed first-degree heart block in utero, with mechanical PR intervals ranging from 150-160 milliseconds. Each of these subjects was treated prophylactically with dexamethasone when prolongation of the PR interval was noted. In the case of the fetus with a mechanical PR interval of 150 milliseconds, dexamethasone was started due to an abrupt lengthening of the mechanical PR interval concurrent with an active lupus flare. Two of the 3 fetuses had regression of the mechanical PR interval to the normal range after initiation of therapy. No progression of the congenital heart block occurred throughout the pregnancy in any of the fetuses. Two of the infants had normal conduction immediately after birth and were clinically stable. One infant had continued first-degree AV block with a PR interval of 164 milliseconds by 12-lead electrocardiogram at last follow-up, but otherwise was doing well.

Interestingly, 1 fetus born to a subject with Sjögren syndrome and hypothyroidism was initially followed up for first-degree heart block, but progressed to Mobitz type 1 second-degree heart block (Wenckebach) at 19 weeks' gestation. This subject was admitted to the hospital and treated with intravenous steroids and IVIG, with fetal rhythm subsequently reverting to first-degree heart block. The subject continued oral dexamethasone throughout the remainder of the pregnancy. The fetus remained stable in first-degree AV block throughout the remainder of the pregnancy, with persistent first-degree AV block and evidence of diastolic dysfunction by echocardiogram noted after delivery and through last assessment.

Maternal autoantibodies

Maternal autoantibody level data are summarized in Table 2. Eighty percent (n = 24) of mothers had semiquantitative assessment of autoantibodies during the course of the pregnancy. In all, 96% of the laboratory samples included in this portion of the analysis were processed at our institution. Figure 1 demonstrates that subjects with pregnancies complicated by fetal heart block of any degree did not have significantly higher levels of anti-Ro antibodies (median difference, 38; $P = .94$). Maternal anti-La antibody level data are summarized in Figure 2. Ten subjects had elevated anti-La antibody levels. All of the women with elevated anti-La antibody levels also had elevated anti-Ro antibody levels. Anti-La levels were significantly higher in pregnancies affected by fetal heart block of any degree compared to those with normal fetal conduction (median difference, 227.5; $P = .04$). An OR regarding elevated maternal anti-La antibody levels and development of congenital heart block was notably elevated at 6.2, however these results did not reach statistical significance (95% CI, 0.8–81.6; $P = .07$). There were no significant relationships found between maternal levels of anti-Smith or anti-RNP antibodies and the development of fetal heart block. There was no significant difference in anti-Ro or anti-La levels when mothers receiving antiinflammatory medications and the untreated group were compared. Two subjects, one carrying a fetus with complete heart block and the other with normal fetal conduction, also had significantly elevated antibody levels. These subjects were not included in the analysis due to the results being reported in different units of measurement that could not be accurately converted. Two subjects did not have quantitative antibody level data available, so they also were not included in this portion of the analysis.

Maternal therapy with antiinflammatory agents

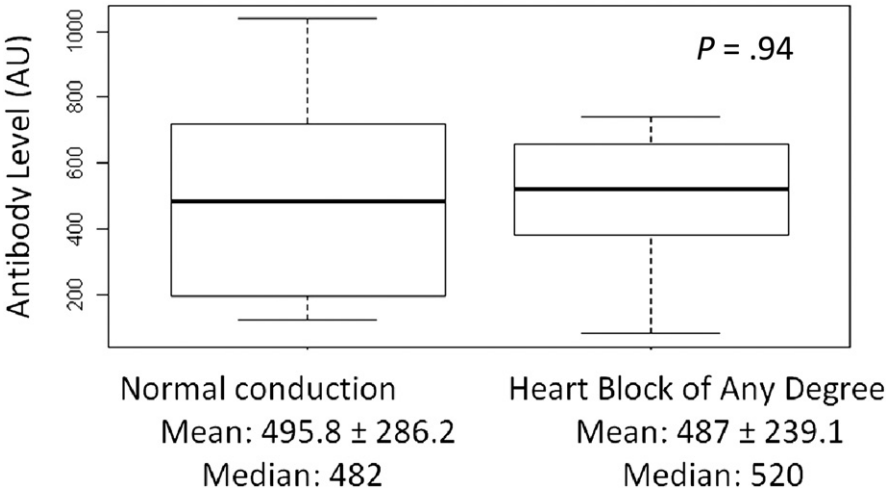
Results regarding maternal therapy with antiinflammatory agents throughout pregnancy are summarized in Tables 3 and 4. Of the cohort who received hydroxychloroquine, 86% initiated this medication prior to pregnancy. Additionally, 1 mother was taking hydroxychloroquine when she established care at

our institution at 16 weeks' gestation, however, the specific medication start date could not be confirmed in our medical record. One subject who was chronically maintained on hydroxychloroquine self-discontinued her medication when she learned of the pregnancy; this therapy was subsequently resumed at 16 weeks' gestation. Prednisone was also started prior to pregnancy in all but 1 of the treated subjects. Notably, 94% of the fetuses (n = 15) born to subjects treated with either hydroxychloroquine or low-dose oral prednisone throughout pregnancy maintained normal conduction, compared to only 59% in the untreated group (OR, 0.1; 95% CI, 0.002–0.98; P = .04). When maternal therapy with hydroxychloroquine alone was considered, 93% of subjects treated (n = 13) had fetuses maintaining normal conduction throughout the pregnancy, compared to 63% in the untreated group (OR, 0.14; 95% CI, 0.002–1.35; P = .09). Notably, none of the subjects with pregnancies complicated by complete fetal heart block received antiinflammatory therapy prior to the diagnosis of complete heart block.

Comment

The results of this study suggest that maternal therapy with antiinflammatory agents throughout pregnancy may provide a protective effect against the development of congenital heart block. Once complete fetal heart block develops, it is irreversible and leads to significant morbidity and potential mortality for the infant.[15-17] It has been demonstrated that the fetal rhythm can rapidly and dramatically change from normal AV conduction to complete heart block in a matter of days.[18] The significant morbidity and mortality associated with congenital heart block and the rapidity with which it can develop in utero makes this both a challenging and important problem. With no surrogate predictors of fetal heart block available to date, cardiologists routinely use echocardiography to monitor the fetal rhythm throughout the pregnancy. However, the PR Interval and Dexamethasone Evaluation (PRIDE) trial[8] and recent work by Jaeggi et al[9] demonstrated that fetal AV prolongation did not necessarily precede more advanced heart block. Given this, the appropriate screening strategy for at-risk fetuses remains poorly defined. Furthermore, many management strategies to prevent congenital heart block, primarily targeted at reducing the fetal inflammatory response induced by maternal autoantibodies, have been largely unsuccessful. Routine maternal therapy with fluorinated corticosteroids such as dexamethasone or betamethasone is not currently recommended due to significant side effects, including intrauterine growth restriction, oligohydramnios, infant adrenal suppression, and learning disabilities.[19,20] The 2010 Preventive IVIG Therapy for Congenital Heart Block (PITCH) trial concluded that prophylactic maternal treatment with low-dose IVIG every 3 weeks from 12-24 weeks' gestation was not effective in pre-

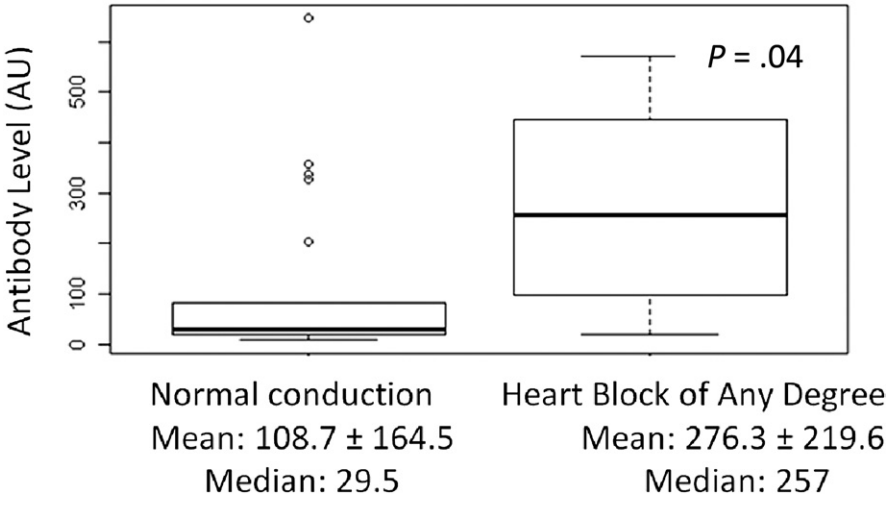
FIGURE 1
Anti-Ro level: normal conduction vs fetal heart rate block of any degree



AU, arbitrary unit.

Tunks. Predictors and prophylaxis for fetal heart block. Am J Obstet Gynecol 2013.

FIGURE 2
Anti-La level: normal conduction vs fetal heart rate block of any degree



AU, arbitrary unit.

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TABLE 3
Proportion of mothers treated with either hydroxychloroquine or daily prednisone and incidence of congenital heart block

	Heart block	Normal conduction	Total
Antiinflammatory therapy	1	15	16
No antiinflammatory therapy	7	10	17
Total	8	25	33

Proportional data were assessed using Fisher exact test.

Tunks. Predictors and prophylaxis for fetal heart block. Am J Obstet Gynecol 2013.

venting complete fetal heart block or in reducing maternal antibody titers.[14]

Hydroxychloroquine, now commonly used in the management of rheumatic diseases such as systemic lupus erythematosus and rheumatoid arthritis, has an immunomodulatory effect that has been well documented to decrease inflammation.[21] Studies demonstrate that hydroxychloroquine readily crosses the placenta, with approximately equal concentrations found in maternal and cord blood samples.[22] While currently labeled a Pregnancy Class C medication, hydroxychloroquine is believed to be safe for use throughout pregnancy to treat lupus flares, with no increased incidence of pregnancy loss, prematurity, congenital anomalies, or other fetal toxicities.[23] Our study corroborates the recent work by Izmirly et al[12,13] that demonstrated a lower incidence of cardiac complications in fetuses born to mothers who were treated with hydroxychloroquine. However, to our knowledge, no prospective studies confirming the efficacy of using this medication as a prophylactic agent for congenital heart block have been completed.

Prior studies have found that prednisone is largely metabolized to inactive metabolites prior to crossing the placenta and may be of questionable benefit in decreasing an inflammatory process in the fetus. However, it has been suggested in case reports that prednisone lowers maternal autoantibody antibody burden.[20,24] Given the theoretical benefit of a lower anti-Ro antibody exposure to the fetus leading to a less robust fetal inflammatory response, we also believe the use of low-dose, daily prednisone in pregnant women with significant rheumatologic disease warrants further investigation.

While recent data concluded that the quantitative amount of anti-Ro antibodies is correlated to the risk of cardiac complications, this was not seen in our cohort.[5] However, our study may have underestimated this association due to a significant portion of the cohort being treated with antiinflammatory agents. Studies to date assessing the role of anti-La antibodies in the pathogenesis of fetal heart block are controversial. Smaller studies demonstrated that anti-La antibodies have enhanced binding to laminin, a key component of the sarcolemmal membrane, which suggests that anti-La antibodies may be important in the development of fetal heart block.[25] However, a recent prospective cohort study by Jaeggi et al[5] concluded that cardiac complications are associated with moderate to high anti-Ro antibody levels, irrespective of anti-La antibody level. Our data suggest that elevated anti-La levels, particularly when seen in combination with high levels of anti-Ro antibody, may be a significant marker of fetal heart block. We therefore suggest further investigation to confirm semiquantitative anti-La antibody level as a reliable marker for fetal heart block. The development of such a surrogate predictor of fetal heart block would be a major advancement in the care of this patient population.

Our study is limited by its retrospective design and relatively small sample size that was obtained from a single center. The sample size precluded our ability to investigate for interaction between maternal autoantibody levels and antiinflammatory therapy. Because the quantification of autoantibody levels is not standardized across medical centers, we excluded 2 patients whose laboratory samples were drawn at outside facilities from this portion of the analysis. Anti-Ro levels from both subjects, one in a pregnancy complicated by complete heart block and the other with normal fetal conduction, were elevated relative to the reference range provided by the laboratory responsible for processing the samples. It is unclear how these data would have affected our results. However, subject medication information was available for both of these subjects, which permitted inclusion in the effect of medication portion of our analysis.

In conclusion, our data suggest that prophylactic treatment with either hydroxychloroquine or daily low-dose prednisone may provide a protective effect regarding development of congenital heart block. Future clinical trials are needed to confirm this potential benefit. Pregnancies complicated by fetal heart block did not have a significantly higher level of maternal anti-Ro antibodies in our cohort, but this may have been mitigated by maternal therapy with antiinflammatory medications. Our study suggests that an elevated anti-La antibody

TABLE 4
Proportion of mothers treated with hydroxychloroquine and incidence of congenital heart block

Variable	Heart block	Normal conduction	Total
Hydroxychloroquine	1	13	14
No hydroxychloroquine	7	12	19
Total	8	25	33

Proportional data were assessed using Fisher exact test.

Tunks. Predictors and prophylaxis for fetal heart block. Am J Obstet Gynecol 2013.

level may be an important marker of fetal heart block. ■

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