Maternal and Fetal Factors Associated With Mortality and Morbidity in a Multi–Racial/Ethnic Registry of Anti-SSA/Ro–Associated Cardiac Neonatal Lupus

Peter M. Izmirly, MD; Amit Saxena, MD; Mimi Y. Kim, ScD; Dan Wang, MS; Sara K. Sahl, MPH; Carolina Llanos, MD; Deborah Friedman, MD; Jill P. Buyon, MD

Background—Cardiac manifestations of neonatal lupus include conduction disease and, rarely, an isolated cardiomyopathy. This study was initiated to determine the mortality and morbidity of cardiac neonatal lupus and associated risk factors in a multi–racial/ethnic US-based registry to provide insights into the pathogenesis of antibody-mediated injury and data for counseling.

Methods and Results—Three hundred twenty-five offspring exposed to maternal anti-SSA/Ro antibodies with cardiac neonatal lupus met entry criteria. Maternal, fetal echocardiographic, and neonatal risk factors were assessed for association with mortality. Fifty-seven (17.5%) died, 30% in utero. The probability of in utero death was 6%. The cumulative probability of survival at 10 years for a child born alive was 86%. Fetal echocardiographic risk factors associated with increased mortality in a multivariable analysis of all cases included hydrops and endocardial fibroelastosis. Significant predictors of in utero death were hydrops and earlier diagnosis, and of postnatal death were hydrops, endocardial fibroelastosis, and lower ventricular rate. Isolated heart block was associated with a 7.8% case fatality rate, whereas the concomitant presence of dilated cardiomyopathy or endocardial fibroelastosis quadrupled the case fatality rate. There was a significantly higher case fatality rate in minorities compared with whites, who were at a lower risk of hydrops and endocardial fibroelastosis. Pacing was required in 70%; cardiac transplantation was required in 4 children.

Conclusion—Nearly one fifth of fetuses who develop cardiac neonatal lupus die of complications predicted by echocardiographic abnormalities consistent with antibody-associated disease beyond the atrioventricular node. The disparity in outcomes observed between minorities and whites warrants further investigation. **(*Circulation*. 2011; 124:1927-1935.)**

Key Words: antibodies ■ cardiomyopathy ■ heart block ■ morbidity ■ mortality

Neonatal lupus (NL), initially described in the late 1970s, represents a pathological readout of passively acquired autoimmunity.[1–4] Identification of advanced fetal heart block in the absence of structural abnormalities predicts the presence of maternal autoantibody responses against the ribonucleoproteins SSA/Ro and SSB/La in >85% of cases.[5] Of the affected offspring, 10% to 15% will have a life-threatening cardiomyopathy, occasionally without associated conduction disease.[6–9] Prospective studies of pregnancies in women with the candidate antibodies have estimated the risk of cardiac NL at ≈2% if the mother has had no previously affected pregnancies.[10–13] Recurrence rates in subsequent pregnancies are approximately 8- to 9-fold this risk.[14–19] In addition, the occurrence rate of cardiac NL after a child with cutaneous NL is ≈6-fold higher.[20] Maternal health status does not appear to be a contributing factor to the risk of having a child with cardiac NL, but the relationship to severity of disease has not been addressed.[14,21]

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Available data on estimates of the morbidity and mortality associated with cardiac NL have been derived from several groups in different countries, spanning 2 decades.[5,14,15,22–25] These studies differ in cohort size, ranging from 55 fetuses[14] to 175 fetuses.[25] The overall case fatality rates range from 11%[22] to 29%.[5] The percentages of children receiving pacemakers vary from 63%[15] to 93%.[22] However, these studies did not uniformly require the presence of maternal anti-SSA/Ro or SSB/La antibodies as an inclusion criterion. For several studies, up to 40% of the cases included were not

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From the Division of Rheumatology, Department of Medicine, New York University School of Medicine, New York (P.M.I., A.S., S.K.S., J.P.B.); Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY (M.Y.K., D.W.); Department of Clinical Immunology and Rheumatology, Pontificia Universidad Catolica de Chile; Santiago, Chile (C.L.); and Division of Pediatric Cardiology, New York Medical College, Valhalla (D.F.).

Correspondence to Peter M. Izmirly, MD, NYU School of Medicine, TH-407, New York, NY 10016. E-mail Peter.Izmirly@nyumc.org

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associated with maternal antibodies.[5,22–24] Recognizing that heart block may have different origins, this latter point is relevant because conclusions may have been drawn on distinct nosologic conditions. Moreover, these studies do not provide maternal racial/ethnic breakdowns, which could affect outcomes.

Accordingly, this study was initiated to determine the mortality and morbidity of cardiac NL in a large US-based cohort inclusive of different racial/ethnic backgrounds in which cardiac phenotype is well defined and exposure to maternal anti-SSA/Ro and/or anti-SSB/La is universal. It is anticipated that these data and any identified risk factors will have a significant impact on physician counseling and ultimate decision making by parents prospectively facing cardiac NL or who have an affected offspring.

Methods

Study Population

Cardiac NL cases were identified from the Research Registry for Neonatal Lupus (RRNL), which was established in 1994. Evaluation of deidentified information was approved by the Institutional Review Board of the New York University School of Medicine. Enrollment of a family in the RRNL requires verification of maternal anti-SSA/Ro or SSB/La antibodies (with the exception of anti-RNP antibodies in mothers of children with cutaneous NL) and documentation that at least 1 child has NL. The affected children were born between January 1963 and April 2010.

Inclusion/Exclusion Criteria

Three hundred twenty-five children met the following inclusion criteria: enrollment in the RRNL by September 30, 2010; documentation of maternal antibodies reactive with SSA/Ro and/or SSB/La (based on results from a commercial or hospital laboratory or performed in the research laboratory of J.P.B.); confirmation of cardiac NL, defined here as the presence of high-grade heart block (second or third degree) documented by ECG or echocardiogram, history of pacemaker, or statement in the medical record; and/or presence of cardiac injury or cardiomyopathy, which specifically included evidence of a mononuclear infiltrate in the endocardium, myocardium, and pericardium, endocardial fibroelastosis (EFE), and/or dilated cardiac chambers with evidence of decreased cardiac output on echocardiogram. Children born with isolated first-degree heart block (n=8) or isolated sinus bradycardia (n=2) were excluded from this study given the low likelihood of death or requirement of a pacemaker.

Study Design and Data Collection

This retrospective study analysis was based on review of medical records in the RRNL. The date of death and cause of the death were recorded. Maternal risk factors analyzed included mother's age at time of birth, mother's race/ethnicity, and maternal health status as assessed by rheumatologists' notes in the charts. Maternal use of nonfluorinated steroids, fluorinated steroids, β-agonists such as terbutaline, and hydroxychloroquine during pregnancy was also noted. Neonatal risk factors analyzed included the presence of associated cutaneous NL (described as annular or elliptical lesions on the face, scalp, trunk, or extremities and verified by medical records, biopsy results, and/or photographs[20]), the presence of hepatic and/or hematologic laboratory abnormalities, which may be attributed to anti-SSA/SSB antibodies,[26] sex, date of birth, gestational age at diagnosis and delivery, and method of delivery. In addition, the presence of carditis was also noted and defined as follows: presence of mononuclear infiltrate on the histological preparation of the fetal endocardium, myocardium, or pericardium from an autopsy or cardiac biopsy. Fetal echocardiographic parameters analyzed included ventricular rate at detection and lowest documented ventricular rate. The presence of EFE was identified when there were abnormal areas of echogenicity on the endocardial surface of the cardiac chambers and/or valve leaflets on echocardiogram or endocardial fibrosis on biopsy or autopsy. Dilated cardiomyopathy (DCM) was defined as increased size of the left ventricle or multiple chambers in the absence of chamber wall hypertrophy with associated decreased contractility on echocardiogram. Hydrops fetalis was defined as an abnormal accumulation of fluid in at least 2 fetal compartments, including subcutaneous tissue, pleura, pericardium, or the abdominal cavity. Identification of valvular disease was based on in utero or neonatal echocardiography demonstrating moderate to severe stenosis and/or regurgitation involving the aortic, mitral, or pulmonic valves (Tricuspid regurgitation was excluded because of its functional relationship with the underlying cardiac disease). In addition, the presence of an atrial septal defect, ventricular septal defect, or patent ductus arteriosus was also noted if they were identified on an echocardiogram >28 days after birth or required surgical intervention. Morbidity assessments included whether the child received a pacemaker and the timing of initial placement, as well as information on cardiac transplantation.

Maternal Antibody Testing

Maternal antibody status was established at either the New York University School of Medicine Immunology Laboratory or another Clinical Laboratory Improvement Amendments-approved outside laboratory. However, 80% of the antibody testing was done at New York University because the RRNL strongly encourages the collection of blood samples for research purposes. In addition, received samples were tested for anti-Ro52 antibodies in the laboratory of the senior author (J.P.B.) by ELISA using recombinant protein as previously described.[27]

Statistical Analysis

Survival distributions for mortality were estimated by the Kaplan-Meier method using approximate weeks since conception as the time scale for deaths that occurred in utero and years after a live birth in the live analysis. The distribution of time to pacemaker implantation was estimated, taking into account death as a competing risk event.[28] To identify potential risk factors for mortality and to estimate corresponding HRs, the method of Lee et al[29] for clustered survival data was applied to account for the correlation in data among multiple offspring from the same mother. Multivariable models were fit using a backward elimination approach based on an initial model that included all covariates that were significant at the $P<0.20$ level in bivariate analyses. Separate survival analyses were also performed on deaths that occurred in utero versus after a live birth. For the former, gestational age was used as the time scale, and neonates born alive were censored at the time of birth. For the analysis of deaths after a live birth, weeks since birth (ie, age in weeks) was used as the time scale, and only live births were included in the analysis. Two-sided values of $P<0.05$ were considered statistically significant.

Results

Patient Demographics

A total of 325 children from 297 mothers met the final inclusion criteria. Twenty-one (6.5%) had second-degree heart block, 257 (79.1%) had third-degree heart block, and 34 (10.5%) had periods of both second- and third-degree heart block. In addition, 8 (2.5%) had an isolated cardiomyopathy, and 5 (1.5%) had a cardiomyopathy associated with first-degree heart block. Of 13 second-degree heart block cases exposed to dexamethasone in utero, 4 reversed to first-degree heart block or normal sinus rhythm, and only 3 required permanent pacemaker placement. Of 8 second-degree heart block cases not exposed to dexamethasone in utero, 1 reverted spontaneously and 4 required pacemakers.

The maternal demographics, health status, and antibody status are listed in Table 1. The majority of mothers were

Table 1. Maternal Demographics

Race/ethnicity (n=297), n (%)	
White	223 (75.1)
Black	27 (9.1)
Hispanic	26 (8.8)
Asian	14 (4.7)
Mixed	7 (2.4)
Diagnosis at time of pregnancy (n=325), n (%)	
Asymptomatic/UAS	176 (54.2)
SLE	45 (13.8)
SS	75 (23.1)
SLE/SS	29 (8.9)
Maternal antibody status, n (%)	
Anti-SSA/Ro antibody (n=297)	297 (100)
Anti-SSB/La antibody (n=294)	189 (64.3)
Anti–52-kDa Ro antibody (n=250)	227 (90.8)

UAS indicates undifferentiated autoimmune syndrome; SLE, systemic lupus erythematosus; and SS, Sjögren's syndrome. Maternal health status was defined at the time of each pregnancy. Because 325 cases came from 297 mothers, the health status of the mother may have progressed from 1 pregnancy to a subsequent pregnancy; thus, maternal diagnoses at the time of pregnancy for all 325 offspring are included. The race/ethnicity and antibody status were only included once.

white (75.1%). Overall, most mothers either were asymptomatic or had insufficient symptoms for a formal diagnosis of either systemic lupus erythematosus (SLE) or Sjögren's syndrome (SS) at the time of pregnancy. Thus, for many of these women, anti-SSA/Ro and/or anti-SSB/La antibodies were first identified only after the diagnosis of cardiac NL in the fetus. Antibodies to SSA/Ro occurred in 100%, and SSB/La antibodies accompanied the anti-SSA/Ro response in 64.3%. In addition, of 250 mothers in whom the anti–52-kDa Ro antibody status was tested, 227 (90.8%) were positive.

Case Fatality Rate and Cause of Death

Overall, there were 57 deaths (17.5%) among the 325 children with cardiac NL. Eighteen fetuses died in utero, the majority before 30 weeks of gestation (Figure 1A). At 35 weeks of gestation, 251 (77.7%) fetuses with cardiac NL were alive in utero. The probability of dying in utero was 6%. Of 307 children (251 plus 56 delivered before 35 weeks of gestational age) born alive, 39 died after birth with the majority occurring before 1 year postpartum (Figure 1B). The cumulative probability of survival at 10 years for a child born alive was 86% (n=114).

The cause of the 57 cardiac neonatal deaths was considered primarily cardiac related in 40 (70.2%). Of these 40, 37 were complications of a cardiomyopathy, 1 was a transplant rejection, and 2 were secondary to pacemaker complications. In 4 cases (7.0%), the pregnancy was electively terminated after identification of hydrops. Infection was considered the primary cause of death in 5 (8.8%), with respiratory syncytial virus accounting for 3 and bacterial pneumonia and sepsis accounting for the remaining 2. In 8 cases (14.0%), medical records were insufficient to determine the cause of death (Table 2).

Maternal and Fetal Echocardiographic and Neonatal Risk Factors Associated With Mortality

Table 3 displays the results of the bivariate analysis of maternal, neonatal, and fetal echocardiographic data variables and risk of death occurring both in utero and after birth, as well as the overall risk of death and the associated hazard ratios (HRs) for all pregnancies. In the overall analysis, whites were less likely to die (HR=0.47; P=0.005). In addition, there was a trend toward increased mortality in those offspring whose mothers had an established diagnosis of SLE and/or SS at the time of pregnancy (HR=1.57; P=0.095) and the presence of anti-SSB/La antibody (HR=1.68; P=0.093). The presence of carditis was associated with an increase in mortality (HR=8.40; P<0.0001). Several fetal echocardiographic risk factors were associated with a statistically significant increase in mortality, including the presence of hydrops (HR=15.37; P=<0.0001), DCM (HR=6.65; P<0.0001), EFE (HR=6.45; P<0.0001), and the presence of valvular diseases (HR=4.50; P=0.0001). A higher ventricular nadir rate was protective (HR=0.95; P=0.003). In a multivariable analysis using Cox models, the only significant overall predictors of mortality were hydrops (HR=15.1; P<0.0001), the presence of carditis (HR=4.60; P<0.0002), EFE (HR=3.69; P<0.0001), and maternal diagnosis of SLE and/or SS (HR=3.44; P=0.0001).

Separate bivariate analyses were performed, and the respective HRs of fetuses dying in utero and those born alive are reported in Table 3. For the in utero deaths, several variables were significantly associated with an increased mortality in bivariate analyses: hydrops (HR=26.60; P=<0.0001), the presence of carditis (HR=6.62; P=0.0006), DCM (HR=6.49; P=0.0004), a more recent year of pregnancy (HR=1.09; P=0.0042), and use of fluorinated steroids (HR=3.95; P=0.02). Trends were also seen for an increased mortality with the presence of EFE (HR=3.06; P=0.06) and the use of terbutaline (HR=2.48; P=0.07). In contrast, a later gestational age at initial detection of cardiac NL (HR=0.86; P=0.007) was protective. In a multivariable analysis using Cox models, the only significant predictors of mortality for in utero deaths were hydrops (HR=29.67; P<0.0001), the presence of carditis (HR=8.66; P<0.0001), a more recent year of pregnancy (HR=1.10; P=0.01), and a later gestational age at diagnosis of cardiac NL (HR=0.80; P=0.02).

For those children who died after birth, the following variables were significantly associated with an increased mortality in bivariate analyses: hydrops (HR=12.21; P<0.0001), the presence of carditis (HR=10.38; P<0.0001), EFE (HR=9.91; P<0.0001), DCM (HR=6.80; P<0.0001), the presence of associated hepatic/hematologic abnormalities (HR=4.47; P<0.0001), valvular disease (HR=6.21; P=0.0002), and preterm delivery (HR=3.18; P=0.0005). In addition, there was a trend toward increased mortality in those patients whose mother had an established diagnosis of SLE and/or SS at the time of pregnancy (HR=1.78; P=0.081). There was a significantly decreased risk for mortality in whites compared with minorities in analyses of deaths occurring after birth (HR=0.45; P=0.014). A higher ventricular nadir rate (HR=0.92; P<0.0001) and later week of delivery (HR=0.78; P<0.0001) were protective. In a

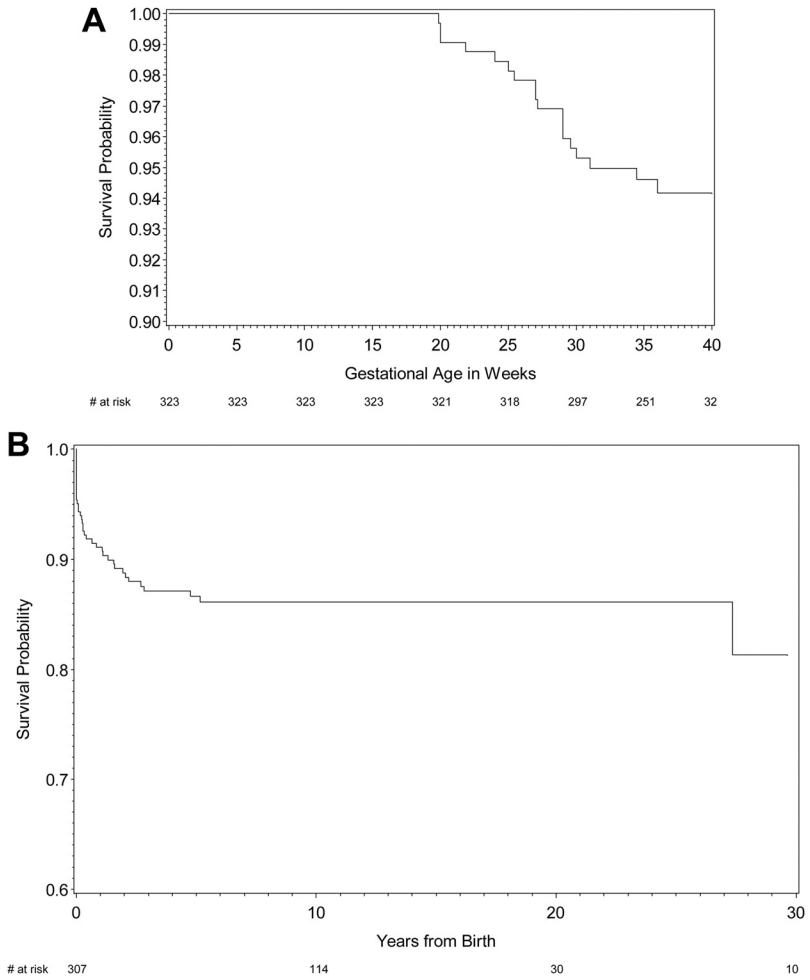

Figure 1. A, Kaplan-Meier survival estimates of fetal cardiac neonatal lupus (NL) in utero. Of note, the exact gestational age at birth was unknown for 2 cases, which were excluded from the analysis. The *x* axis represents the number of cases at the corresponding gestational age. **B**, Kaplan-Meier survival estimates of children with cardiac NL born alive.

multivariable analysis of predictors in offspring born alive using Cox models, the only significant predictors of mortality were hydrops (HR=7.83; $P=0.0007$), EFE (HR=17.31; $P<0.0001$), and a maternal diagnosis of SLE and/or SS at the time of pregnancy (HR=2.85; $P=0.02$). A higher ventricular nadir rate was protective (HR=0.94; $P<0.0001$). There was a trend toward a later week of delivery (HR=0.88; $P=0.06$) associating with a decrease in mortality.

Table 4 displays the case fatality rates for various cardiac NL manifestations. Overall, isolated advanced congenital heart block was associated with a 7.8% (15 of 193) case fatality rate, whereas the concomitant presence of DCM or EFE more than quadrupled the case fatality rate.

Higher Case Fatality Rate Among Nonwhite Mothers

Table 5 shows the case fatality rate stratified by race/ethnicity. Specifically, 14.3% of children with cardiac NL born to white mothers died compared with a case fatality rate of 32.1% observed for black mothers, 25.0% for Hispanic mothers, 26.7% for Asian mothers, and 22.2% for mixed-race mothers. There was a significantly higher case fatality rate in minorities compared with whites in the overall group and for the children who died after birth, but not for fetuses dying in utero. Although the association of race/ethnicity and mortality was not maintained in multivariable analyses, white fetuses were at lower risk of hydrops ($P=0.05$), EFE ($P=0.05$), and carditis ($P=0.03$), variables highly predictive of mortality.

Morbidity Associated With Cardiac NL

Represented in Figure 2 is the cumulative probability of pacemaker implantation after a live birth. By 1 year, ≈50% of the patients were paced, the majority occurring in the first month of life. At 10 years, the cumulative probability of

Table 2. Cause of Cardiac Neonatal Lupus Death

Outcome (n=57)	n (%)
Cardiac related	40 (70.2)
Cardiomyopathy (hydrops/EFE/DCM)	37
Transplant rejection	1
Complications from pacemaker	2
Infectious complications	5 (8.8)
RSV	3
Pneumonia/sepsis	2
Unknown	8 (14.0)
Elective pregnancy termination with evidence of hydrops on echocardiography	4 (7.0)

EFE indicates endocardial fibroelastosis; DCM, dilated cardiomyopathy; and RSV, respiratory syncytial virus.

Table 3. Maternal, Fetal Echocardiographic, and Neonatal Mortality Risk Factors

	Cardiac NL Pregnancies (n=325)				
	Deceased (n=57)	Living (n=268)	HR Overall	HR IU	HR AB
Maternal risk factors					
Maternal age (mean) (n=325), y*	29.5 (57)	29.8 (268)	1.00 (0.95–1.05)	1.03 (0.95–1.11)	0.99 (0.92–1.06)
White (n=325), % (n)	61.4 (57)	78.4 (268)	0.47¶ (0.27–0.80)	0.49 (0.18–1.29)	0.45¶ (0.24–8.85)
Maternal anti-La (n=322), % (n)	75.4 (57)	63.8 (265)	1.68‖ (0.92–3.08)	1.37 (0.48–3.90)	1.85 (0.87–3.90)
Maternal anti–52-kDa Ro (n=275), % (n)	89.4 (47)	91.7 (228)	0.90 (0.38–2.14)	ND†	0.59 (0.24–1.44)
Maternal diagnosis of SLE or SS (n=325), % (n)	56.1 (57)	43.7 (268)	1.57‖ (0.92–2.67)	1.18 (0.45–3.09)	1.78‖ (0.93–3.39)
Nonfluorinated steroids (n=313), % (n)	23.2 (56)	14.8 (257)	1.63 (0.88–3.02)	1.66 (0.53–5.21)	1.58 (0.76–3.28)
Fluorinated steroids (n=318), % (n)	50.9 (57)	47.1 (261)	1.27 (0.75–2.18)	3.95¶ (1.26–12.38)	0.81 (0.42–1.56)
Terbutaline (n=314), % (n)	18.9 (53)	15.3 (261)	1.36 (0.69–2.67)	2.48‖ (0.93–6.67)	0.95 (0.37–2.41)
Hydroxychloroquine (n=318), % (n)‡	1.8 (57)	3.4 (261)	ND	ND	ND
Neonatal risk factors					
Female sex (n=323), % (n)	52.7 (55)	56.0 (268)	1.04 (0.62–1.75)	0.81 (0.33–1.96)	1.16 (0.61–2.20)
Associated NL rash (n=323), % (n)§	14.3 (35)	14.1 (256)	NA	NA	0.96 (0.37–2.47)
Associated liver/heme NL (n=290), % (n)§	30.6 (36)	7.1 (254)	NA	NA	4.47# (2.15–9.32)
Carditis (n=251), % (n)	31.0 (41)	2.4 (209)	8.40# (4.49–15.72)	6.62# (2.25–19.48)	10.38# (4.73–22.78)
Gestational age at detection (n=321), wk	24.8 (56)	26.9 (265)	0.98 (0.95–1.01)	0.86¶ (0.77–0.96)	0.99 (0.97–1.01)
Delivery by cesarean section (n=297), n (%)§	79.5 (39)	78.7 (258)	NA	NA	1.31 (0.58–2.95)
Preterm delivery (<37 wk) (n=307)§	70.0 (40)	41.2 (267)	NA	NA	3.18# (1.66–6.10)
Gestational week of delivery (n=306)§	34.1 (40)	36.9 (266)	NA	NA	0.78 (0.71–0.85)
Year of birth (n=325)*	1996	1997	1.01 (0.98–1.04)	1.09¶ (1.03–1.16)	0.98 (95–1.01)
Fetal echocardiographic risk factors					
Atrial rate nadir (n=178), bpm	128.6 (28)	125.7 (150)	1.01 (0.98–1.04)	1.00 (0.96–1.04)	1.02 (0.99–1.06)
Ventricular rate at detection (n=196), bpm	62.5 (36)	65.0 (160)	0.99 (0.96–1.02)	0.99 (0.96–1.03)	0.99 (0.95–1.03)
Ventricular rate at nadir (n=222), bpm	46.3 (38)	53.7 (184)	0.95¶ (0.92–0.98)	1.00 (0.93–1.07)	0.92# (0.89–0.94)
Endocardial fibroelastosis (n=254), % (n)	32.6 (43)	6.2 (211)	6.45# (3.3–12.61)	3.06‖ (0.97–9.63)	9.91# (4.43–22.17)
Dilated cardiomyopathy (n=257), % (n)	53.3 (45)	9.9 (212)	6.65# (3.70–11.95)	6.49# (2.33–18.11)	6.80# (3.37–13.70)
Hydrops (n=257), % (n)	57.4 (47)	4.8 (210)	15.37# (8.36–28.24)	26.60# (8.04–87.82)	12.21# (5.88–25.36)
Valvular disease (n=255), % (n)	17.8 (45)	2.9 (210)	4.50# (2.10–9.63)	2.46 (0.55–11.06)	6.21# (2.36–16.39)
Atrial septal defect (n=221), % (n)§	12.5 (16)	8.8 (205)	NA	NA	1.40 (0.32–6.21)
Ventricular septal defect (n=224), % (n)‡	0.0 (16)	3.4 (208)	ND	ND	ND
Patent ductus arteriosus (n=221), % (n)§	11.8 (17)	6.9 (204)	NA	NA	1.72 (0.38–7.72)

NL indicates neonatal lupus; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; ND, not done; NA, not applicable. The hazard ratios (HRs) for the overall evaluation, in utero evaluation (HR IU), and after-birth evaluation (HR AB) are reported with their respective 95% confidence intervals. Numbers with each variable denote the number of patients for whom the variable was available for analysis. Parentheses adjacent to the percentages denote the number of patients among those alive or dead who had the parameter available for evaluation.

*HR calculated per increase in maternal age or year of birth.

†Analysis was considered unreliable secondary to all the deaths occurring in the anti–52-kDa Ro–positive patients and none in the anti–52-kDa Ro–negative patients.

‡Hydroxychloroquine and ventricular septal defect were uncommon; therefore, statistical analysis for these variables was considered unreliable and was not done.

§Variable evaluated only in live births.

‖$P<0.10$.

¶$P<0.05$.

#$P<0.001$.

requiring a pacemaker was ≈70%. Two fetuses were paced in utero but died shortly after birth. Additionally, 4 children received a cardiac transplantation, one of whom required 2 transplantations.

Discussion

In this large US-based registry of cardiac NL restricted to maternal anti-SSA/Ro exposure, there were 57 deaths (17.5%), with approximately one third of these offspring

Table 4. Case Fatality Rate Among Manifestations of Cardiac Neonatal Lupus

n	Advanced Block	EFE	DCM	Mortality, n (%)
193	+	−	−	15 (7.8)
12	+	+	−	5 (41.7)
30	+	−	+	11 (36.7)
9	+	+	+	9 (100)
6	−	+	−	0 (0)
6	−	−	+	4 (66.7)
0	−	+	+	NA

EFE indicates endocardial fibroelastosis; DCM, dilated cardiomyopathy; n, number of cases with available echocardiographic data; and +, presence and −, absence of each respective manifestation. Advanced block is second- or third-degree heart block.

dying in utero. There was a significantly higher case fatality rate in minorities compared with whites. In addition, there was a trend toward increased mortality in children of mothers who had an established diagnosis of SLE and/or SS at the time of pregnancy that became significant in the multivariable analysis. Several fetal echocardiographic risk factors were associated with a statistically significant increase in mortality: the presence of hydrops, DCM, EFE, and valvular dysfunction. A higher ventricular nadir rate was protective. In multivariable analysis, the only significant echocardiographic predictors of mortality were hydrops and EFE. Separate analyses on fetuses dying in utero and children dying after birth revealed similar echocardiographic predictors of mortality.

In the analyses limited to in utero deaths, predictors of mortality, in addition to those identified by echocardiogram, included earlier gestational age at the time cardiac NL was first detected. This finding suggests that earlier injury results in more extensive damage to the cardiac structures. If an earlier event targets the majority of the fetal heart, it may result in a more severe lesion, such as cardiomyopathy. In a later event in which the exposed and vulnerable targets are restricted to the isolated conduction system tissues, the insult may not be lethal. The association of in utero death with more recent year of pregnancy, although modest, was initially counterintuitive. This may reflect increased awareness of anti-SSA/Ro–attributed cardiac disease that might otherwise have been categorized as an unexplained fetal demise. Additional predictors of in utero mortality included the use of fluorinated steroids and/or terbutaline. Each of these medications is generally prescribed in more severe cases, which is the likely reason for their association with mortality rather than direct causality. In the analysis limited to children who died after birth, as expected, preterm delivery was associated with an increased mortality. A later week of delivery and a higher ventricular nadir rate were protective, the latter remaining in the multivariable analysis of predictors for mortality in live-born children.

Table 5. Case Fatality by Race/Ethnicity

White (n=245), n (%)	Black (n=28), n (%)	Hispanic (n=28), n (%)	Asian (n=15), n (%)	Other (n=9), n (%)
35 (14.3)	9 (32.1)	7 (25.0)	4 (26.7)	2 (22.2)

Other includes American Indian and mixed-race mothers.

With regard to morbidity, pacemakers were required in the majority of children, with most paced in the neonatal period. Pacemaker placement was not associated with mortality in the overall analysis or live birth analysis, suggesting that pacemaker-induced cardiomyopathy may not be a common cause of mortality in this cohort.

Previous data on risk factors associated with mortality, although available, are limited by the heterogeneity of the cohorts, because not all children have documented exposure to maternal anti–SSA/Ro-SSB/La antibodies. Moreover, most reports reflect cases seen at tertiary medical centers; thus, data may be skewed toward the sickest patients. Impaired left ventricular function has been a common denominator associated with poor prognosis. In a study based in France, all 6 deaths in anti-SSA/Ro–exposed children with congenital heart block were associated with DCM.[22] In an earlier US-based multicenter case series of congenital heart block, the development of cardiomyopathy after birth occurred in 16 fetuses; 4 died and 6 required transplantation.[6] Antibodies were confirmed in 10 mothers. Recently, data from the Association for European Pediatric Cardiology identified impaired left ventricular function to be associated with mortality in 162 children with congenital heart block, of whom 80% were exposed to anti-SSA/SSB antibodies.[25] In our cohort, approximately half the patients with DCM died.

In recent years, EFE has emerged not only as an extension of the cardiac pathogenicity associated with anti-SSA/Ro, but also as a risk factor predicting mortality. Data from the RRNL confirm and extend these earlier observations in that half the patients with EFE died. Jaeggi et al[23] initially demonstrated the poor prognostic significance of EFE in 5 patients. In another study of 13 patients with congenital heart block exposed to anti-SSA/Ro antibodies who developed EFE, 11 (85%) either died or underwent cardiac transplantation.[7] Emphasizing the injurious effect of anti-SSA/Ro on the endocardium per se, 2 fetuses with EFE absent any conduction abnormalities died, and 1 child with isolated EFE received a transplant.[8] However, the severity of EFE was not confirmed in a recent case series of 5 children with isolated EFE in which 4 children were alive at 4 years, 3 of whom had normal heart function.[9] In another study comprising 20 cases of anti-SSA–associated EFE, an 80% survival rate at a median follow-up of 3 years was observed in those treated with intravenous immunoglobulin and steroids at the time of diagnosis.[30]

A novel finding not previously addressed by any study of cardiac NL was the higher case fatality rate in children born to nonwhite mothers (who make up 25% of the RRNL), an observation that was consistent across each of the racial/ethnic groups. Overall, nonwhites had a significantly higher case fatality rate than whites, although the association of race/ethnicity and mortality was not maintained in multivariable analyses. This was likely due to the observation that white fetuses were at lower risk of hydrops and EFE, variables highly predictive of mortality. One possible explanation is that more extensive cardiac injury occurs in minor-

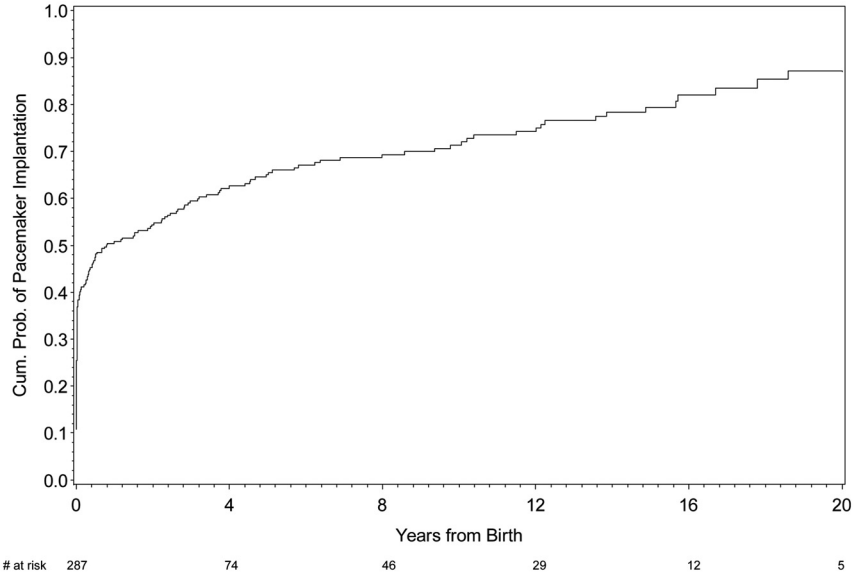

Figure 2. The Kaplan-Meier curves reflecting the probability of pacemaker implantation. Of note, 2 cases of cardiac neonatal lupus that were paced in utero were omitted from the analysis.

ities. Candidate neonatal factors could include genetics, a possibility difficult to explore given the low number of affected children in each minority group. To date, genetic studies have been limited to whites.[31] The absence of racial/ethnic information in any of the published cohorts precludes comparison of these data with other studies. Further studies are needed to validate this association and to determine whether access to medical care accounts for this disparity.

Another previously unreported finding in this study is that associated hepatic/hematologic NL, but not cutaneous NL, is associated with an increased morbidity in live-born children. The liver abnormalities may have been due to hepatic congestion secondary to cardiac failure. However, the finding of a mononuclear infiltrate in several livers evaluated on autopsy supports an organ-specific inflammatory process similar to that proposed for the initial phase of cardiac injury. Cytopenias may add to the overall burden of disease by decreasing oxygenation of tissues, increasing the risk of bleeding and the risk of infection. Moreover, cytopenias may represent increased pathogenicity of the autoantibodies. In addition, mortality was associated with a maternal diagnosis of SLE or SS at the time of pregnancy. This observation was unexpected because it predicted that mothers with known rheumatic disease and the presence of autoantibodies before pregnancy might be more likely to have had optimal surveillance. Although medications such as nonfluorinated steroids, which would more often have been prescribed to patients with established rheumatic disease, might have explained the increased mortality rates, this was not found to be the case. Perhaps maternal illness per se conferred a less favorable in utero environment; it is generally accepted that SLE is associated with premature birth.[32] Finally, the association of SLE and/or SS with mortality could possibly have been a reflection of maternal race/ethnicity because nonwhites may be more frequently represented in mothers with SLE.[33,34] However, this was not observed; SLE mothers in this study were equally distributed between whites and nonwhites.

There are several limitations to this study, all of which are inherent in rare diseases. The low numbers of minorities make it difficult to discern why they have a higher case fatality rate. The race/ethnicity of the mother was used as a proxy for the child given the data available because the father's race/ethnicity was not a mandate of the RRNL and not systematically solicited. The low numbers of in utero deaths (18) limit the statistical power for related analyses. Although the data presented suggest that the probability of in utero death occurring before 20 weeks is zero, this observation may be misleading, because women enrolled in the registry are often totally asymptomatic and unaware of the presence of anti-SSA/Ro antibodies until detection of cardiac NL. Thus, obstetric evaluation beyond routine care may not have occurred before the early to mid second trimester. Moreover, death before 20 weeks may be due to many causes, and without proof of a cardiac disorder, unambiguous attribution to cardiac NL was not possible. The data in this study were largely collected in a retrospective manner, and in some pregnancies, not all of the data were available, which reduced the available sample size for the multivariable analyses. In addition, patients with available data may not be a random sample of the underlying study population, which could potentially lead to biased estimates of relative risk. The exact cause of the cardiac NL death was unknown in 7 cases; however, 5 deaths occurred within 6 months of birth, suggesting that cardiac NL was a contributing cause.

The significant influence of carditis on mortality is potentially biased because its diagnosis is dependent on histological evaluation of tissue. Predictably, biopsies were largely performed in the sickest of cases, the vast majority of whom had associated DCM and/or EFE on echocardiography. Of the 5 children with carditis who lived, 1 required cardiac transplantation. In addition, carditis was seen on several autopsies. The finding of a mononuclear infiltrate supports the hypothesis that an inflammatory process involving more than the conduction system contributes to the increase in mortality.

Conclusions

The overall case fatality rate of NL was 17.5%; pacing was required in ≈70% by 10 years of age; and 4 children required cardiac transplantation. Mortality was predicted by echocardiographic abnormalities consistent with antibody-associated disease beyond the atrioventricular node. The case fatality rate was higher in children born to nonwhite mothers, which requires further investigation.

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Disclosures

None.

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CLINICAL PERSPECTIVE

The cardiac manifestations of neonatal lupus include advanced conduction disease and rarely an isolated cardiomyopathy. This study, which included 325 offspring exposed to maternal anti-SSA/Ro antibodies with cardiac neonatal lupus, was used to determine the mortality, morbidity, and associated risk factors in a multi–racial/ethnic US-based registry. The case fatality rate was 17.5%. A third of the cases died in utero. The cumulative probability of survival at 10 years for a child born alive was 86% (most dying within a year of birth). Fetal echocardiographic risk factors associated with a statistically significant increase in mortality in a multivariate analysis included hydrops, endocardial fibroelastosis, an earlier diagnosis of cardiac neonatal lupus, and a lower ventricular rate. Overall, isolated advanced heart block was associated with a 7.8% case fatality rate, whereas the concomitant presence of dilated cardiomyopathy or endocardial fibroelastosis more than quadrupled the case fatality rate. There was a significantly higher case fatality rate in minorities compared with whites, who were at a lower risk of hydrops and endocardial fibroelastosis. Pacing was required in 70% by 10 years, and 4 children underwent cardiac transplantation. Data from this cohort reveal that nearly one fifth of fetuses who develop cardiac neonatal lupus die of complications predicted by echocardiographic abnormalities consistent with antibody-associated disease beyond the atrioventricular node.