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Neonatal Lupus: Advances in Understanding Pathogenesis and Identifying Treatments of Cardiac Disease

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Abstract

Purpose of Review—Cardiac manifestations of neonatal lupus (cardiac-NL) include anti-SSA/Ro-SSB/La mediated conduction system disease and endocardial/myocardial damage resulting in cardiomyopathy. This review will focus on recent data regarding updates on the proposed pathogenesis of disease, morbidity and mortality, and preventative and treatment therapies.

Recent Findings—Evidence from animal models suggests that reactivity to the p200 region of the Ro52 protein, as well as antibody targeting of L-Type calcium channels may be important in the development of cardiac-NL. In vitro studies support a protective role of beta-2 glycoprotein 1 (prevents anti-Ro binding to apoptotic cells) and pathologic roles of the urokinase-plasminogen activator/receptor system (leads to activation of TGF-β), and endothelin-I secretion by macrophages in mediating tissue injury. Genetic studies highlight the fetal MHC in the development of disease, and a multigenerational study demonstrates that mothers of NL children accumulate genetic risk factors preferentially from the NL child's grandparents. Retrospective studies identify demographic and echocardiographic risk factors for morbidity and mortality, and address the role of fluorinated steroids, IVIG, and hydroxychloroquine for prevention and treatment of disease.

Summary—Animal studies, in vitro experiments, genetic analysis, and clinical-translational research in cardiac-NL reveal novel insights and targets for therapy in this often devastating disease.

Keywords

Neonatal Lupus; congenital heart block; anti-Ro52; anti-SSA/Ro; cardiomyopathy; hydroxychloroquine

Introduction

The association between maternal autoantibodies to 52kD SSA Ro (Ro52), 60kD SSA Ro (Ro60), and 48kD SSB/La proteins and the development of fetal cardiac disease is well appreciated. While advanced conduction system abnormalities have been considered the most characteristic cardiac manifestations of the neonatal lupus (NL) syndromes, the spectrum of injury likely extends to the working myocardium and endocardium. For affected families and their physicians, publications in this past year have been highly informative with advances both at the bench and bedside. This review will focus on new data related to pathogenesis, genetics, maternal and fetal risk factors of poor prognosis, and translation of

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DISCLOSURES
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these findings to therapy. Throughout the text, the term “cardiac-NL” refers to antibody associated heart block as well as more extensive cardiac injury.

Pathogenesis of Disease

The penetrance of NL in an anti-SSA/Ro positive mother who is primigravida or has had healthy children approximates 2%[1]. The rarity of disease suggests that the pathogenesis of cardiac injury is not solely related to maternal antibodies. However, it remains possible that antibody reactivity to a specific epitope is responsible for initiation of injury or is more pathogenic than other antibodies. Supportive evidence for specific pathogenicity was provided in a recent study which focused on reactivity to the p200 region (aa200-239) of the Ro52 protein[2]. In a rat model, 1st degree atrioventricular(AV) block and sinus bradycardia developed in 100% and 81% of pups respectively after transfer of maternal antibodies specific for p200. Pups exposed to antibodies targeting N- or C-terminal epitopes of Ro52 did not show electrocardiographic abnormalities. This work extends previous studies demonstrating similar electrocardiographic abnormalities in rats after passive transfer of IgG fractions containing anti-SSA/Ro-SSB/La from mothers of children with cardiac-NL[3]. These findings suggest that anti-p200 contributes to early, and possibly reversible, injury[2]. However, the significance of 1st degree block in humans has been challenged in a recent study that concluded, based on serial echocardiograms of 165 anti-SSA/Ro exposed fetuses, that fetal AV prolongation does not reliably predict progressive heart block [4]. Despite the limitations raised and the possibility that the rodent model may not fully recapitulate human conditions, the anti-p200 rat model may be extremely useful to further investigate the contribution of fetal genetics to fibrotic replacement of the AV node.

In considering advanced block as a multistep process, two non-mutually exclusive hypotheses have been proposed to explain the mechanism by which maternal autoantibodies to normally sequestered intracellular antigens initiate injury. One hypothesis is based on molecular mimicry wherein antibodies cross-react with L-Type calcium channels (LTCC) and cause dysregulation of calcium homeostasis[5]. Another posits that intracellular anti-SSA/Ro-SSB/La antigens translocate to the surface of cardiomyocytes undergoing apoptosis during physiological remodeling and thus become accessible to extracelluar antibody[6]. Several recent papers have provided advances for both hypotheses. Based on the prediction that overexpression of LTCC should rescue, whereas knockouts should worsen the electrocardiographic abnormalities, Karnabi and colleagues reported that transgenic pups with overexpression of LTCC, exposed to anti-SSA/Ro-SSB/La antibodies via passive immunization of the mothers, had significantly less sinus bradycardia and AV block compared to non-transgenic pups[7]. LTCC knockout pups born to immunized mothers had sinus bradycardia, advanced AV block, and decreased fetal parity.

Relevant to the “apoptotic” theory of cardiac-NL, in which the formation of pathogenic antibody-apoptotic cell immune complexes promotes pro-inflammatory and pro-fibrotic responses, Reed et al demonstrated that beta-2 glycoprotein I (β2GPI) prevented opsonization of apoptotic cardiomyocytes by maternal anti-Ro60 IgG[8]. Plasmin-mediated cleavage of β2GPI abrogated the inhibition of anti-Ro60 binding, promoting the formation of pathogenic anti-Ro60 IgG-apoptotic cardiomyocyte complexes. Umbilical cord β2GPI blood levels were significantly lower in anti-Ro exposed neonates with cardiac-NL compared to unaffected siblings. These data suggest intact β2GPI in the fetal circulation may be a novel cardioprotective factor [8].

The pathogenesis of disease may be fueled by exaggerated apoptosis as observed in the hearts of several fetuses dying with cardiac-NL[9]. A clue to this observation was the finding that binding of maternal anti-SSA/Ro antibodies to fetal apoptotic cardiocytes

impairs their removal by healthy cardiocytes and increases urokinase plasminogen activator (uPA)/uPA receptor (uPAR)-dependent plasmin activation[10]. Briassouli and colleagues advanced this finding by demonstrating that anti-SSA/Ro binding to apoptotic cardiocytes triggers TGF-β activation, an effect secondary to increased uPAR-dependent uPA activity. TGF-B activation might act as an amplifier in the cascade of events that promote myofibroblast transdifferentiation and scar[11].

Applicable to the potential cross-talk between inflammatory and profibrosing pathways initiated by opsonized apoptotic cardiocytes, Alvarez and colleagues identified human fetal cardiac fibroblasts as a source of TGF-β[12]. Supernatants from macrophages incubated with immune complexes comprised of Ro60, hY3 ssRNA, and affinity-purified anti-Ro60 antibodies induced fibroblast secretion of TGF-β, which was inhibited by treating the macrophages with an antagonist of Toll-Like Receptor-7 (TLR7). Under the same conditions, the induced fibroblast secretion of TGF-β was also decreased by inhibitors of the enodothelin-1 (ET-1) receptors ETa or ETb, and by an anti-ET-1 antibody. In vivo support for the contribution of ET-1 was based on immunohistochemistry of hearts from two fetuses dying with complete block both revealing the presence of ET-1-producing mononuclear cells in the septal region in areas of calcification and fibrosis[12]. The totality of data suggest that ET-1 may be one factor responsible for the profibrosing effects generated by stimulated macrophages[12].

Genetic Contributions to Cardiac-NL

A focus on variation at the Major Histocompatibility Complex (MHC) was a logical choice for genetic studies, since the extended HLA–A1;B8;DR3 haplotype block contains risk alleles for inflammation and certain autoimmune diseases, and is strongly associated with anti-SSA/Ro-SSB/La antibodies[13–16]. The same extended haplotype might contribute to a “double hit”, one in the mother and one in her offspring. For example, Strandberg et al demonstrated in a rodent model that maternal MHC regulated the generation of anti-Ro52 antibodies and that fetal MHC determined susceptibility of the development of a prolonged PR interval[17].

The role of fetal genetics in development of human disease was investigated in a genome-wide association study of 116 Caucasian cardiac-NL children and 3,351 controls, using a 370,000 SNP platform[18]. The 17 most significant associations were found in the HLA region at 6p21.3. The strongest association, found at rs3099844, is near the class-III MHC region and 94 kb from the TNFα gene, which contains the rs1800629 polymorphism previously associated with cardiac-NL[19]. Outside of the HLA, no individual locus previously implicated in autoimmune diseases achieved genome-wide significance. However, a cluster of associated SNPs at 21q22 were in proximity to the REG-ETS2/WDR4 transcription factor that serves as a “brake” to both apoptosis and inflammation, represses the expression of interleukin-8, and plays a role in augmenting the expression of TGF-β receptor type-2. Maternal inheritance may be a limitation of the study since it is difficult to distinguish whether inheritance reflects transmission of genes related to maternal autoimmunity and/or represents enrichment of genes biologically important to disease pathogenesis[18].

A missense variant at rs7775397 within the *C6orf10* gene, which codes for an uncharacterized protein and lies in the Class III–Class II boundary was also associated with cardiac-NL in the GWAS[18]. This SNP and the TNFα promoterrs 1800629 were evaluated in a multigenerational family study to determine the role of maternal grandparents in the development of the autoimmune phenotype of NL-mothers[20]. Genotyping was performed in families consisting of 41 NL-mothers, 38 grandmothers and 29 grandfathers. There was

an increased frequency of the two candidate genetic variants in the NL-mothers compared to HAPMAP controls. These frequencies were significantly different between NL-mothers and grandmothers, but were more similar between the grandfathers and NL-mothers. The clustering of each genetic variant in NL-mothers was related to a preferential skewing of inheritance from grandparents, as shown by a Transmission Disequilibrium Test (TDT) of complete trios of mothers and both maternal grandparents. Despite the limited sample size, the TDT analyses were strongly statistically significant because of the magnitude of the effect associated with these HLA-region SNPs. These results imply that mothers accumulate genetic determinants specific to NL, which are not present in grandparents. The preferential transmission of risk alleles represents a selection pattern which demonstrates the “perfect storm” of events leading to cardiac-NL. Further study is required to distinguish whether transmission of these genetic risk variants a) directly contributes to the pathogenesis of NL, b) is restricted to the generation of maternal autoantibodies, or c) is in linkage disequilibrium with the true causal genetic factors[20].

Factors Contributing to Mortality

Two recent large retrospective studies addressed mortality rates and associated risk factors in cardiac-NL[21,22]. These studies corroborate and extend findings of previous publications which included smaller cohorts and a heterogenous mix of autoantibody exposures[23–28]. Data from the RRNL, a multi-racial/ethnic US-based registry of anti-SSA/Ro exposed fetuses with NL revealed 57(17.5%) died from complications of cardiac-NL; 30% dying in utero. Fetal echocardiographic risk factors associated with increased mortality included hydrops, endocardialfibroelastosis (EFE), earlier diagnosis of cardiac-NL and lower ventricular rate. The presence of EFE and dilated cardiomyopathy was associated with an increased case fatality rate of 51.9% and 53.3%, respectively, compared to those who only had isolated advanced block (7.8%). Fetuses born to minorities had a higher case fatality rate, possibly because they were at higher risk for developing hydrops and EFE. Pacing was required in 70% of children and 4 underwent cardiac transplantation[21]. In a multicenter study including 175 patients with advanced heart block from Europe and Brazil, of which 75% were exposed to anti-SSA/Ro-SSB/La antibodies, 91% resulted in live births and 93% of those were alive after the neonatal period[22]. Risk factors associated with mortality included gestational age <20 weeks at diagnosis, ventricular rate <50 bpm, fetal hydrops, and impaired left ventricular function at diagnosis. By one year of life, 69% were paced.

Approach to Prevention of Disease

Previous literature suggests that use of fluorinated steroids with beta-mimetics for fetal heart rates <55 improves survival in complete block[29]. However, in the European/Brazilian study, there was no significant effect of fluorinated steroids on survival at birth or at one month of age, regardless of anti-SSA/Ro exposure[22]. With the exception of gestational age at diagnosis, all other risk factors for mortality were similar between mothers treated and untreated with fluorinated steroids. No improvement was seen in the mortality of fetuses with multiple risk factors despite fluorinated steroids. There was no consensus on treatment guidelines, some referral centers not treating any patient regardless of fetal status and others treating all cases[22]. In the RRNL study, fluorinated steroids were associated with an increased mortality in fetuses dying in utero, which was attributed to more severe underlying disease[21].

Both studies also addressed the use of fluorinated steroids for the treatment of 2nd degree block[21,22]. The combined dataset support a trend towards benefit with regression of incomplete block. Specifically, 35%(7/20) of fetuses exposed to fluorinated steroids reverted

to normal sinus rhythm or 1st degree block compared to 6.25%(1/16) in those not exposed to steroids, p=0.053 (Table 1). Long term data were unavailable in the majority of cases. Data on which children with 2nd degree AV block in utero required pacing was only provided in one study preventing a combined analysis. Thus, further studies are needed to determine the effectiveness of steroids in treating incomplete blocks.

Recently several papers have explored the role of Intravenous Immunoglobulin (IVIG) in the prevention[30,31] and treatment[32,33] of cardiac-NL. Parallel multicenter, prospective, open-label studies in the U.S.[30] and Europe[31]addressed whether IVIG reduces the recurrence of cardiac-NL. IVIG (400 mg/kg) was given every 3 weeks from gestational weeks 12–24 to prevent advanced heart block. Of the 18 mothers completing the U.S. study, there were 3 cases of advanced block. In the European study, 3 cases were identified in 15 mothers. Combining data from both studies, there were 6(18%) recurrences in 33 women who had previous pregnancies complicated by cardiac-NL. Since each study was designed to conclude inefficacy of IVIG if 6/54 fetuses developed advanced block, the trials were terminated.

Regarding treatment of established cardiac-NL, a recent study looked at the use of IVIG in combination with steroids for severe cases in which cardiomyopathy/EFE was identified[32]. In this retrospective study, mothers carrying an affected fetus (N=9) or children recently born with cardiac-NL (N=11) were treated with IVIG (approximately 1 g/kg given once or repeated up to 3 times). Of the twenty cases treated with IVIG, 16 were alive after a median follow up of 2.9 years and none required cardiac transplantation. The absence of a control arm limited firm conclusions. However, the authors were encouraged by the 80% survival with IVIG treatment compared to three historical case series in which 78%(25/32) of cases died or required cardiac transplantation[34–36]. However, in a recent study the mortality rate of cardiomyopathy/EFE was approximately 50%[21] and in a second smaller series of five children with isolated EFE, four were alive at four years, three of whom had normal heart function[37]. Accordingly, the treatment benefit of IVIG for EFE remains inconclusive.

Based on experimental evidence supporting a role of TLR signaling in the pathogenesis of cardiac-NL[6] a recently published case control study[38] explored the hypothesis that hydroxychloroquine (HCQ), an inhibitor of TLR ligation[39], might reduce the risk of disease. Children born to mothers with SLE and anti-SSA/Ro antibodies comprised the cases (50 cardiac-NL) and controls(151 non-cardiac-NL). Seven (14%) cardiac-NL children were exposed to HCQ compared with 56(37%) controls (p=0.002; OR 0.28;95% CI 0.12–0.63). Multivariable analysis yielded an OR associated with HCQ use of 0.46(p=0.10;95% CI 0.18–1.18). Although HCQ was no longer a statistically significant predictor of cardiac-NL, the estimate of the OR remained in the direction of a protective effect, consistent with the results from the overall unadjusted analysis[38].

Environmental Influence on the Risk of Disease

Maternal and fetal factors associated with development of cardiac-NL were studied in a Swedish population-based cohort[40], which included 190 anti-SSA/Ro exposed pregnancies. Older maternal age (29.5 vs 26.6) but not parity, was significantly associated with cardiac-NL. However, a two-year age difference is challenging to use as a counseling tool or as an insight into the pathogenesis of disease. In this cohort, cardiac-NL was present in 58.5% of births with gestational susceptibility weeks 18–24 occurring during January–March, compared to 39.0% of all births during the remainder of the year. The authors hypothesize that this finding is explained by a decrease in light exposure during the winter months in Sweden which impacts vitamin D levels. The average vitamin D level in each

month, calculated based on samples from healthy Swedish women, significantly inversely correlated with the ratio of cardiac-NL to healthy pregnancies for which gestational week 21 (the median susceptibility week) fell in that particular month[40]. The authors also note that other winter-linked events, such as viral infections, may have accounted for their observations.

Conclusion

Evidence from animal models suggests that reactivity to the p200 region of the Ro52 protein, as well as antibody targeting of L-Type calcium channels, may contribute to the development of cardiac-NL. In vitro studies support a protective role of beta-2 glycoprotein 1 and a pathologic role of the urokinase-plasminogen activator/receptor system on apoptotic cardiocytes and endothelin-I secretion by macrophages in the cascade to heart block. Genetic studies highlight the fetal MHC in the development of disease, and a multigenerational study demonstrates that mothers of NL children accumulate genetic risk factors preferentially from the NL child's grandparents. The ultimate goal, to identify disease specific genes associated with cardiac-NL, is of paramount importance in order to understand the molecular pathways that amplify the injurious effects of the maternal autoantibodies. Retrospective studies identify demographic and echocardiographic risk factors such as non Caucasian race, earlier time of in utero detection, slower heart rate, and cardiomyopathy as risk factors associated with morbidity and mortality. The use of hydroxychloroquine during pregnancy may provide protection against the development of heart block and future prospective studies evaluating the reduction of recurrence rates are needed.

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References

1**. Buyon, J. Neonatal lupus. In: Lahita, RG.; Tsokos, G.; Buyon, JP.; Koike, T., editors. Systemic Lupus Erythematosus. 5. San Diego: Academic Press; 2011. p. 541This chapter is an updated comprehensive review of the topic from bench to bedside and covers all clinical manifestations of neonatal lupus

2**. Ambrosi, Aurelie; Dzikaite, Vijole; Park, Jeongsook, et al. Anti-Ro52 monoclonal antibodies specific for amino acid 200–239, but not other Ro52 epitopes, induce congenital heart block in a rat model. Ann Rheum Dis. 2012; 71:448–454. This is an important study which utilizes a rat model to establish the pathogenicity of the maternal autoantibody. The work suggests that initial injury may be mediated, in part, by antibodies to a specific epitope of Ro52. These studies may facilitate further exploration into the mechanism of clinically meaningful damage. [PubMed: 22084395]

3. Mazel JA, El-Sherif N, Buyon J, Boutjdir M. Electrocardiographic abnormalities in a murine model injected with IgG from mothers of children with congenital heart block. Circulation. 1999; 99(14): 1914–8. [PubMed: 10199891]

4**. Jaeggi ET, Silverman ED, Laskin C, et al. Prolongation of the atrioventricular conduction in fetuses exposed to maternal anti-Ro/SSA and anti-La/SSB antibodies did not predict progressive heart block. A prospective observational study on the effects of maternal antibodies on 165

fetuses. J Am Coll Cardiol. 2011; 57:1487–92. This single center study addresses the utility of serial fetal echocardiograms in susceptible pregnancies. While firm conclusions as to the value of such intense monitoring remain, the authors question whether first degree block defined by PR prolongation truly represents early anti-Ro mediated disease and/or warrants treatment. [PubMed: 21435519]

5. Karnabi E, Boutjdir M. Role of calcium channels in congenital heart block. Scand J Immunol. 2010; 72(3):226–34. [PubMed: 20696020]
6. Clancy RM, Alvarez D, Komissarova E, et al. Ro60-associated single-stranded RNA links inflammation with fetal cardiac fibrosis via ligation of TLRs: a novel pathway to autoimmune-associated heart block. J Immunol. 2010; 184:2148–55. [PubMed: 20089705]

7**. Karnabi E, Qu Y, Mancarella S, Boutjdir M. Rescue and worsening of congenital heart block-associated electrocardiographic abnormalities in two transgenic mice. J Cardiovasc Electrophysiol. 2011; 22(8):922–30. This murine study molecularly extends the calcium channel hypothesis. [PubMed: 21352396]

8**. Reed JH, Clancy RM, Purcell AW, et al. β2-glycoprotein I and protection from anti-SSA/Ro60-associated cardiac manifestations of neonatal lupus. J Immunol. 2011; 187(1):520–6. This translational study suggests that β2-glycoprotein I may be an important protein that protects the fetal heart from anti-Ro60 mediated injury. [PubMed: 21602492]

9. Clancy RM, Kapur RP, Molad Y, et al. Immunohistologic evidence supports apoptosis, IgG deposition and novel macrophage/fibroblast crosstalk in the pathologic cascade leading to congenital heart block. Arthritis Rheum. 2004; 50(1):173–16. [PubMed: 14730614]
10. Briassouli P, Komissarova EV, Clancy RM, Buyon JP. Role of the urokinase plasminogen activator receptor in mediating impaired efferocytosis of anti-SSA/Ro-bound apoptotic cardiocytes: Implications in the pathogenesis of congenital heart block. Circ Res. 2010; 107(3): 374–87. [PubMed: 20558828]

11**. Briassouli P, Rifkin D, Clancy RM, Buyon JP. Binding of anti-SSA antibodies to apoptotic fetal cardiocytes stimulates urokinase plasminogen activator (uPA)/uPA receptor-dependent activation of TGF-β and potentiates fibrosis. J Immunol. 2011; 187(10):5392–401. This in vitro study suggests that the cascade to fibrosis of the fetal cardiac conducting system may be caused, in part, by plasmin mediated activation of TGF-β which occurs as a consequence of anti-Ro binding to an apoptotic cardiocyte. [PubMed: 22013113]

12**. Alvarez D, Briassouli P, Clancy RM, et al. A novel role of endothelin-1 in linking Toll-like receptor 7-mediated inflammation to fibrosis in congenital heart block. J Biol Chem. 2011; 286:3044–54. This in vitro study identified endothelin-1 for the first time as a participant in the fibrosing pathway to heart block.

13. Hamilton R, Harley J, Bias WB, et al. Two Ro (SS-A) autoantibody responses in systemic lupus erythematosus. Correlation of HLA-DR/DQ specificities with quantitative expression of Ro (SS-A) autoantibody. Arthritis Rheum. 1988; 31(4):496–505. [PubMed: 2451920]
14. Harley JB, Reichlin M, Arnett FC, et al. Gene interaction at HLA-DQ enhances autoantibody production in primary Sjogren's syndrome. Science. 1986; 232(4754):1145–7. [PubMed: 3458307]
15. Scofield RH, Frank MB, Neas BR, et al. Cooperative association of T cell beta receptor and HLA-DQ alleles in production of anti-Ro in systemic lupus erythematosus. Clin Immunol Immunopathol. 1994; 72:335–41. [PubMed: 7914842]
16. Graham RR, Ortmann W, Rodine P, et al. Specific combinations of HLA-DR2 and DR3 class II haplotypes contribute graded risk for disease susceptibility and autoantibodies in human SLE. Eur J Hum Genet. 2007; 15(8):823–30. [PubMed: 17406641]
17. Strandberg LS, Ambrosi A, Jagodic M, et al. Maternal MHC regulates generation of pathogenic antibodies and fetal MHC-encoded genes determine susceptibility in congenital heart block. J Immunol. 2010 Sep 15; 185(6):3574–82. [PubMed: 20696861]
18. Clancy RM, Marion MC, Kaufman KM, et al. Identification of candidate loci at 6p21 and 21q22 in a genome-wide association study of cardiac manifestations of neonatal lupus. Arthritis Rheum. 2010; 62(11):3415–24. [PubMed: 20662065]

19. Clancy RM, Backer CB, Yin X, et al. Cytokine polymorphisms and histologic expression in autopsy studies: contribution of TNF-alpha and TGF-beta 1 to the pathogenesis of autoimmune-associated congenital heart block. J Immunol. 2003; 171(6):3253–61. [PubMed: 12960355]

20**. Saxena A, McDonnell E, Ramos PS, et al. Preferential transmission of genetic risk variants of candidate loci at 6p21 from asymptomatic grandparents to mothers of children with neonatal lupus. Arthritis Rheum. 2012 Mar; 64(3):931–9. This is the first study to examine the transmission of genetic traits and the distribution of autoantibodies and clinical disease in two generations. [PubMed: 22031281]

21**. Izmirly PM, Saxena A, Kim MY, Wang, et al. Maternal and fetal factors associated with mortality and morbidity in a multi-racial/ethnic registry of anti-SSA/Ro associated cardiac neonatal lupus. Circulation. 2011; 124:1927–35. This work represents the largest study assembled and identifies maternal and fetal risk factors for mortality in cardiac manifestations of neonatal lupus. [PubMed: 21969015]

22**. Eliasson H, Sonesson SE, Sharland G, et al. Fetal Working Group of the European Association of Pediatric Cardiology. Isolated atrioventricular block in the fetus: a retrospective, multinational, multicenter study of 175 patients. Circulation. 2011; 124:1919–26. This work addresses issues similar to the study above but also suggests that treatment with fluorinated steroids may not confer survival advantage. [PubMed: 21986286]

23. Jaeggi ET, Hornberger LK, Smallhorn JF, Fouron JC. Prenatal diagnosis of complete atrioventricular block associated with structural heart disease: combined experience of two tertiary care centers and review of the literature. Ultrasound Obstet Gynecol. 2005; 26:16–21. [PubMed: 15937969]

24. Waltuck J, Buyon J. Autoantibody associated congenital heart block: Outcome in mothers and children. Annals Int Med. 1994; 120:544–51.

25. Buyon JP, Hiebert R, Copel J, et al. Autoimmune-associated congenital heart block: Mortality, morbidity, and recurrence rates obtained from a national neonatal lupus registry. J Am Coll Cardiol. 1998; 31:1658–66. [PubMed: 9626848]

26. Villain E, Coastedoat-Chalumeau N, Marijon E, et al. Presentation and prognosis of complete atrioventricular block in childhood, according to maternal antibody status. J Am Coll Cardiol. 2006; 48:1682–7. [PubMed: 17045907]

27. Jaeggi ET, Hamilton RM, Silverman ED, et al. Outcome of children with fetal, neonatal or childhood diagnosis of isolated congenital atrioventricular block. A single institution's experience of 30 years. J Am Coll Cardiol. 2002; 39:130–7. [PubMed: 11755298]

28. Lopes LM, Tavares GM, Damiano AP, et al. Perinatal outcome of fetal atrioventricular block: one-hundred-sixteen cases from a single institution. Circulation. 2008; 118:1268–75. [PubMed: 18765396]

29. Jaeggi ET, Fouron JC, Silverman ED, et al. Transplacental fetal treatment improves the outcome of prenatally diagnosed complete atrioventricular block without structural heart disease. Circulation. 2004 Sep 21; 110(12):1542–8. [PubMed: 15353508]

30. Friedman DM, Llanos C, Izmirly PM, et al. Evaluation of Fetuses in the Preventive IVIG Therapy for Congenital Heart Block (PITCH) study. Arthritis Rheum. 2010; 62:1138–46. [PubMed: 20391423]

31. Pisoni CN, Brucato A, Ruffatti A, et al. Failure of intravenous immunoglobulin to prevent congenital heart block: Findings of a multicenter, prospective, observational study. Arthritis Rheum. 2010; 62:1147–52. [PubMed: 20131278]

32**. Trucco SM, Jaeggi E, Cuneo B, et al. Use of intravenous gamma globulin and corticosteroids in the treatment of maternal autoantibody-mediated cardiomyopathy. J Am Coll Cardiol. 2011; 57:715–23. This study suggests a potential benefit of IVIG at anti-inflammatory doses (approximately 1 gm/kg) in treating endocardialfibroelastosis associated with anti-Ro exposure. [PubMed: 21292131]

33. Ruffatti A, Milanesi O, Chiandetti L, et al. A combination therapy to treat second-degree anti-Ro/La-related congenital heart block. a strategy to avoid stable third-degree heart block? Lupus. 2011 Dec 20. [Epub ahead of print].

34. Moak JP, Barron KS, Hougen TJ, et al. Congenital heart block: development of late-onset cardiomyopathy, a previously underappreciated sequela. J Am Coll Cardiol. 2001; 37:238–242. [PubMed: 11153745]

35. Nield LE, Silverman ED, Taylor GP, et al. Maternal anti-Ro and anti-La antibody-associated endocardialfibroelastosis. Circulation. 2002; 105:843–848. [PubMed: 11854125]

36. Nield LE, Silverman ED, Smallhorn JF, et al. Endocardialfibroelastosis associated with maternal anti-Ro and anti-La antibodies in the absence of atrioventricular block. J Am Coll Cardiol. 2002; 40:796–802. [PubMed: 12204513]

37**. Guettrot-Imbert G, Cohen L, Fermont L, et al. A new presentation of neonatal lupus: 5 cases of isolated mild endocardialfibroelastosis associated with maternal Anti-SSA/Ro and Anti-SSB/La antibodies. J Rheumatol. 2011; 38:378–86. This is a case series which further emphasizes that endocardialfibroelastosis (EFE) is part of the spectrum of cardiac manifestations of neonatal lupus. In isolation, EFE carries a variable prognosis. [PubMed: 21078712]

38. Izmirly PM, Kim MY, Llanos C, et al. Evaluation of the Risk of Anti-SSA/Ro-SSB/La Antibody Associated Cardiac Manifestations of Neonatal Lupus in Fetuses of SLE Mothers Exposed to Hydroxychloroquine. Ann Rheum Dis. 2010; 69:1827–30. [PubMed: 20447951]

39. Lafyatis R, York R, Marshak-Rothstein A. Antimalarial agents: Closing the gate on toll-like receptors? Arthritis Rheum. 2006; 54:3068–3070. [PubMed: 17009223]

40**. Ambrosi A, Salomonsson S, Eliasson H, et al. Development of heart block in children of SSA/SSB-autoantibody-positive women is associated with maternal age and displays a season-of-birth pattern. Ann Rheum Dis. 2012; 71:334–340. This study suggests that months associated with diminished Vitamin D exposure may add risk to the development of cardiac manifestations of neonatal lupus. [PubMed: 21953338]

KEY POINTS

- Evidence from animal models suggests that reactivity to the p200 region of the Ro52 protein, as well as antibody targeting of L-Type calcium channels, may contribute to the development of cardiac-NL.
- In vitro studies support a protective role of beta-2 glycoprotein 1 and a pathologic role of the urokinase-plasminogen activator/receptor system on apoptotic cardiocytes and endothelin-I secretion by macrophages in the cascade to heart block.
- Retrospective studies identify demographic and echocardiographic risk factors such as non Caucasian race, earlier time of in utero detection, slower heart rate, and cardiomyopathy as risk factors associated with morbidity and mortality.

Table 1

Combined Data of Fluorinated Steroid Treatment in 2nd Degree AV Block

	Treated with Fluorinated Steroids reverting to NSR or 1st Degree Block at Birth	**Untreated Group Reverting to NSR**
Research Registry for Neonatal Lupus	4/13	1/8
Fetal Working Group of the European Association of Pediatric Cardiology	3/7	0/8
Total	7/20 (35%)	1/16 (6.25%)

p=0.0531