Cardiac manifestations of neonatal lupus erythematosus: guidelines to management, integrating clues from the bench and bedside

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SUMMARY

One of the strongest clinical associations with autoantibodies against components of the SSA/Ro–SSB/La ribonucleoprotein complex is the development of congenital heart block in an offspring, an alarming prospect facing 2% of primigravid mothers with these reactivities. This risk is increased tenfold in women who have had a previous child with congenital heart block. Accumulated evidence suggests that anti-SSA/Ro and anti-SSB/La antibodies are necessary but insufficient for fetal disease. Basic and clinical research is heavily focused on identifying fetal and environmental factors that convert disease susceptibility to disease development. A disturbing observation that has emerged from current research efforts is the rapidity of disease progression, with advanced heart block and life-threatening cardiomyopathy being observed less than 2 weeks after detection of a normal sinus rhythm. Once third-degree block is unequivocally identified, reversal has never been achieved, despite dexamethasone treatment. Accordingly, strategies aimed at preventing disease before irrevocable scarring ensues assume a high priority. One approach has been the implementation of serial echocardiography to monitor for a prolonged PR interval. Intravenous immunoglobulin is being evaluated as a potential prophylactic approach in mothers who have previously had an affected child.

KEYWORDS anti-SSA/Ro antibodies, congenital heart block, dexamethasone, neonatal lupus, PR interval

REVIEW CRITERIA

Published articles for inclusion in this Review were identified from the authors' extensive records of papers on cardiac manifestations of neonatal lupus dating from 1977 to the present. All papers identified were English-language, full-text papers.

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INTRODUCTION

The biology of human viviparity involves a variety of fetal–maternal relationships, several of which might facilitate the occurrence of passively acquired autoimmunity;[1] neonatal lupus erythematosus (NLE) is one example of a pathologic consequence of this autoimmunity. NLE comprises several fetal and neonatal manifestations that share in common the *in utero* exposure to maternal anti-SSA/Ro antibodies (with or without anti-SSB/La antibodies).[2] The name is misleading, and often a cause of undue concern, because the neonate does not have systemic lupus erythematosus (SLE) and, often, neither does the mother. The most common manifestations are cutaneous and cardiac, the former resembling the lesions observed in SLE and likely responsible for the name given to this disease. Tissue injury in the fetus is presumed to be dependent on neonatal Fc receptor (FcRn)-mediated transplacental passage of maternal IgG autoantibodies.[3] Disease in the offspring parallels the presence of maternal antibodies in the fetal and neonatal circulation, and disappears, except for cardiac injury, with the clearance of the maternal antibodies by the eighth month of postnatal life. The transient nature of the rash reflects the effect of passively acquired autoantibodies on an organ system with the capacity of continual regeneration. In contrast, these regenerative processes apparently do not occur in cardiac tissue; third-degree block is irreversible to date. The signature cardiac lesion is atrioventricular block (congenital heart block [CHB]), but in 15–20% of cases there is an associated fatal cardiomyopathy.[4,5] Most affected children require permanent heart pacing before adulthood, with 60% paced during the neonatal period.[6,7] This Review will focus solely on the cardiac manifestations of NLE.

RISK OF CHB IN A PREGNANT WOMAN WITH ANTI-SSA/RO ANTIBODIES

Two prospective studies have reached a similar conclusion regarding the frequency of CHB in an offspring exposed to maternal anti-SSA/Ro

antibodies. In an Italian cohort, Brucato *et al.*[8] reported that 2 of 112 infants born to 100 women with anti-SSA/Ro antibodies, followed prospectively through pregnancy, had third-degree heart block. This group did not comment on lesser degrees of block, such as first or second degree, or on previous pregnancy history, but highlighted the absence of third-degree block in the offspring of the 53 women in their cohort who had SLE. In a subsequent US-based prospective study, the overall results were similar, with third-degree block developing in 3 of 98 pregnancies in 95 anti-SSA/Ro-positive women;[9] notably, one of the three women whose fetuses had third-degree block did have an established diagnosis of SLE. As more data accumulate, the early observation that maternal disease status is independent of fetal outcome is being confirmed.

Although high titers of anti-SSA/Ro antibodies are characteristic of high-risk mothers, this fact might not be informative for the treating physician. The reason is that anti-SSA/Ro antibodies are inherently of high titer, and high titers can be found in the sera of mothers giving birth to unaffected children. In addition, commercial laboratories vary in their testing procedures, and the definition of 'high titer' is not necessarily comparable across laboratories. In contrast, borderline positive levels of anti-SSA/Ro antibodies or antibodies that seem to be transiently positive are almost never associated with CHB.

Perhaps not all anti-SSA/Ro antibodies are truly pathogenic. Salomonsson *et al.*[10,11] have confirmed and extended our earlier work on epitope mapping of the SSA/Ro 52 kDa protein response and risk of CHB.[12] Based on a study of 9 CHB mothers and 26 anti-SSA/Ro-positive mothers of healthy children, this group posited that antibodies against amino acids 200–239 of SSA/Ro 52 kDa (p200) predicted CHB with greater certainty than the currently available testing for either SSA/Ro 60 kDa or SSA/Ro 52 kDa.[10] Utilizing an extensive serum bank from the Research Registry for Neonatal Lupus (RRNL), we identified an equivalent frequency of maternal anti-p200 antibody exposure in affected and unaffected children.[13] An international exchange of antisera is ongoing to facilitate further investigation on this issue.

Thus, for pregnancy counseling of a woman with anti-SSA/Ro antibodies who is primigravid or has only had healthy children, the risk given for CHB in an offspring should be 2%. In addition, having had one healthy child does not decrease the risk, as CHB can occur as frequently in the first or second child.[14] High-titer anti-SSA/Ro antibodies are characteristic, and anti-SSB/La antibodies might add a few percentage points.[15] The data thus far suggest that a maternal diagnosis of SLE is not a factor. The recurrence rate for CHB in a subsequent pregnancy is close to 20%.[2]

CURRENT THINKING REGARDING PATHOGENESIS

One difficulty in identifying a pathogenic effect of an autoantibody is accounting for the heterogeneity of effects. CHB is a stellar example in that not only is the injury rare, but the extent of injury is varied. Accordingly, CHB is likely to represent the sum of several components. The maternal component is presumably an autoantibody, which, by binding to its cognate antigen, initiates the first step toward injury. One major impediment to our further understanding of CHB pathogenesis is the fact that these antigens have an intracellular localization. To hypothesize that the target is a cardiac surface protein containing a cross-reactive epitope recognized by anti-SSA/Ro and anti-SSB/La antibodies is logical; however, a direct pathologic consequence of inhibiting the function of the target cells, as in neonatal myasthenia gravis,[16] or type II hypersensitivity via antibody-dependent cell-mediated cytotoxicity, such as in hemolytic disease of the newborn,[17] would predict an even higher incidence as well as recurrence of CHB in subsequent pregnancies than have been observed.[2,6]Alternatively, the candidate antigen might be located intracellularly and translocated to the surface during development of the fetal heart.

What is accepted is that without the maternal component, CHB would not ensue; thus, the antibody is a prerequisite but not sufficient factor for the development of CHB. Attempts to generate a robust, reproducible animal model exploiting the potential pathogenicity of the antibody as an isolated factor have not met with success. A fetal component and an environmental component must have roles in the ultimate development of injury. As recurrence of CHB in a subsequent pregnancy is almost tenfold greater than the risk in a first pregnancy, the genetics of a particular fetus might reasonably be considered a second component. The fact that identical twins are more often discordant than concordant for CHB suggests that an environmental factor

present *in utero* might be a third component.[2] In aggregate, the environmental factor would be expected to amplify the extent of injury in susceptible fetuses exposed to antibodies generated in susceptible mothers.

If one accepts that the autoantibody is responsible for initiating injury, then understanding the mechanism by which this occurs is important. The first challenge is to explain the mechanism of 'necessity' (i.e. how maternal autoantibodies against intracellular antigens bind tissue and perturb cardiac function). Boutjdir *et al.* extended two previous reports[18,19] regarding the arrhythmogenic effects of anti-SSA/Ro and anti-SSB/La antibodies by demonstrating that affinity-purified anti-SSA/Ro 52 kDa antibodies induce atrioventricular block in an isolated human fetal heart and inhibit inward calcium fluxes through L-type calcium channels in human fetal ventriculocytes (whole cell and single channel).[20] Although these observations support the idea that maternal antibodies perturb ion flux across the cardiocyte membrane, and as such might be a relevant factor in CHB, a molecular basis has yet to be defined (e.g. definitive cross-reactivity of anti-SSA/Ro and anti-SSB/La with calcium channel receptor), particularly with regard to inflammation and subsequent fibrosis. Antibodies to the cardiac 5-HT_4 serotoninergic receptors (hypothesized to be crossreactive with SSA/Ro 52 kDa) are only rarely present in sera from affected children.[21,22]

Immunohistological evaluation of hearts from fetuses that died of CHB has revealed exaggerated cardiocyte apoptosis, clusters of macrophages in zones of fibrosis that colocalize with IgG and apoptotic cells, tumor necrosis factor and transforming growth factor (TGF)-β mRNA expression in these cells, and extensive collagen deposition in the conducting system.[23] These *in vivo* observations are supported by *in vitro* studies. Specifically, the consideration of exaggerated cardiocyte apoptosis as the initial link between maternal autoantibodies and tissue injury led to the observation that cardiocytes are capable of phagocytosing autologous apoptotic cardiocytes, and that anti-SSA/Ro and anti-SSB/La antibodies inhibit this function.[24] Recognizing that this perturbation of physiologic efferocytosis (phagocytosis of apoptotic cells) might divert uptake to professional FcγR-bearing phagocytes fits well with earlier work that demonstrated macrophage secretion of proinflammatory and fibrosis-inducing cytokines when coincubated with apoptotic cardiocytes bound by anti-SSA/Ro and anti-SSB/La antibodies.[25,26] That macrophages engage Toll-like receptors via binding to the RNA moiety of the target autoantigen is clearly an area that might provide an additional clue to pathogenesis.

Finally, building on the premise that fetal genetics contributes to injury, continued genotyping of anti-SSA/Ro-exposed affected and unaffected siblings has revealed significant skewing in the frequency of polymorphisms in two genes: *FCGR3A* (which encodes FcγRIIIa; RM Clancy, unpublished data) and *TGFB1* (which encodes TGF-β1),[27] whose expressed proteins potentially contribute to increased IgG binding to macrophages and to fibrosis, respectively. The discordance of disease in monozygotic twins prompted the novel line of research into the role of hypoxia as an amplification factor on the distal fibrosing component. *In vitro* studies suggest that hypoxia can modulate cyclic AMP and promote a myofibroblast phenotype in cardiac fibroblasts. Footprints of hypoxic injury showed that hypoxia-inducible factor 1α is expressed in affected hearts, and that levels of erythropoietin were increased in several cord blood samples of surviving fetuses.[28] Figure 1 is an illustration of the proposed cascade from maternal antibody to tissue injury.

TRANSLATING THE BASIC RESEARCH TO MANAGEMENT

Prenatal considerations

The substantial morbidity and mortality associated with CHB and the readily available technology for identification of CHB *in utero* have prompted the search for effective therapies. Ideally, as CHB is most often identified between weeks 18 to 24 of gestation,[2] intrauterine therapy should be possible. Guidelines for the management of fetuses identified with CHB, and fetuses with a normal heartbeat but at high risk of developing CHB, are not established. Moreover, it has been observed that conduction defects can progress after birth. McCue *et al.*[29] have reported a neonate with first-degree block at birth that resolved at 6 months. In contrast, Geggel and colleagues[30] reported an infant born with second-degree block who progressed to third-degree block by 9 weeks of age. Perhaps most disturbing is our own published observation on the postnatal progression of CHB. Nine neonates in the RRNL[6] had a prolonged PR interval on electrocardiography at birth,

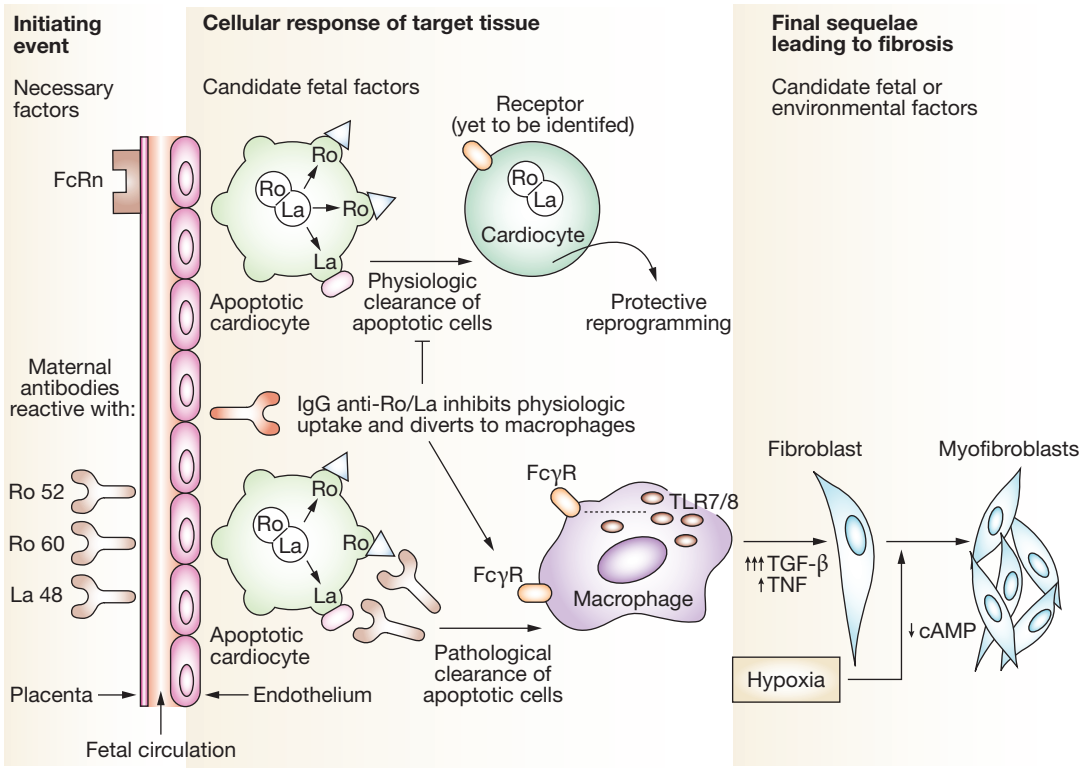

Figure 1 The pathogenesis of congenital heart block: current working hypothesis. This schematic presents an overview of the putative mechanisms of autoantibody-induced injury leading to congenital heart block. The molecular characterization of the link between anti-SSA/Ro or anti-SSB/La antibodies and cardiac injury is a challenging task, given the intracellular localization of the cognate antigen. Apoptosis is a critical part of this process. The mechanisms of apoptotic clearance in the heart involve the participation of resident cardiocytes. As depicted in this schematic, maternal anti-SSA/Ro and anti-SSB/La antibodies in the fetal circulation might inadvertently divert normal clearance of apoptotic cardiocytes by healthy cardiocytes toward clearance by professional macrophages (via FcγR) with release of inflammatory and/or fibrosing cytokines. Components of our proposed cascade include macrophages (representing the inflammatory component) and fibroblasts (representing the scarring component). Abbreviations: cAMP, 3',5'-cyclic adenosine monophosphate; FcγR, Fc γ receptors; FcRn, Fc receptor n; TGF-β, transforming growth factor β; TLR, Toll-like receptor; TNF, tumor necrosis factor.

four of whom progressed to more-advanced atrioventricular block. Two children diagnosed *in utero* with second-degree block were treated with dexamethasone and reverted to normal sinus rhythm by birth, but ultimately progressed to third-degree block. Four children had second-degree block at birth; of these, two progressed to third-degree block.[31]

Treating established CHB

From an immunological perspective, reduction of a generalized inflammatory response has traditionally been considered a logical approach for the prevention or treatment of heart block. The use of maternal oral dexamethasone therapy has been popularized by several groups, but its scientific merit and associated risks are questionable. In a retrospective chart review, our own group initially investigated[32] the use of this medication by evaluating cases from the RRNL. In 28 of the 47 mothers identified to be carrying a fetus with CHB, treatment with a fluorinated steroid (e.g. dexamethasone or betamethasone) was instituted. In 21 treated mothers whose fetuses had third-degree block at presentation, the block was not reversible. Three treated fetuses with alternating second and third-degree block eventually developed permanent third-degree block. There were four interesting cases in which second-degree block reversed to first-degree block at birth; however, long-term follow-up revealed that two of these

fetuses subsequently progressed to second-degree block.[31] In the group of 22 pregnancies in which maternal steroids were not given, 18 had irreversible third-degree heart block, 2 had second-degree alternating with third-degree block that progressed to third-degree block, as did the 2 patients with second-degree block.[32] It was concluded from this retrospective study that there was no difference in mortality, prematurity, final degree of heart block or the need for pacemaker in fetuses whose mothers were treated with or without steroids. It was noted that the presence of pericardial or pleural effusions as well as ascites and hydrops seemed to improve with the use of steroids. Also, there was a suggestion of reversal of less-advanced block, which, in theory, could forestall the need for a pacemaker. Overall, this study, albeit limited in the number of patients and based on retrospectively collected data, helped to popularize the use of fluorinated steroids as a treatment for CHB identified *in utero*.

Jaeggi *et al.*[33] reported extensive clinical data on their cohorts of prenatally diagnosed complete atrioventricular block without structural heart disease. This was a single-institution timed series that evaluated the latest standardized treatment approaches. Between 1990 and 2003, CHB was diagnosed in 37 pregnancies (4 mothers did not have anti-SSA/Ro antibodies). Twenty one of these women were treated with oral dexamethasone at 4 mg or 8 mg daily for 2 weeks, followed by 4 mg daily for at least 3 weeks. Of these 21 women, 9 were also treated with β-adrenergic stimulation owing to low fetal heart rate (<55 bpm). In the 21 fetuses exposed to the regimen of dexamethasone and protocol-driven sympathomimetics, both the live birth rate and 1-year survival rate was 95%, compared with a live birth rate of 77% and 1-year survival rate of 46% for those fetuses not exposed to therapy ($P<0.02$ for comparison of 1-year survival). These authors concluded that maternal dexamethasone with β-adrenergic stimulation for bradycardia was an effective treatment program.

The potential efficacy of dexamethasone for less-advanced heart block led to the consideration of this approach in an interesting case report. Rosenthal *et al.*[34] performed serial echocardiography in a pregnant mother who previously had a child with CHB. Early evidence of myocardial dysfunction at 21 weeks of gestation prompted the initiation of oral dexamethasone 4 mg daily. Echocardiography 2 weeks later revealed nearly complete resolution of the effusion and improvement in myocardial function. Electrocardiography at birth showed first-degree block that was also seen by fetal Doppler imaging. The interpretation of this study was that pre-emptive dexamethasone therapy limited the conduction injury to first-degree block and prevented more-advanced block. This encouraging observation provided part of the impetus and validation for the PR Interval and Dexamethasone Evaluation (PRIDE) study described below.

Meijboom and colleagues[35] reported a case of progression of incomplete atrioventricular block to third-degree block, despite the use of dexamethasone. Moreover, complications of dexamethasone in this case included intrauterine growth retardation, oligohydramnios, prolonged adrenal suppression, and late learning disabilities. Disturbed by this case experience, these investigators reviewed the literature on the use of steroids for treating CHB. Ninety-three cases (published in 19 articles) were identified in which CHB was treated with maternal steroids. Importantly, complete block was always irreversible, only 3 of the 13 cases of incomplete heart block improved, and there were multiple adverse effects. Fluorinated steroids were the glucocorticoid preparation used, as only betamethasone and dexamethasone cross the placenta unmetabolized, while prednisone and prednisolone are inactivated by placental 11β-hydroxysteroid dehydrogenase. The adverse effects of steroid treatment included intrauterine growth retardation, oligohydramnios, adrenal suppression, learning disabilities and decreased brain growth, as well as late hypertension and possible diabetes. This European group, therefore, concluded that maternal dexamethasone therapy as prevention or treatment for CHB is questionable at best, and not recommended clinically.

Regarding potential neuropsychological impairment, Brucato *et al.*[36] reported normal IQ scores and absence of learning disabilities or dyslexia in 11 children exposed to prolonged dexamethasone *in utero* for treatment of CHB. This same group has also described normal T-cell development and function in seven children with CHB exposed to dexamethasone during fetal development.[37] Our current approach to CHB diagnosed *in utero* is presented in Table 1.

Table 1 Therapeutic approach for congenital heart block diagnosed *in utero*.

Clinical situation	Treatment
Third-degree block, no hydrops fetalis	Evaluation by serial echocardiography; no therapy
Second-degree block or alternating second/third-degree block	Treatment with 4 mg oral dexamethasone daily. If progression to third-degree block occurs, taper dexamethasone dose to discontinuation. If reversal to NSR or lesser forms of block occurs, continue to delivery at term
Prolonged mechanical PR interval (first-degree block)	Repeat echocardiography in 24 h. If first-degree block persists, treatment with 4 mg oral dexamethasone daily. If progression to third-degree block occurs, taper dexamethasone dose to discontinuation. If reversal to NSR occurs or first-degree block persists, taper or individualize therapy
Block associated with signs of myocarditis, CHF and/or hydropic changes	Treatment with 4 mg oral dexamethasone daily until improvement
Severely hydropic fetus	Consider termination. Treatment with 4 mg oral dexamethasone daily plus apheresis to rapidly remove maternal antibodies

Abbreviations: CHF, chronic heart failure; NSR, normal sinus rhythm.

MONITORING THE PR INTERVAL: EUROPEAN AND US EXPERIENCE

As fetuses presenting with third-degree block might not benefit from treatment, there are two critical times to intervene: when the PR interval is prolonged but atrial signals continue to reach the ventricles (first or second-degree block); or when signs of myocardial dysfunction alone are present. From a clinical perspective, there is a clear need to identify an early marker of CHB; from a basic science perspective, the knowledge that antibodies can induce lesser degrees of injury would be important. What we tried to find out in a US-based observational study (the PRIDE study[9]) was whether, in addition to causing complete block, these same antibodies can cause less-advanced block before they cause complete block. In the PRIDE study, echocardiography was performed serially, beginning at 16 weeks of gestation in pregnant women known to have anti-SSA/Ro antibodies. The primary outcome measure was the mechanical PR interval, defined using the gated-pulsed Doppler technique as the time interval from the onset of the mitral A wave (atrial systole) to the onset of the aortic pulsed Doppler tracing (ventricular systole) within the same left ventricular cardiac cycle. Secondary outcomes included evaluation of myocardial function. The goal was to determine the earliest noninvasive echocardiographic marker of injury.

In total, 118 pregnant women with anti-SSA/Ro antibodies were enrolled, of which 98 completed an evaluable course. The protocol entailed weekly fetal echocardiography from 16 to 26 weeks of gestation, and biweekly from 26 to 34 weeks. PR intervals >150 ms (mean + 3 SD) were considered abnormally prolonged, consistent with first-degree block. Ninety-two fetuses had normal PR intervals throughout the study. NLE developed in 10 cases, 4 of which had rash only. Three fetuses had third-degree block, none of whom had a preceding abnormal PR interval (note that in two of these fetuses more than 1 week elapsed between echocardiographic evaluations). Tricuspid regurgitation preceded complete block in one fetus, and atrial echodensity preceded the block in a second fetus. Three fetuses had a PR interval greater than 150 ms; two of these, each detected before 21 weeks, reversed within 1 week after institution of 4 mg of dexamethasone. Whether dexamethasone was curative or incidental could not be assigned. A third case developed first-degree block at birth (32 weeks' gestation) after normal PR intervals *in utero*, as demonstrated by electrocardiography; the block persists at age 3 years. Importantly, no conduction abnormalities developed after a normal electrocardiogram at birth. Heart block (combining all degrees) occurred in 3 (19%) of 16 pregnancies in mothers with a previous CHB child and in 3 (4%) of 74 mothers with no previously affected children.

Sonesson *et al.*[38] reported the first prospective study in which the mechanical PR interval was used to identify early conduction disease in 24 pregnancies of mothers with anti-SSA/Ro antibodies. In contrast to the low percentage of fetuses affected in the US study, one-third of the fetuses in this European study had signs of a prolonged

PR interval. While one explanation for this high frequency might have been the inclusion requirement for antibodies reactive against SSA/Ro 52 kDa in all patients, resulting in an 'enriched' cohort, this seroreactivity was also observed in 80% of the mothers in PRIDE. As information on previous pregnancies was not provided, no inference can be made as to whether the increased incidence of injury reflects recurrence rates rather than index cases. Perhaps most importantly, the definition of a prolonged PR interval was set at 135 ms (mean + 2 SD, derived from their previous studies in nearly 300 pregnancies[39]). Re-evaluation of the PRIDE study utilizing this lower threshold revealed a consistency between the two studies, with about one-third of the fetuses in PRIDE having a prolonged PR interval according to the Sonesson criterion. In all PRIDE fetuses, however, a PR of 135–150 ms spontaneously reversed by the next echocardiogram. In the Sonesson study, only two fetuses had a prolonged PR interval as defined by the PRIDE criterion. One of these two fetuses had a PR approaching 150 ms at 24 weeks, which decreased to 145 ms by 26 weeks; no information regarding treatment was provided. The other fetus had second-degree block that reversed to first-degree after treatment, but it was not clear whether there was an initial progression through first-degree prior to second-degree. The one fetus reported to progress from a prolonged PR interval to third-degree block within 6 days had a PR of 140 ms. The plasticity of the PR interval prolongation was further supported by the return of all abnormal values obtained on newborn electrocardiography to normal values several weeks later.

The two critical issues raised by both the PRIDE and Sonesson studies are the clinical significance of a prolonged PR interval and the biological implications of a prolonged PR interval with regard to tissue injury. An isolated prolongation of the PR interval can be transient, related to vagal tone, medication use or reversible injury, or it might be permanent or progress to a more marked delay because of physical injury to the specialized electrical pathway (e.g. inflammation or scarring). Prolongation might represent a variant of the normal state, and only in retrospect does it have clinical significance if it is either sustained after birth or progresses to more advanced block. A PR interval that exceeds the expected 95% confidence interval of a normal population can be transient, sustained or progressive. Perhaps the final outcome depends on the influence of fetal and environmental factors; these permissive factors might be present in certain fetuses and not in others, thus accounting for the rarity of clinical disease. If prolongation of the PR interval does represent tissue injury, regardless of how minimal, it might be so rapid as to go unnoticed.

Accurate identification of fetuses in which first-degree block unambiguously represents a warning sign would be a major advance, as early disease can be reversible. This identification requires a definition that is acceptable to the managing physicians, and needs to identify fetuses that are likely to develop sustained or progressive damage if left untreated. This task is particularly challenging because dexamethasone and betamethasone therapy poses both maternal and fetal risks.

Given the identification of advanced block and severe cardiomyopathy within 1 week of a normal echocardiogram, and the most frequent detection time being at or before 24 weeks' gestation, it would seem appropriate to perform weekly monitoring between 16 and 24 weeks. The goal of this monitoring would be to identify a biomarker of reversible injury, such as a PR interval prolongation above 150 ms, moderate or severe tricuspid regurgitation, and/or atrial echodensity.

INTRAVENOUS IMMUNOGLOBULIN G: A POTENTIAL PROPHYLACTIC APPROACH

The morbidity and mortality associated with third-degree heart block suggests the need for a new prophylactic therapy (other than dexamethasone) to be given early in pregnancy before the onset of disease, perhaps targeted to the highest-risk pregnancies, such as those women with a prior affected fetus. Therapy should either be targeted to eliminating the 'necessary' factor (i.e. 'no antibody, no disease') or modifying the inflammatory component before it provokes an irreversible scarring phenotype of the fibroblast.[40] IgG pooled from the plasma of healthy donors (intravenous immunoglobulin [IVIG] therapy) is a promising agent that might have an effect at several levels of the proposed pathologic cascade. In a study of 8 pregnancies in mothers with anti-SSA/Ro antibodies and a previous child with CHB, treatment with 1 gm/kg IVIG at the 14th and 18th week of gestation prevented CHB in 7 cases.[41] Although even one case of CHB is disappointing, it is less than the predicted recurrence rate (20%). The dosing schedule of IVIG might, however, not have been optimal. Arguably,

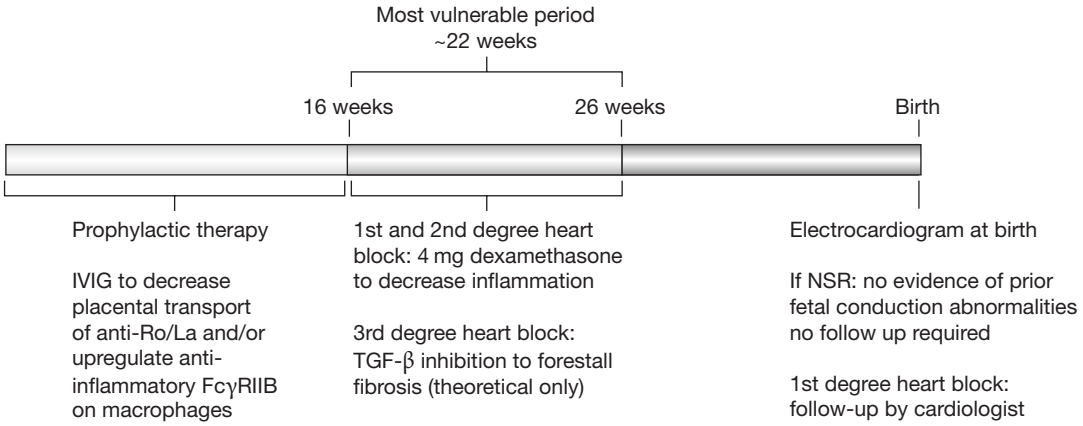

Figure 2 Translational approach for managing and preventing congenital heart block. Weekly fetal echocardiography should be performed in mothers with anti-SSA/Ro antibodies to monitor for an abnormal PR interval, and treatment could be provided as shown. Abbreviations: FcγR, Fcγ receptor; IVIG, intravenous immunoglobulin; NSR, normal sinus rhythm; TGF-β, transforming growth factor β.

initiation of IVIG at 14 weeks might be too late, as it is at least 2 weeks after maternal antibody transfer has become effective; these 2 weeks might be a critical time for prevention. Furthermore, discontinuation at 18 weeks may be premature.

In addition to its efficacy in affording resistance to infections, the intravenous administration of high doses of IgG has been beneficial in a variety of immune-mediated and inflammatory diseases and is FDA-approved as a treatment for primary immunodeficiency, idiopathic thrombocytopenia purpura, Kawasaki disease, B-cell chronic lymphocytic leukemia with hypogammaglobulinemia, pediatric HIV infection, and for allogenic bone marrow transplant in adults.[42] Many of the proposed effects of IVIG might be entirely nonspecific, mediated through the constant regions of IgG. These include blocking FcRn, which would enhance autoantibody half-life and blockade of stimulatory FcγRs, and stimulating activity of the inhibitory FcγR, FcγRIIB. [43,44] Of relevance to CHB, FcRn is the receptor that mediates placental transport of maternal IgG to the fetus.[3] It has recently been emphasized that the highly sialylated IgG fraction of IVIG confers enhanced anti-inflammatory activity.[45]

IVIG might, therefore, be particularly effective in preventing the passively acquired autoimmune aspects of CHB. There are several potential mechanisms for this effect. The first two relate to lowering, or even eliminating, maternal antibody in the fetal circulation (maternal perspective): increased catabolism of maternal antibody, and decreased placental transport of maternal antibody. By decreasing antibody levels, fewer antibodies would be available to bind apoptotic cardiocytes. Thus, the initial cascade to injury might be abrogated. The third consideration is the effect of IVIG transported into the fetal circulation, where it might act to upregulate surface expression of the inhibitory FcγRIIB receptor on fetal macrophages, thereby decreasing secretion of tumor necrosis factor and TGF-β (fetal perspective). In this context, it is possible that the presence of FcγR polymorphisms might influence the response to IVIG therapy. An antiapoptotic effect of IVIG would be highly speculative, which would certainly be relevant to the pathogenesis of CHB; we have accumulating evidence that apoptosis of cardiocytes provides an essential link between antibody and fibrosis.

The PITCH study (Preventive IVIG Therapy for Congenital Heart Block) is currently enrolling patients.[46] Sample size calculations utilize Simon's two-stage optimal design. Based on a two-sided significance level of 0.05, a power of 90% to show a reduction of risk to 5% given the prediction that 18% of untreated subjects will get some degree of heart block, the first stage will enroll 19 mothers who have had a previous child with CHB or rash to receive IVIG (400 mg/kg IVIG every 3 weeks) from 12 to 24 weeks gestational age. If fewer than 3 mothers have children with second or third-degree heart block, then an additional 35 mothers will be enrolled into the second stage of the study (for a total of 54 subjects). At the end of the trial, the treatment

will be considered efficacious and worthy of further study if fewer than 6 mothers out of 54 have a child with advanced heart block. The secondary outcomes to be evaluated include: first-degree block, signs of myocardial injury in the absence of any conduction defects, or isolated endocardial fibroelastosis. The rationale for the dose of IVIG used (400 mg/kg), which is traditionally considered a replacement dose and not an anti-inflammatory dose such as 1 g/kg, was based on the immaturity of placental transport in the early second trimester and the fetus as the targeted patient. The effect of IgG dose on maternal antibody lowering as a potential biomarker related to efficacy will be of interest. Although the dose of IVIG is relatively low, the theoretical risk of exacerbating the state of hyperviscosity and increased thrombophilia already present during pregnancy is acknowledged.

CONCLUSIONS

Clearly, the ideal approach to CHB is prevention, as available histological data demonstrate that, in CHB, the atrioventricular node is replaced by fibrosis, and is not likely to regain function. Figure 2 summarizes a theoretical translational model for prevention and management of CHB. Therapy should either be targeted to eliminate the 'necessary' factor ('no antibody, no disease') or to modify the inflammatory component before it provokes an irreversible scarring phenotype of fibroblasts.

KEY POINTS

- Mothers with anti-SSA/Ro antibodies face a 2% risk of having a child with congenital heart block if it is a first pregnancy or if previous babies have all been healthy
- A previous child with congenital heart block raises the risk of having another by almost tenfold
- Normal sinus rhythm can progress to complete block in 7 days; thus, frequent monitoring of a pregnancy in a mother with anti-SSA/Ro antibodies is appropriate
- A mechanical PR interval of greater than 150 ms is consistent with first-degree block, and warrants an immediate discussion regarding the use of a fluorinated steroid to potentially reverse the situation
- Intravenous immunoglobulin is currently being evaluated as a prophylactic therapy

References

1 Buyon JP *et al.* (1996) The effects of pregnancy on autoimmune diseases. *Clin Immunol Immunopath* **78:** 99–104
2 Buyon JP and Clancy RM (2006) Neonatal lupus. In *Dubois' Lupus Erythematosus*, edn 7, 1058–1080 (Eds Wallace DJ and Hahn BH) Philadelphia: Lippincott Williams & Wilkins
3 Leach JL *et al.* (1996) Isolation from human placenta of the IgG transporter, FcRn, and localization to the syncytiotrophoblast: implications for maternal-fetal antibody transport. *J Immunol* **157:** 3317–3322
4 Jaeggi ET *et al.* (2002) Outcome of children with fetal, neonatal or childhood diagnosis of isolated congenital atrioventricular block. *J Am Coll Cardiol* **39:** 130–137
5 Moak JP *et al.* (2001) Congenital heart block: development of late-onset cardiomyopathy, a previously underappreciated sequela. *J Am Coll Cardiol* **37:** 238–242
6 Buyon JP *et al.* (1998) Autoimmune-associated congenital heart block: mortality, morbidity, and recurrence rates obtained from a national neonatal lupus registry. *J Am Coll Cardiol* **31:** 1658–1666
7 Waltuck J and Buyon J (1994) Autoantibody-associated congenital heart block: outcome in mothers and children. *Annals Int Med* **120:** 544–551
8 Brucato A *et al.* (2001) Risk of congenital heart block in newborns of mothers with anti-Ro/SSA antibodies detected by counterimmunoelectrophoresis. *Arthritis Rheum* **44:** 1832–1835
9 Friedman DM *et al.* (2008) Utility of cardiac monitoring in fetuses at risk for congenital heart block: the PR Interval and Dexamethasone Evaluation (PRIDE) prospective study. *Circulation* **117:** 485–493
10 Salomonsson S *et al.* (2002) A serologic marker for fetal risk of congenital heart block. *Arthritis Rheum* **46:** 1233–1241
11 Salomonsson S *et al.* (2005) Ro/SSA autoantibodies directly bind cardiomyocytes, disturb calcium homeostasis, and mediate congenital heart block. *J Exp Med* **201:** 11–17
12 Buyon JP *et al.* (1994) Autoantibody responses to the "native" 52 kDa SS-A/Ro protein in neonatal lupus syndromes, systemic lupus erythematosus and Sjögren's syndrome. *J Immunology* **152:** 75–84
13 Clancy RM *et al.* (2005) Maternal antibody responses to the 52 kDa SSA/Ro p200 peptide and the development of fetal conduction defects. *Arthritis Rheum* **52:** 3079–3086
14 Solomon DG *et al.* (2003) Birth order, gender and recurrence rate in autoantibody-associated congenital heart block: implications for pathogenesis and family counseling. *Lupus* **12:** 646–647
15 Gordon P *et al.* (2004) Anti-52 kDa Ro, anti-60 kDa Ro, and anti-La antibody profiles in neonatal lupus. *J Rheum* **31:** 2480–2487
16 Vincent A *et al.* (2000) Molecular targets for autoimmune and genetic disorders of neuromuscular transmission. *Eur J Biochem* **267:** 6717–6728
17 Kreier JP (2002) *Infection, Resistance and Immunity*, edn 2. Oxford, UK: Taylor & Francis
18 Alexander E *et al.* (1992) Anti-Ro/SS-A antibodies in the pathophysiology of congenital heart block in neonatal lupus syndrome, an experimental model: *in vitro* electrophysiologic and immunocytochemical studies. *Arthritis Rheum* **35:** 176–189
19 Garcia S *et al.* (1994) Cellular mechanism of the conduction abnormalities induced by serum from anti-Ro/SSA-positive patients in rabbit hearts. *J Clin Invest* **93:** 718–724
20 Boutjdir M *et al.* (1998) Serum and IgG from the mother of a child with congenital heart block induce conduction abnormalities and inhibit L-type calcium channels in a rat heart model. *Pediatr Res* **80:** 354–362

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21 Buyon JP *et al.* (2002) Cardiac 5-HT_4 serotoninergic receptors, 52 kD SSA/Ro and autoimmune-associated congenital heart block. *J Autoimmunity* **19:** 79–86
22 Kamel R *et al.* (2005) Autoantibodies against the serotoninergic 5-HT_4 receptor and congenital heart block: a reassessment. *J Autoimmun* **25:** 72–76
23 Clancy RM *et al.* (2004) Immunohistologic evidence supports apoptosis, IgG deposition and novel macrophage/fibroblast crosstalk in the pathologic cascade leading to congenital heart block. *Arthritis Rheum* **50:** 173–182
24 Clancy RM *et al.* (2006) Impaired clearance of apoptotic cardiocytes linked to anti-SSA/Ro-SSB/La antibodies in pathogenesis of congenital heart block. *J Clin Investigation* **116:** 2413–2422
25 Clancy RM *et al.* (2002) Transdifferentiation of cardiac fibroblasts, a fetal factor in anti-SSA/Ro-SSB/La antibody-mediated congenital heart block. *J Immunol* **169:** 2156–2163
26 Miranda-Carús ME *et al.* (2000) Anti-SSA/Ro and anti-SSB/La autoantibodies bind the surface of apoptotic fetal cardiocytes and promote secretion of tumor necrosis factor α by macrophages. *J Immunol* **165:** 5345–5351
27 Clancy RM *et al.* (2003) Cytokine polymorphisms and histologic expression in autopsy studies: contribution of TNF-α and TGFβ1 to the pathogenesis of autoimmune-associated congenital heart block. *J Immunol* **171:** 3253–3261
28 Clancy RM *et al.* (2007) Role of hypoxia and cAMP in the transdifferentiation of human fetal cardiac fibroblasts: implications for progression to scarring in autoimmune-associated congenital heart block. *Arthritis Rheum* **56:** 4120–4131
29 McCue CM *et al.* (1977) Congenital heart block in newborns of mothers with connective tissue disease. *Circulation* **56:** 82–90
30 Geggel RL *et al.* (1988) Postnatal progression from second- to third-degree heart block in neonatal lupus syndrome. *J Ped* **113:** 1049–1052
31 Askanase AD *et al.* (2002) Spectrum and progression of conduction abnormalities in infants born to mothers with anti-Ro/La antibodies. *Lupus* **11:** 145–151
32 Saleeb S *et al.* (1999) Comparison of treatment with fluorinated glucocorticoids to the natural history of autoantibody-associated congenital heart block. *Arthritis Rheum* **42:** 2335–2345
33 Jaeggi ET *et al.* (2004) Transplacental fetal treatment improves the outcome of prenatally diagnosed complete atrioventricular block without structural heart disease. *Circulation* **110:** 1542–1548
34 Rosenthal D *et al.* (1998) A new therapeutic approach to the fetus with congenital complete heart block: pre-emptive, targeted therapy with dexamethasone. *Obstet Gynecol* **92:** 689–691
35 Breur JMPJ *et al.* (2004) Treatment of fetal heart block with maternal steroid therapy: case report and review of the literature. *Ultrasound Obstet Gynecol* **24:** 467–472
36 Brucato A *et al.* (2006) Normal neuropsychological development in children with congenital complete heart block who may or may not be exposed to high-dose dexamethasone *in utero*. *Ann Rheum Dis* **65:** 1422–1426
37 Airo' P *et al.* (2006) Characterization of T-cell population in children with prolonged fetal exposure to dexamethasone for anti-Ro/SS-A antibodies associated congenital heart block. *Lupus* **15:** 553–561
38 Sonesson SE *et al.* (2004) Signs of first-degree heart block occur in one-third of fetuses of pregnant women with anti-SSA/Ro 52 kD antibodies. *Arthritis Rheum* **50:** 1253–1261
39 Andelfinger G *et al.* (2001) Reference values for time intervals between atrial and ventricular contractions of the fetal heart measured by two Doppler techniques. *Am J Cardiol* **88:** 1433–1436
40 Clancy RM *et al.* (2002) Transdifferentiation of cardiac fibroblasts, a fetal factor in anti-SSA/Ro-SSB/La antibody-mediated congenital heart block. *J Immunol* **169:** 2156–2163
41 Kaaja R and Julkunen H (2003) Prevention of recurrence of congenital heart block with intravenous immunoglobulin and corticosteroid therapy: comment on the editorial by Buyon *et al.* [letter]. *Arthritis Rheum* **48:** 281–282
42 Looney RJ and Huggins J (2006) Use of intravenous immunoglobulin (IVIG). *Best Pract Res Clin Haematol* **18:** 3–25
43 Samuelsson A *et al.* (2001) Anti-inflammatory activity of IVIG mediated through the inhibitory Fc receptor. *Science* **291:** 445–446
44 Nimmerjahn F and Ravetch JV (2008) Anti-inflammatory actions of intravenous immunoglobulin. *Annu Rev Immunol* **26:** 513–533
45 Anthony RM *et al.* (2008) Recapitulation of IVIG anti-inflammatory activity with a recombinant IgG Fc. *Science* **320:** 373–376
46 Preventive IVIG Therapy for Congenital Heart Block (PITCH) [http://clinicaltrials.gov/ct2/show/NCT00460928?term=NCT00460928&rank=1] (accessed 13 January 2009)