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PREVENTION AND TREATMENT IN UTERO OF AUTOIMMUNE ASSOCIATED CONGENITAL HEART BLOCK

Amit Saxena, MD[1], **Peter M. Izmirly, MD**[1], **Barbara Mendez, MD**[1], **Jill P. Buyon, MD**[1], and **Deborah M. Friedman, MD**[2]

[1]New York University School of Medicine, Department of Medicine, Division of Rheumatology

[2]New York Medical College, Department of Pediatrics, Division of Pediatric Cardiology

Abstract

Transplacental transfer of maternal anti-Ro and/or anti-La autoantibodies can result in fetal cardiac disease including congenital heart block and cardiomyopathy, called cardiac Neonatal Lupus (NL). Thousands of women are faced with the risk of cardiac NL in their offspring, which is associated with significant morbidity and mortality. There are no known therapies to permanently reverse third degree heart block in NL, although several treatments have shown some effectiveness in incomplete heart block and disease beyond the atrioventricular node. Fluorinated steroids taken during pregnancy have shown benefit in these situations, although adverse effects may be concerning. Published data are discordant on the efficacy of fluorinated steroids in the prevention of mortality in cardiac NL. β-agonists have been used to increase fetal heart rates in utero. The endurance of β-agonist effect and its impact on mortality are in question, but when used in combination with other therapies, they may provide benefit. No controlled experiments regarding the use of plasmapheresis in cardiac NL have been performed, despite its theoretical benefits. Intravenous immunoglobulin was not shown to prevent cardiac NL at a dose of 400 mg/kg, although it has shown effectiveness in the treatment of associated cardiomyopathy both in utero and after birth. Retrospective studies have shown that hydroxychloroquine may prevent the recurrence of cardiac NL in families with a previously affected child, and a prospective open-label trial is currently recruiting patients in order to fully evaluate this relationship.

Keywords

congenital heart block; cardiomyopathies; neonatal lupus; prevention; treatment

Neonatal lupus (NL) has become an important model of passively acquired autoimmunity since the observation in the late 1970s that nearly all sera from mothers of children with isolated congenital heart block (CHB) contain specific autoantibodies.[1] It has since been described that antibodies reactive with Ro and/or La ribonucleoproteins cross the placenta, enter the fetal circulation via trophoblast FcγRn receptors, and presumably injure the fetus, most often during the 16–24th gestational weeks.[2,3] Although advanced conduction abnormalities are the signature phenotype of anti-Ro associated cardiac disease, often

Corresponding Author: Amit Saxena, MD, 301 East 17th Street, Room 1610A, New York, NY 10003, Telephone Number – (212) 263-0743, Fax Number – (212) 263-7706, Amit.Saxena@nyumc.org.

referred to as cardiac NL (albeit the child does not have lupus and often neither does the mother at that time), the spectrum of fibrosis can extend to or uniquely affect the myocardium and endocardium. [4,5] In contrast to the heart disease, other neonatal manifestations highly associated with maternal anti-Ro and/or La antibodies are transient and disappear with the clearance of maternal antibodies from the neonatal circulation. These include skin lesions and dysfunction of the liver and blood elements. The cardiac injury is clearly the most serious manifestation, with lifelong consequences. The estimated prevalence of anti-SSA/Ro antibodies is approximately 0.5%.[1] Thus, thousands of women in the United States will be faced with the risk of cardiac NL in their offspring.

Prospective studies of pregnancies in women with the candidate antibodies and no previously affected children have estimated the risk of cardiac NL at approximately 2%.[6–9] The risk of recurrent cases of cardiac NL in mothers with a previously affected child is 17%.[10] However, the risk of morbidity and mortality in affected children is extremely significant. Among prior reports the mortality rate varies from a low of 10% (in a cohort of 57 fetuses of which 72% were exposed to anti-Ro antibodies) to a high of 29% (in a cohort of 35 of which 89% were exposed to the antibodies).[11, 12] The percentages of children receiving pacemakers vary from 63% to 93%.[13–15] Given the clinical importance of NL, its unclear pathogenesis and the absence of either an effective or clearly prophylactic treatment, the U.S. based Research Registry for Neonatal Lupus (RRNL) was established by NIAMS in September 1994 to provide a source of well documented cases, inclusive of mothers and their entire families.[13] In the RRNL review of 325 cases all exposed to anti-Ro antibodies, the mortality rate was 17.5%.[16] Of the 57 deaths, eighteen (31.6%) occurred in utero, and 26 (45.6%) occurred within the first 6 months of life. [16] The majority of post-natal deaths occurred in the first year. The cumulative probability of requiring a pacemaker at 10 years was 70%.[16] More than half were implanted by one year of age, the majority being placed within the first month of life. [16] Cardiac transplantation has been required in several cases as well.[16]

To date, no pharmacological therapy has resulted in permanent reversal of third degree CHB in NL. However, the maternal use of fluorinated steroids during pregnancy has shown some efficacy in treating second degree heart block and cardiac disease beyond the atrioventricular node, and β-agonists have been used to increase fetal heart rates in utero. Intravenous immunoglobulin (IVIG) has been studied for prevention of disease, and has been used in treatment of associated cardiomyopathy. Hydroxychloroquine (HCQ) is currently being studied as a potentially promising approach to prevention of cardiac NL (Table 1).

Fluourinated Steroids

Fluorinated steroids such as dexamethasone or betamethasone cross the placenta during pregnancy, while non-fluorinated steroids (such as prednisone) are inactivated by placental 11 β-dehydrogenase-type 2 expressed in syncytial trophoblast cells, which cover placental chorionic villi and form an interface between the fetal and maternal circulation.[17] Available data on the prevention of cardiac NL with fluorinated steroids is limited. In a study from Japan, cardiac NL did not develop in any case exposed to steroids compared to 24.5%

unexposed.[18] However this study combined fluorinated and non-fluorinated steroids and included initial and recurrent pregnancies which have different risks for developing cardiac NL. In a study from France, limited to pregnancies subsequent to a cardiac NL pregnancy, there were no cases of cardiac NL in either the treated or untreated group.[19] The authors pointed out that even though there were no cardiac NL cases in the 6 pregnancies exposed to fluorinated steroids, 2 resulted in still births, 2 in spontaneous abortions and 2 live births with intrauterine growth restriction. These poor outcomes may represent the significant untoward side effects of steroid treatment.

With regard to treatment, combining the data from two published cohorts, it was shown that 7 (35%) of 20 cases of fetal second degree heart block in which maternal fluorinated steroids were given reverted to normal sinus rhythm or first degree block compared to 1 (6.25%) of 16 in the untreated group, which yielded a p value of 0.053.[20] Long term data were not available for the majority of cases. Published data are discordant regarding the efficacy of fluorinated steroids in the prevention of mortality in cardiac NL. A study from Canada reported a mortality rate of 10% in the treated group compared to 54% in the untreated group at one year.[21] However, the study used historical controls which had higher rates of poor prognostic factors. In contrast, a European study did not observe a treatment benefit; specifically, the one month mortality rate was 4% in the treated group compared to 5% in the untreated group.[22] This study contained only a small number of cases treated with fluorinated steroids in which there were associated poor prognostic factors. In an Italian study of 28 cardiac NL cases, treatment with dexamethasone produced a rapid improvement in the degree of fetal hydrops in 3 of 5 cases, and several case reports have also documented efficacy of fluorinated steroids for treating hydrops.[23–26] Recently presented data from the RRNL suggests that exposure to fluorinated steroids may improve survival at 6 months in cases where hydrops was present.[27] Of 27 fetuses exposed to steroids, 14 (51.9%) died compared to 9 of the 10 (90%) of cases not exposed (p=0.059). [27] A multicenter retrospective review of 20 cases with antibody associated cardiomyopathy/endocardial fibroelastosis (EFE) in which 17 were treated with prenatal dexamethasone described 4 deaths from hydrops, but the remaining 16 had normal systolic function at a mean follow up of 2.9 years.[28] However, 9 of the cases also received IVIG during pregnancy, 15 received post natal corticosteroids, and 14 received post natal IVIG, which may confound interpretation of the effect of fluorinated steroids in treatment of cardiac disease.

Although fluorinated steroids may show promise for providing benefit in cardiac NL, there is potential for major maternal and fetal side effects, including adrenal insufficiency and fetal neurodevelopmental and growth abnormalities. Therefore, further study is warranted to identify the benefit for fetuses with cardiac NL stratified by poor prognostic factors such as EFE, dilated cardiomyopathy, and hydrops.

β-Agonists

Terbutaline is the most commonly used β2-adrenergic receptor agonist in the treatment of cardiac NL, although salbutamol and ritodrine have also been used. Sympathomimetic medications were initially noted to result in fetal tachycardia as a side effect during use as tocolytic agents.[29] The use of β-agonists in NL has been considered due to the finding that

fetal ventricular rates less than 55 beats per minute (bpm) are frequently associated with cardiac decompensation due to low cardiac output.[30] Several case reports have described successful treatment with β-agonists, with increases in fetal heart rate, improvement in cardiac function and completion of pregnancies.[31–34] In a study of 21 fetuses with third degree atrioventricular block, seven mothers with fetal ventricular rates less than 60 bpm were given terbutaline, six of whom had an initial increase in heart rate.[35] Four maintained a heart rate greater than 60 bpm and survived to birth, although one died at 3 weeks of age from respiratory distress syndrome. Two fetuses returned to a heart rate less than 55 despite terbutaline and died. These findings bring into question the endurance of β-agonist treatment, as well as its impact on mortality. Two of the seven fetuses in the above study were also exposed to dexamethasone, one of which had associated hydrops fetalis and died at 2 days of age.[35] In the previously discussed study by Jaeggi et al documenting the effectiveness of treatment in preventing mortality in complete heart block, the group treated with fluorinated steroids was also exposed to β-agonists if fetal heart rates fell below 55 bpm.[21] Only four of nine treated had an increase in heart rate, but nevertheless, one year survival of fetuses exposed to β stimulation combined with dexamethasone was improved. Similarly, Cuneo et al studied a management strategy including dexamethasone treatment at heart block diagnosis and terbutaline if the heart rate was less than 56.[36] Thirteen of 29 fetuses received terbutaline, resulting in a significant increase in fetal heart rate and a 100% live birth rate. In both the Jaeggi et al[21] and Cuneo et al[36] combination treatment studies, adverse effects from fluorinated steroid treatments were noted, but no significant complications from β-agonist therapy were described. However, patients sometimes are unable to tolerate the palpitations, anxiety, and headaches that can be associated with β-agonist treatment.

Plasmapheresis

Plasma exchange in women at risk for having a child with cardiac NL may theoretically aid in the prevention and treatment of disease, as plasmapheresis lowers levels of the pathogenic anti- Ro and La antibodies required for disease development. However, this treatment has never been used independently of steroids and only case reports have been published. Several have not identified any benefit in treating previously developed heart block with plasmapheresis.[37–40] Ruffatti et al described two cases with 2nd degree heart block treated with a combination of plasmapheresis, dexamethasone and IVIG which improved to normal atrioventricular conduction, and eventual first degree heart block at the time of birth.[41] It is impossible to know if one particular therapy or the combination was responsible for these findings, however. Plasmapheresis was studied as a prophylactic treatment in 7 women with high titer anti- Ro and La antibodies. One developed heart block, although this mother consistently showed high titers of the autoantibodies despite plasmapheresis.[42] A woman with a prior child affected by cardiac NL was given prophylactic prednisone and plasmapheresis, and another was given a combination of dexamethasone, azathioprine and plasmapheresis; both cases resulted in the birth of a healthy infant.[43,44] However, given the known recurrence rate of 17%, it is unknown if the treatment played any role in preventing cardiac disease. No controlled experiments regarding the use of plasmapheresis in cardiac

NL have been performed, and due to the costly and time consuming process, it does not play a significant role in its management.

Intravenous Immunoglobulin

Two prospective studies evaluated IVIG to prevent cardiac NL in fetuses of mothers who were anti- Ro positive and had a previously affected child.[45,46] Several hypotheses for how IVIG could prevent cardiac tissue damage include a) increased elimination of maternal anti-Ro and anti-La through IVIG saturation of FcγRn accelerating IgG catabolism in the maternal circulation b) decreased placental transport of anti-Ro and anti-La via FcγRn and c) modulation of inhibitory signaling on macrophages, with consequent reduction of the inflammatory response and fibrosis.[47–49] Twenty mothers in the American cohort and 15 in European group were given IVIG at 400mg/kg every 3 weeks from 12–24 weeks of gestation. Cardiac NL developed in 15% and 20% in the American and European groups, respectively.[45,46] The trials were terminated early, and it was concluded that IVIG at the above dose was ineffective at reducing the recurrence rate of cardiac NL. However, it is unknown if higher doses, such as 1g/kg, would be efficacious. In a previously published report, Kaaja and Julkonen treated 8 pregnant mothers with a prior CHB child with 1g/kg of IVIG at 14 and 18 weeks of gestation, and only 1 developed cardiac NL.[50]

IVIG has shown promise in the treatment of fetal cardiac disease specifically when associated with cardiomyopathy. Brucato et al treated two fetuses with complete heart block and severe myocarditis with IVIG 400 mg/kg/d for five days with prompt resolution of the echocardiographic signs of myocarditis and corresponding clinical improvement.[51] As noted previously, in the study by Trucco et al regarding outcomes following IVIG and corticosteroid therapy, twenty patients were treated with IVIG at approximately 1g/kg administered at one or multiple times.[28] Maternal IVIG was given in 9 cases, and 14 infants received IVIG after birth. Their results indicated that 16/20 (80%) patients were alive at a median follow up of 2.9 years and none required cardiac transplantation.[28] This suggested a benefit of IVIG in patients with fetal cardiomyopathy/EFE related to NL in combination with fluorinated steroids. In general IVIG administration is well tolerated and relatively safe, although it does expose both the mother and fetus to foreign blood products and large fluid volumes.

Hydroxychloroquine

A potentially promising approach to prevention of cardiac NL is the use of HCQ. Antimalarials, including HCQ, are among the most frequently prescribed medications in patients with a rheumatic disease, acting as an inhibitor of toll-like receptor ligation.[52] Toll-like receptor signaling has recently been shown (in an in-vitro model system) to play a role in the inflammation and fibrosis that result in cardiac NL, thus revealing a potential target for prevention of the disease.[52,53] A case-control study explored the hypothesis that HCQ might reduce the risk of disease.[54] This initial study was limited to children born to mothers with systemic lupus erythematosus (SLE) and anti-Ro antibodies, and comprised 50 cardiac NL cases and 151 non-cardiac NL controls. Seven (14%) cardiac NL children were exposed to HCQ compared with 56 (37%) controls (p=0.002; OR 0.28). A multivariable analysis

yielded an OR associated with HCQ use of 0.46 (p=0.10). 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.[54] The restriction of this study to mothers with SLE, in an attempt to minimize confounding by indication, limited the number of cases available to address whether HCQ prevents recurrent cardiac NL. A subsequent study was performed to evaluate whether HCQ reduces the increased risk of recurrence of cardiac NL, independent of maternal health status.[55] Using an international cohort, 257 pregnancies in mothers with a previous child with cardiac NL were evaluated (40 exposed and 217 unexposed to HCQ). The recurrence rate of cardiac NL in fetuses exposed to HCQ was 7.5% (3/40) compared to 21.2% (46/217) in the unexposed group (p=0.05). There were no deaths in the HCQ exposed group compared to a case fatality rate of 22% in the unexposed group. In both multivariable and propensity score analyses, the latter an alternative approach to adjust for possible confounding by indication, HCQ use remained significantly associated with a decreased risk of cardiac NL. These data suggest that HCQ may protect the fetus from disease in those exposed to the pathogenic antibody as evidenced by a previous sibling with cardiac NL.[55] HCQ has been used safely and regularly during pregnancy, and has been associated with prevention of SLE flares.[56–58] In a limited placebo-controlled, randomized, double-blind trial of 10 patients with SLE receiving HCQ and 10 receiving placebo, neither congenital abnormalities nor ophthalmologic or auditory abnormalities were detected up to a minimum follow up of 1.5 years.[57] The Preventive Approach to Congenital Heart Block with Hydroxychloroquine (PATCH) is an open-label prospective trial (NCT01379573) that is currently recruiting in order to further identify the utility of HCQ to prevent the recurrence of cardiac NL in high-risk women with a previously affected child.

Conclusion

There are no specific guidelines for the prevention or treatment of cardiac NL, however several studies have provided evidence for a general approach to the disease. While utility of maternal fluorinated steroids to prevent cardiac NL onset or mortality has not been proven, their use in incomplete heart block, cardiomyopathy and hydrops fetalis has been associated with improved outcomes. β-agonists can increase fetal heart rates in those with congenital heart block, but their endurance and impact on mortality remain in question. No controlled experiments regarding the use of plasmapheresis in cardiac NL have been performed. IVIG at a dose of 400 mg/kg did not prevent the recurrence of cardiac NL in mothers with a previously affected child, but it has shown promise in treating fetal cardiomyopathy. Hydroxychloroquine exposure during pregnancy has been associated with a decreased recurrence of cardiac NL, and an open label prospective trial is currently recruiting to further investigate this association.

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Table 1

Overview of Prevention and Treatment Studies in Cardiac Neonatal Lupus

Study	Intervention	Number of Participants	Outcomes
Izmirly et al[16] Eliasson et al[22]	FS use in cases with 2nd degree AV Block (R)	20 treated, 16 untreated	Higher percentage reverting to 1st degree AV block or normal sinus rhythm in treated group (p=0.053)
Izmirly[27]	FS use in cases with hydrops fetalis (R)	27 treated, 10 untreated	Lower 6 month mortality in treated group (p=0.059)
Jaeggi[21]	FS use in cases at diagnosis of heart block (R)	21 treated, 16 untreated	Lower 1 year mortality in treated group (p<0.02)
Eliasson[22]	FS use in cases with 2nd and 3rd degree AV block (R)	67 treated, 108 untreated	No significant difference in mortality between groups
Buyon et al[43] Pisoni et al[46]	IVIG 400 mg/kg q3weeks from GW 12–24 in mothers with previous cardiac NL child (P)	33 treated	6 cases of cardiac NL (18% recurrence rate)
Izmirly[55]	HCQ exposure throughout pregnancy in mothers with previous cardiac NL child (R)	40 treated, 217 untreated	Decreased recurrence rate of cardiac NL in treated group (p=0.050)

FS = Fluorinated Steroids; AV = atrioventricular; IVIG = Intravenous Immunoglobulin; HCQ = Hydroxychloroquine; R = Retrospective Analysis; P = Prospective Study; GW = _____