CASE REPORT

# Complete Congenital Heart Block in the Offspring of an Asymptomatic Woman with Isolated High Titer Anti-Ro Antibody

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## ABSTRACT

Among pregnant women, 1-2% are anti-Ro positive and while half of them have symptoms of connective tissue disease, the rest are asymptomatic. The presence of anti-Ro is of concern because of the risk of congenital heart block in the child.

We report the case of an asymptomatic 27-year-old G2P1(1001) woman, who presented with persistent fetal bradycardia in her 21st week of gestation (AOG) and was found to have elevated titers for anti-Ro (>320 U/ml). Hydroxychloroquine 200 mg/day and prednisone 10 mg/day were given from the 33rd week of gestation up until the delivery. At 37 weeks AOG, she delivered a live male neonate with a complete heart block. On the 6th day of life, the infant remained bradycardic, hence a pacemaker was inserted and heart rate maintained at 100-120 bpm. On subsequent follow-ups, the mother and child did not develop any systemic manifestations and the infant was thriving well.

While a diseased condition may not be apparent in a pregnant anti-Ro positive woman, the risk of neonatal lupus (NL) is demonstrated in this patient's case. This report illustrates how prenatal care of an asymptomatic woman led to the discovery of a fetal abnormality and served to prepare the family and the medical team to ably handle the birth and subsequent care of a neonate with NL.

*Keywords: neonatal lupus, congenital complete heart block, positive anti-Ro*

## INTRODUCTION

Anti-Ro antibodies are found in 40–80 percent of patients with Sjogren's syndrome and 50 percent of systemic lupus erythematosus (SLE) patients, while anti-La antibodies are found in 15–40 percent of Sjogren's patients and 10–20 percent of SLE patients. These antibodies to Ro and La are associated with a variety of clinical features among patients with SLE. Correlations with anti-Ro antibodies and SLE have been found with photosensitive skin rash and 75 percent of patients with subacute cutaneous lupus erythematosus are anti-Ro positive. Antibodies to Ro have been found to be deposited directly into skin. Associations have also been found between anti-Ro antibodies and thrombocytopenia, lymphopenia, anemia, or interstitial pneumonitis. Many SLE patients who are ANA negative have anti-Ro antibodies. Anti-Ro and anti-La antibodies are also passed across the placenta to the fetus and both antibodies are associated with neonatal dermatitis or congenital heart block (CHB), a syndrome called neonatal lupus (NL).[1] Antibodies to Ro have been reported as the most common autoantibody detected in the general population. Among unselected pregnancies, 1-2% have been found seropositive for anti-Ro. While 50%



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of seropositive women have symptoms of connective tissue disease, the rest are asymptomatic. Moreover, only 1-5% of seropositive women will have an offspring with NL.[2]

CHB is the most common cause of sustained fetal bradycardia, defined as fetal heart rate <100 bpm for at least 40 minutes. The incidence of CHB at birth has been reported to be approximately 1 in 20,000 and it can happen in either morphologically normal and abnormal hearts. In morphologically normal hearts, complete CHB can be isolated, secondary to long QT syndrome, or develop from viral myocarditis. However, more than 90% of complete CHB in structurally normal hearts is secondary to cardiac NL,[3] a condition where maternal antibodies to the ribonucleoproteins Ro and La bind to fetal myocardial cells, causing inflammation and scarring.

This case report aims to bring into awareness the condition of NL manifesting as CHB, a syndrome distinct from SLE among infants, that may occur in the offspring of a woman with anti-Ro antibodies, who may or may not have symptoms of an autoimmune connective tissue disease.

## CASE PRESENTATION

A 27-year-old G2P1(1001) woman, on the 21$^{st}$ week of gestation, had an incidental finding of fetal bradycardia (80 beats/minute). She was asymptomatic and had no known comorbidities. She had no systemic manifestations: fever, cutaneous and mucosal lesions, photosensitivity, sicca symptoms, recurrent headaches, seizure, chest and abdominal pain, hematuria, frothy urine, oliguria, arthralgia/arthritis, neuropathy and weight loss. She had no exposure to alcohol, chemicals or radiation. Hypertension was the only known medical condition in the family. Her previous pregnancy was unremarkable and she gave birth to a term healthy neonate.

The fetal bradycardia noted on ultrasound was further investigated. Fetal 2D echocardiogram revealed persistent sinus bradycardia in the absence of cardiac structural abnormality with no evidence of cardiac decompensation and fetal distress. In a structurally normal fetal heart with bradycardia, a conduction disorder from an immune cause was considered. However, the patient was unable to comply with immunologic work-up.

At 33 weeks AOG, the patient had preterm labor. The fetal heart rate remained bradycardic at 80 bpm. Fetal biometry showed a single live fetus, cephalic, biophysical profile 10/10 with adequate amniotic fluid index (11.6 cm), estimated fetal weight 2099 grams (56$^{th}$ percentile), and findings of elevated umbilical and right uterine artery indices. Tocolysis was initiated and dexamethasone 6 mg x 4 doses was given to facilitate fetal lung maturity.

During the admission, the patient was entirely asymptomatic and physical examination findings were within normal limits. On laboratory examination, further maternal workup, ECG, biochemical and hematological parameters were within normal limits. Complete blood count showed no signs of anemia, leukopenia and thrombocytopenia (Hgb 125 g/L, Hct 0.37 WBC 12.7 x $10^9$/L, platelet 305 x $10^9$/L, neutrophil 0.82, lymphocytes 0.14, monocytes 0.04), urinalysis was clean with no hematuria, pyuria, proteinuria and cast (yellow, clear; PH 6.5 specific gravity 1.013, albumin negative, active sediments negative, RBC 0 WBC0 EPI 2/hpf, bacteria 20/hpf, Mucus 3/hpf), renal function was adequate with a creatinine of 40 umol/L. Infectious work up for syphilis, human immunodeficiency virus, viral hepatitis and rubella were all negative and thyroid function turned out normal (TSH 1.9 mU/L, FT4 10 pmol/L). Immunological tests revealed positive for antinuclear anti-body (21 U/ml), strongly positive Anti Ro/SSA (>320 U/ml) and the rest were negative: Anti La/SSB (0.7 U/ml), Anti Smith (0), Anti dSDNA (0), APAS panel (SCT 28.4 s, DRVVT 1.1 s, LAC_ S 31 s, LAC_C 27.4 s, ACA IgG 0 GPL-U/ml and ACA IgM 7.7 MPL-U/ml.

Based on the maternal history, clinical and laboratory findings, a systemic connective tissue disease was unlikely, hence there was no maternal indication for immunosuppression. However, the medical team decided to start hydroxychloroquine 200 mg/day and prednisone 10 mg/day at 33 weeks AOG up until the delivery in an attempt to decrease the maternal autoimmune response and fetal cardiac inflammatory injury.

At 37 weeks AOG, she underwent elective cesarean section and delivered a live male neonate weighing 2800 g. Heart rate at birth was 90-120 bpm and APGAR scores at 1 and 5 minutes were 8 and 9, respectively. Post-delivery, the neonate was stable on room air. The ECG confirmed a third-degree AV block (Figure 1) and 2D echo showed patent ductus arteriosus and foramen ovale, and normal cardiac chambers with good biventricular contractility. On physical and laboratory evaluation, there were no other abnormalities, aside from cardiac. On the succeeding days, the infant's HR was down-trending to as low as 68 bpm, hence he underwent permanent single chamber pacemaker insertion on the 6$^{th}$ day of life. Post operatively, the heart rate was maintained at 100-120 bpm. He remained stable and was discharged on the 9$^{th}$ day of life. On subsequent follow-ups, the mother and child remained well.

## DISCUSSION

Anti-Ro is an autoantibody against ribonucleoprotein Ro 52 and Ro 60. This antibody is often associated with rheumatologic conditions such as primary Sjogren syndrome, SLE and rheumatoid arthritis,[4] but its presence can also be found among healthy people.[5] Anti-Ro is the most common specific autoantibody detected in the general population of North America,[6] China[7] and Japan,[8] and all of these countries saw a higher prevalence of anti-Ro in women, and its frequency increases with age starting at 20 years old. Seropositivity to anti-Ro is of concern because of the risk of having a child with NL.

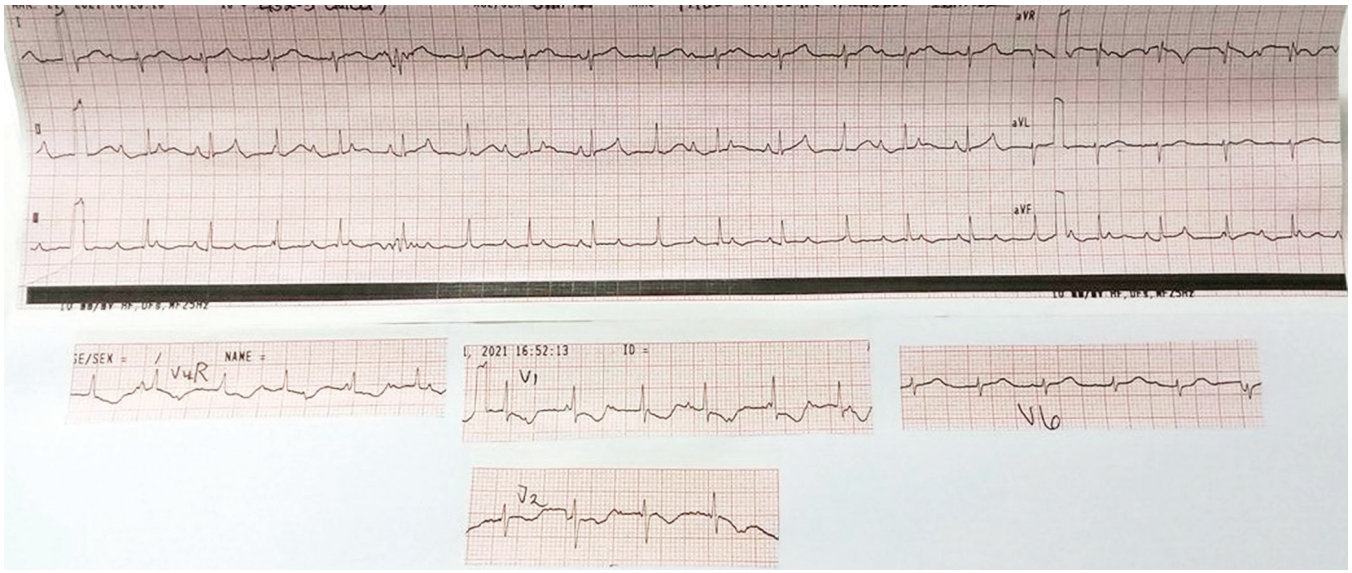


**Figure 1.** Neonatal ECG shows third-degree AV block, normal axis for age, no hypertrophy and chamber enlargement.

NL is an autoimmune disease that is acquired in utero after exposure to antibodies produced by the maternal immune system against Ro and La antigens, this is regardless of whether or not the mother has symptoms of or is diagnosed with a connective tissue disease (CTD). NL is characterized by varying degrees of system involvement: cardiac, dermatologic, hematologic, gastrointestinal and neurologic.[9] It is the cardiac complication that is worrisome as it can lead to irreversible damage and subsequent increase in neonatal mortality rate to 30%.[10] Fortunately NL is a rare occurrence, affecting one in 20,000 live births and it has been observed that both seropositive mothers with or without concomitant CTD, have a similar incidence rate of 1-5% for NL.[11]

Research has shown that the development of NL is influenced not only by the interaction between the transplacental passage of antibodies, but also by fetal genetics (specific HLA-DQ alleles, polymorphism on chromosome 19q13 encoding TGF B) and environmental factors (hypoxia).[12] Such interactions could explain the rarity of NL and may also shed light on why the patient's first born was unaffected.

The common presentations for NL are cardiac and cutaneous involvement, but it is the cardinal NL that prognosticates as it poses a 30% neonatal mortality rate. There are two mechanisms of how maternal anti-Ro and anti-La can cause cardiac havoc: 1) inflammation with fibrosis in the conduction system and myocardium, and 2) inhibition of L-type calcium channels. All of which may lead to CHB, endocardial fibroelastosis and heart failure, CHB being the most frequent.[13] In our case, CHB was entertained due to the sustained fetal bradycardia on ultrasound.

Current data suggest that antibody-related cardiac complications correlate with higher anti-Ro titers and that it occurs exclusively when the fetus is exposed to levels of >50 U/ml, irrespective of anti-La. Interestingly, anti-Ro which is often associated with anti-La have a distinct phenotypic pattern. Jaeggie et al., observed that in CHB-related NL, anti-La was cardio-protective since none of the fetuses had concomitant myocardial inflammation and endocardial fibroelastosis, as compared to those positive for anti-Ro. Another distinct feature of the anti-La subgroup was their predisposition to develop non cardiac abnormalities (cutaneous, hematologic).[14,15] On this note, the patient's isolated high titer anti-Ro may explain the gravity of the neonate's cardiac manifestation.

In general, the standard prenatal evaluation does not include anti-Ro and anti-La, but it is prudent to check them in high risk population, such as those with autoimmune symptoms, established connective tissue disorders (SLE, Sjogren, RA), prior children with known congenital heart blocks, and fetal bradycardia on ultrasound.

In the 2020 American College of Rheumatology (ACR) guidelines for reproductive health in rheumatic disease, they conditionally recommend that pregnant women with anti-Ro and/or anti-La antibodies with no history of an infant with NL should undergo serial fetal echocardiography less frequent than weekly, and if with prior infant with NL, the recommendation is weekly monitoring. These surveillance would start between 16 and 18 weeks AOG and continue through week 26.[16]

The challenge in the patient's case arose from her being an asymptomatic carrier of high titer anti-Ro, presenting for the first time during pregnancy for fetal complication. Due to the fact that NL can lead to advanced and irreversible CHB, the concern for aggressive workup on the mother and child is needed at the moment when fetal bradycardia is suspected. The consideration of antibody related CHB should be at every physicians' differentials. A good back-

ground knowledge that cardiac NL exists would mean escalating the workup and potentially expedite the needed appropriate treatment. A clear algorithm on the approach of these kinds of patients would be of help especially for non-specialists.

In recent years there has been stronger evidence on the approach to seropositive (Anti-Ro positive) pregnant women with rheumatic disease. Studies published by Izmirly et al. observed that the administration of hydroxychloroquine (HCQ) in pregnant women with lupus can reduce the risk of fetal heart block.[17,18] Recently, the ACR has produced a guideline on reproductive health management in rheumatic disease, and they conditionally recommend treatment of pregnant seropositive mothers with established connective tissue disease (CTD) with HCQ and the drug is proven to be safe and is advocated by EULAR.[19] HCQ has also been proven to work in secondary prevention and in a recent multicenter open label clinical trial known as the PATCH study, they have ascertained the effectiveness of daily 400mg HCQ in preventing cardiac NLE for the subsequent pregnancies of mothers who had a history of a child with NL. In this paper, they saw that HCQ significantly reduced the recurrence of CHB by >50%.[20] It is hypothesized that hydroxychloroquine's role in prophylactic treatment, stems from its ability to inhibit the interaction of anti-Ro with toll-like receptor 7, thus hampering the cascade of cardiac inflammation and fibrosis.[21] The initiation of HCQ treatment on the aforementioned studies were done at the moment when pregnancy was established, however there was no mention of what gestational age is best to start treatment. It is important to recognize that fetal heart block most often develops at 18 to 24 weeks gestation, coinciding with the time of transplacental antibody transfer and development of the human fetal conduction system.[22] Given this time window, it now brings up the importance of increasing the threshold for diagnosis in high-risk women and obtain anti-Ro antibodies before 21 weeks and on this note, it might be best to start HCQ no later than 24 weeks. In our patients' case, HCQ 200 mg/day was started at 33 weeks AOG and the initiation might have been too late to reverse any cardiac damage. In hindsight, the benefit of HCQ could have been maximized when it was started prior to 24 weeks AOG and increased to a dose of 400 mg/day.

Another proposed treatment are fluorinated steroids. This came from the observations that it dampens the fetal inflammatory response and improves AV conduction in 1st and 2nd degree AV blocks.[23,24] An interesting approach proposed by Buyon JP et al. is to begin treatment once first-degree heart block is established. The recommendation is maternal intake of oral dexamethasone 4 mg per day or betamethasone 3 mg per day for one week and fetal echocardiography monitoring. Treatment is then discontinued if the first-degree block progresses to complete block. If the block remains at first degree or reverts to normal sinus rhythm, the benefits and the risks of continuing steroid treatment should be carefully weighed.[25] Depending on fetal echocardiography evolution, dexamethasone may be continued up to 24-26 weeks gestations, when the critical period reaches the end.[26] However earlier reports of its benefits have now been countered by recent papers and mounting evidence from the US, France, and Netherlands, showing that steroids are futile in the management,[27-29] and should be weighed against its possible materno-fetal complications. For now, the role of steroids for fetal CHB remains unclear and we need more randomized control trials to establish its definitive role. In our patient, she was given dexamethasone 6 mg/day for 4 days at 33 weeks AOG for the sole purpose of facilitating lung maturity. In instances such as this case, when the child already has a complete and irreversible 3rd degree AV block, treatment with steroids and HCQ are likely ineffective and the best option for treatment is pacemaker implantation after birth.[30]

Other possible treatment options for cardiac NL include maternal administration of IVIG and plasmapheresis. There are divergent outcomes from case reports on plasmapheresis,[31,32] while IVIG does not prevent CHB nor reduce maternal antibody titers as pointed out in the PITCH study.[33] Research on novel remedies, like peptide-based therapies, is ongoing. These short immunogenic peptides serve as decoy targets for pathogenic autoantibodies and are meant to reduce antibody binding to their cellular targets (calcium channels), thus reducing damage.[34] However, no clinical candidate utilizing this mechanism has emerged for nearly 30 years of reports in the literature for this approach. The science behind this postulated theory is promising and with the advances in monoclonal antibody technology, evolution in molecular design and structural biology techniques, it will just be a matter of time that we see studies that would validate the use of engineered decoy molecules for NL.[35]

Autoimmune CHB carries a mortality rate of 30%, with 70% of deaths occurring in utero[36] and 70% of the survivors eventually requiring pacemaker implantation. Among the live births, the mean 10-year survival rate was 86%, with a mean gestational age of delivery between 34-37 weeks and a caesarean section rate of 75%. Risk factors associated with greater perinatal mortality included endocardial fibroelastosis, hydrops, earlier diagnosis of CHB (<20 weeks AOG), delivery at <32 weeks gestation, decreased ventricular rate and high umbilical arterial resistance.[36] For our case, the neonate had two poor prognosticators: decreased ventricular rate and elevated arterial resistance on the umbilical and right uterine artery, thus making him at high risk and necessitating cesarean delivery and pacemaker insertion on the 6th day of life.

The long term prognosis of mothers with babies having NL is reasonably good. Only approximately 50% eventually develop a connective tissue disease which in most cases is mild and non-life threatening. The probability of an asymptomatic mother developing SLE by 10 years is 18.6%, and developing probable/definite systemic sclerosis is 27.9%.[37]

NL manifestations do not predict disease progression in an asymptomatic mother. It is also important to consider that the risk of giving birth to a child with NL increases from approximately 2% (if with no prior affected child) to 19% in women with a previous child with NL.[38] Hence, anticipatory reproductive planning is recommended.

## CONCLUSION

This case is that of a neonate born with complete heart block secondary to NL born to an asymptomatic mother positive for anti-Ro with a normal prior pregnancy. Presently, there is no evidence on the best prenatal management for pregnancies with anti-Ro and La in the presence of fetal heart block. Given its associated fetal morbidity and mortality, serial monitoring and anticipatory care from an interdisciplinary team involving rheumatologists, maternal-fetal specialists and cardiologists were essential for a favorable outcome.

### Patient Consent

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

### Statement of Authorship

KNYL contributed in the conceptualization of work and writing of the full manuscript. EOS participated in writing and technical editing of the manuscript and final approval of the version to be published.

### Author Disclosure

Both authors declared no conflicts of interest.

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