

## Review Article

## Neonatal Lupus Erythematosus

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### Abstract

Neonatal lupus is a passively acquired autoimmune disease that occurs in offspring of mothers with anti-SSA/Ro and/or anti-SSB/La antibodies. The primary clinical features are a photosensitive rash that is usually found on the scalp and periorbital areas, congenital heart block with or without cardiomyopathy, cytopenias, disseminated intravascular coagulation, and neonatal cholestasis with or without elevated transaminases. The diagnosis is usually made in utero by detection of a slow fetal heart rate and subsequent fetal echocardiographic confirmation of heart block and/or cardiomyopathy. Prenatal treatment with fluorinated glucocorticoids beginning as soon after detection has favourable outcome for mothers of fetuses with second degree heart block, is of no value for mothers of fetuses with third degree heart block, and controversial for mothers of fetuses with first degree heart block. Prenatal glucocorticoids can be used also in presence of cardiomyopathy associated with neonatal lupus. Hydroxychloroquine has been used in pregnant women who have anti-SSA/Ro antibodies and who have previously given birth to a child with cardiac manifestations. First and second degree block, detected in utero or at birth, can progress to complete heart block. Infants with complete heart block usually require a pacemaker with an excellent prognosis, although development of heart failure may occur.

**Keywords:** Lupus erythematosus; Neonatal lupus syndrome; Congenital heart block

### Abbreviations

ADHD: Attention Deficit Hyperactivity Disorders; ANA: Antinuclear antibody; Anti-RNP: Anti-Ribonucleoprotein; APL: Antiphospholipid; CHB: Congenital heart block; CNS: Central Nervous System; IG: Immunoglobulin; IVIG: Intravenous immunoglobulin; NICU: Neonatal Intensive Care Unit; NLS: Neonatal lupus syndrome; SLE: Systemic lupus erythematosus; SSA/Ro: Anti-Sjogren's syndrome

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A antibody (Anti-Ro antibody); SSB/La: Anti-Sjogren's syndrome B antibody (Anti-La antibody)

### Introduction

Neonatal lupus erythematosus presents group of autoimmune disorders that results from either congenital trans-placental passage of antinuclear and ribonuclear autoantibodies targeting fetal and neonatal tissues (Neonatal Lupus Syndromes( or to less extent from infant's intrinsic deregulated immune system (Primary infantile SLE). Neonatal lupus syndromes (NLS) occurs in infants born to mother with rheumatic conditions including systemic lupus erythematosus (SLE), Sjögren's disease, mixed connective tissue disease, leukocytoclastic vasculitis, various forms of arthritis, immune-mediated thrombocytopenia, thyroiditis, autoimmune hepatitis, and undifferentiated autoimmune syndromes. However, only 1% of infants with positive maternal autoantibodies develop neonatal lupus erythematosus and some cases are born to asymptomatic mothers who are unaware of their autoimmune disorders and get their sero-positivity discovered after an affected infant. Maternal disease activity during pregnancy has been associated with increased frequency of neonatal morbidities and admission to the NICU [1].

Congenital NLS presents mainly with cardiac, dermatologic, and hepatic manifestations and to less extent with hematologic, central nervous system, or splenic abnormalities. Primary infantile SLE frequently involves the kidneys, and requires aggressive immunosuppressive therapy.

### Epidemiology

Neonatal lupus erythematosus is an uncommon disease described mainly in isolated case reports. Neonatal lupus erythematosus occurs in 1 of every 20,000 American live births and in 0.6 of every 100,000 children annually. The presence of human leukocyte antigen B8 (HLA-B8) and human leukocyte antigen DR3 (HLA-DR3) in the mother predisposes the infant to neonatal lupus erythematosus and congenital heart block. Lupus erythematosus of childhood appears to be more common in black, Latin American, and Asian children (3:1 ratio in all races compared with white patients). Female infants have two to three times' higher incidence for developing cardiac and cutaneous neonatal lupus erythematosus compared to male infants.

Congenital complete heart block, diagnosed by mid-trimester fetal echocardiography, was detected in 2% of first-observed pregnancies and 1.8 % of live births to women with positive maternal screening for anti-SSA/Ro antibodies [2-4]. In a prospective study of 98 infants born to mothers with positive anti-SSA/Ro antibodies, three infants had first degree block, three had third degree block, and four had cutaneous neonatal lupus [5].

Anti-SSA/Ro and anti-SSB/La antibodies were present in 91 % of mothers of infants with complete heart block, 73 % of mothers of infants with transient cutaneous neonatal lupus, and 15 % of mothers with lupus and related autoimmune diseases who gave birth to healthy infants [6,7].

The incidence of cardiac manifestations in neonatal lupus increases to about 17 % in women with anti-SSA/Ro and/or anti-SSB/La antibodies who have had a previous child with congenital heart block [8], a previous child with cutaneous neonatal lupus without cardiac manifestations [9], and in women with high titers of anti-SSA/Ro and anti-SSB/La compared to low titers [10]. On the other hand, infants exposed to high titers of anti-SSB/La were more likely to have noncardiac manifestations of neonatal lupus [10].

## Pathogenesis

During fetal life a physiologic process of cell apoptosis occurs resulting in translocation and expression of nuclear antigens and phospholipids on the cell surface displaying immunogenic surface blebs which are continuously cleared. However, if the balance between the rate of production and clearance of this apoptotic debris is impaired, resulting in an excess antigen expression, the immune system forms antibodies to these nuclear antigens and phospholipids. These antinuclear antibodies (ANAs) include anti-Sjögren's syndrome A (SSA/Ro), anti-Sjögren's syndrome B (SSB/La), ribonuclear protein (RNP), and antiphospholipid (APL) antibodies. Autoantibodies often are benign but can also induce inflammatory damage to tissues like blood vessels and organs, leading to clinical autoimmune diseases.

Maternal antibodies are of immunoglobulin G (IgG) nature antibodies which cross the placenta to the fetus in the second trimester reaching maternal concentrations by 30 weeks' gestation, and exceed maternal concentrations by term [11]. Maternal autoantibodies mediate fetal autoimmune disease through formation of antibody complexes with apoptotic antigens in the skin, liver, heart and newly forming bone which when phagocytosed and opsonized initiate proinflammatory process that results in immune-mediated damage to fetal tissues [12,13].

Several studies have established the association between antibodies against the 60 kD extractable nuclear antigens Ro (anti-SSA/Ro) and La (anti-SSB/La) and neonatal lupus. In addition to the traditional Ro antigen of 60kD, another antigen of 52kD has been identified. Antibodies with specificity for the 52 kD component of the SSA/Ro protein (Ro52) are more frequently found and are present at higher concentrations in the serum of children with congenital heart block and their mothers [14,15]. More specifically, maternal anti Ro-52 kD antibodies with primary specificity for a particular peptide fragment (amino acids 200 through 239, p200-239) are significantly associated with the development of CHB [15,16]. Although maternal anti Ro52-p200 antibody exposure was observed in equal frequency in both affected and unaffected offspring [17], higher levels of Ro52 p200 antibodies were observed in mothers of children with CHB compared to those with normal children [18]. Cutaneous NL was present in 16 % of women with anti-SSA/Ro antibodies and was significantly more frequent in those with both anti-SSA/Ro and anti-SSB/La autoantibodies [3].

The pathogenesis of heart block results from binding of anti-SSA/Ro and/or anti-SSB/La antibodies to fetal cardiac tissue, leading to autoimmune injury of the atrioventricular (AV) node and its surrounding tissue [19,20]. Apoptosis induced translocation of SSA/Ro and SSB/La to the surface of fetal cardiomyocytes allows anti-SSA/Ro and anti-SSB/La antibodies to bind to the surface of the fetal cardiomyocytes [21]. Apoptotic cardiomyocytes are then phagocytosed by healthy fetal cardiomyocytes diverting these opsonized cardiomyocytes to uptake by macrophages [22], which release pro-inflammatory cytokines, initiating an inflammation-free

physiologic remodelling of the human fetal heart and resulting in inflammation-induced tissue damage [23]. Tumor necrosis factor alpha and transforming growth factor beta may potentiate the inflammatory and fibrosis components respectively [24]. In addition to inducing tissue damage, anti-SSA/Ro and/or anti-SSB/La antibodies may inhibit calcium channel activation or the cardiac L-type calcium channels which are crucial to action potential propagation and conduction in the AV and SA nodes [25,26].

Maternal antibodies to other antigens like anti-U1 ribonuclear protein antibodies in the absence of anti-SSA/Ro or anti-SSB/La antibodies were found to cause classic rash of NL, but not congenital heart block [27,28].

Genetic predisposition, particularly the HLA alleles DQB1\*02, DRB1\*03, and a polymorphism in the promoter region of the gene for tumor necrosis factor alpha may play a role in skin disease. The frequency of carriage of all three alleles in infants with characteristic lupus rash was twice that of infants with CHB or unaffected infants [29].

## Clinical Presentation

Clinical manifestations and outcomes of different body systems involvement in neonatal lupus are summarized in (Table 1).

## Skin Manifestations

Skin manifestation of NLS occurs in association with the 52-kD SSA/Ro, 60-kD SSA/Ro, 48-kD SSB/La, and U1RNP autoantibodies. The rash typically appears during the first 3 postnatal months, persists for a mean of 4 months, and spontaneously resolves by 6 to 8 months of age parallel with fading of maternal autoantibodies in the infant's circulation. However, residual skin abnormalities occur in 10% to 25% of infants and include telangiectasias, dyspigmentation, pitting, scarring, and skin atrophy.

Neonatal lupus rash is characterized by round or elliptical erythematous, papulosquamous lesions with central clearing, annular erythema, and a fine scale. Blueberry muffin rashes have been also described in cases of neonatal lupus representing extramedullary dermal erythropoiesis secondary to severe intrauterine anemia mediated by maternal autoantibodies. The rash typically involves the face, scalp, neck, trunk, extremities, and intertriginous areas and is frequently induced or exacerbated by ultraviolet light (sunlight or phototherapy).

The histopathology of the erythematous-desquamative lesions shows vacuolar alterations at the dermoepidermal interface and adnexal structures [30]. Some patients present with urticaria-like lesions that have superficial and deep perivascular and periadnexal lymphocytic infiltrates.

## Cardiac Manifestations

The main cardiac manifestations of NLS are injury to the conducting system, myocarditis and ventricular endocardial fibroelastosis through an antibody-mediated injury to fetal and neonatal cardiac conduction tissue, myocardium and endocardium respectively [16,31-33].

Injury to the conducting system presents mainly with congenital heart block (Figure 1) and to less extent with transient sinus bradycardia, QT interval prolongations, and Wolff-Parkinson-White syndrome [34,35]. Neonatal Lupus Syndrome accounts for 85% of all cases of congenital complete heart block [36]. The incidence of heart

System	Clinical manifestations	Treatment (Level of Evidence)	Outcome
Skin	1. Transient lesions	<ul style="list-style-type: none"> <li>• Conservative</li> <li>• Avoid ultraviolet light exposure (III)</li> <li>• Consider topical Corticosteroids (III)</li> </ul>	Spontaneously resolve by 6-8 months
	a. Erythematous, papulosquamous, desquamative rash		
	b. Blueberry muffin rash		
	2. Permanent lesions		
	c. Telangiectasias		
	d. Skin dyspigmentation		
	e. Skin pitting		
	f. Skin scarring		
Cardiac	g. Skin atrophy	<ul style="list-style-type: none"> <li>• Conservative management with close monitoring</li> <li>• Corticosteroids for active carditis (III)</li> <li>• Cardiac pacemaker for life-threatening condition (IIa)</li> <li>• Management of heart failure</li> </ul>	<ul style="list-style-type: none"> <li>• Mortality: 19% of infants with CHB</li> <li>• Cardiac pacemaker: 65% of survivors</li> </ul>
	2. Conductive system affection		
	a. Congenital Heart Block (CHB)		
	b. Transient sinus bradycardia		
	c. Prolonged QT interval		
	d. Wolff-Parkinson- White syndrome		
	3. Inflammatory manifestations		
	a. Myocarditis		
	b. Endocardial fibroelastosis		
	4. Structural defect		
	a. VSD		
	b. PDA		
	c. Patent foramen ovale		
	d. Pulmonary stenosis		
e. Pulmonary valvular dysplasia			
f. ASD			
Haematology	1. Anemia	<ul style="list-style-type: none"> <li>• Conservative for mild cases</li> <li>• IVIG (1 g/kg for 1 to 2 days) for refractory anemia or thrombocytopenia (III)</li> <li>• Corticosteroids (1 to 2 mg/kg for 5 days) for refractory anemia or thrombocytopenia (III)</li> <li>• Anticoagulants for thrombosis (III)</li> <li>• Consult hematology</li> </ul>	Resolve by 3-6 months with fading of maternal antibodies
	2. Thrombocytopenia		
	3. Neutropenia		
	4. Bone marrow failure		
	5. Disseminated intravascular coagulation		
	6. Hyper-coagulation and thrombosis		
Hepatobiliary	1. Neonatal cholestasis	<ul style="list-style-type: none"> <li>• Corticosteroids if severe or persistent hepatitis (III)</li> <li>• Immunosuppressive therapy (III)</li> <li>• Immunosuppressive therapy (III)</li> <li>• Endocrine consultation</li> <li>• Hormonal replacement therapy when indicated</li> <li>• Genetics and orthopaedics consultation</li> </ul>	Resolve by 3-6 months with fading of maternal antibodies
	2. Neonatal hepatitis		
	3. Liver cell failure		
Pulmonary	1. Pneumonitis		
	2. Pulmonary capillaritis		
Renal	1. Glomerulonephritis		
	2. Nephrotic syndrome		
Endocrine	2. Adrenal insufficiency		
Musculoskeletal	Rhizomelic chondrodysplasia punctata		
Neurologic	1. Seizures		
	2. Strabismus		
	3. Opsoclonus		
	4. Truncal hypotonia,		
	5. Spastic paresis		
	6. Myelopathies		
	7. Intra-cerebral haemorrhages		

**Table 1:** Common clinical manifestations and related outcomes of neonatal lupus.

Levels of evidence: Ia - Evidence from Meta-analysis of Randomized Controlled Trials, Ib - Evidence from at least one Randomized Controlled Trial, IIa - Evidence from at least one well designed controlled trial which is not randomized, IIb - Evidence from at least one well designed experimental trial, III - Evidence from case, correlation, and comparative studies, IV - Evidence from a panel of experts.



block in infants born to mothers who have anti-Ro/SSA or anti-La/SSB antibodies is 1% to 2% in the first pregnancy and increases to 16% to 18% in subsequent pregnancies [37,38]. Injury to fetal and neonatal cardiac conduction tissue occurs as a consequence of a cascade of inflammatory events starts with cardiocyte apoptosis and progress through translocation of SSA/Ro and SSB/La antigens to the cardiocyte surface, binding of maternal autoantibodies, macrophage recruitment, secretion of profibrosing factors, and fibrosis of the cardiac conduction system [34,39]. Most cases of CHB are detected before 30 weeks' gestation, with a peak incidence between 20 and 24 weeks [36].

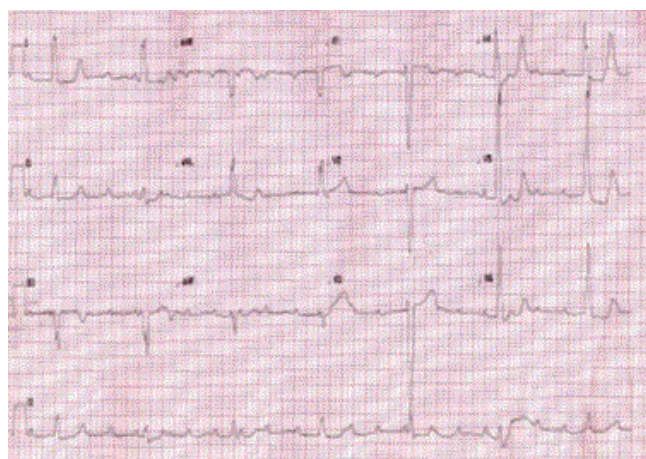


Figure 1: Congenital complete heart block in newborn with NLS.

Myocarditis and ventricular endocardial fibroelastosis occur with NLS as a result of inflammatory cell infiltrates and deposition of immunoglobulin, complement, and fibrin in the myocardium [40]. Myocarditis is often followed by the development of postnatal cardiomyopathy in approximately 10% of infants who have NLS leading to poor prognosis [32].

Neonatal lupus with CHB has been associated with endocardial fibroelastosis which may present early during fetal, during immediate postnatal life, or late as long as five years after the diagnosis of complete heart block [32,41]. Structural heart disease, particularly VSD, has been reported occasionally in association with NL and heart block [42,43]. Other congenital structural cardiac anomalies have been observed in association with NL include persistent patent ductus arteriosus, patent foramen ovale, pulmonary stenosis, pulmonary valvular dysplasia, fusion of chordae tendineae of the tricuspid valve, and ostium secundum type atrial septal defects [42,44].

### Haematological Manifestations

Haematological manifestations of NLS include anemia, neutropenia, thrombocytopenia, bone marrow failure, disseminated intravascular coagulation, and thrombosis. Cytopenias are the classic haematological presentation of neonatal lupus mainly due to immune suppression of the bone marrow by maternal autoantibodies and to less extent due to peripheral destruction of blood components. Maternal auto-antibodies SSA/Ro and SSB/La are associated with neonatal cytopenias and antiplatelet antibodies have been described in association with thrombocytopenia.

Anemia and thrombocytopenia are the most common hematologic manifestations, while neutropenia and aplastic anemia are rare. Hemolytic anemia is a rare manifestation of NLS. Immune

thrombocytopenic purpura with microangiopathic hemolytic anemia and disseminated intravascular coagulation has been reported in an infant who had NLS [45].

Bone marrow aspiration is characterised by the presence of teardrop cells and basophilic stippling. Haematological abnormalities are typically worsened over the first days after birth, and resolve after disappearance of maternal autoantibodies.

Hyper-coagulation and thrombosis has been described with NLS due to transplacentally acquired antiphospholipid (APL) antibodies, especially in the setting of sepsis, indwelling catheters, or other situations where vessel injury predisposes to thromboses [38].

### Hepatobiliary Manifestations

Hepatic involvement occurs in 9% to 25% of infants who have NLS as an isolated disease or within a wider spectrum of the NLS manifestations [3]. The two most common presentations of NLS liver disease are neonatal cholestasis with or without elevated transaminases occurring in the first few weeks after birth and isolated mild elevated transaminases occurring at 2 to 3 months of age [46]. Severe perinatal hepatic dysfunction, often with the phenotype of neonatal iron storage disease, portends a poor prognosis [46]. Histopathology examination, in severe and persistent cases of liver dysfunction, typically shows mild bile duct obstruction, portal fibrosis, and occasional giant cell transformation similar to idiopathic neonatal giant cell hepatitis [47]. Most cases of neonatal lupus have spontaneous resolution of hepatic disease by 3 to 6 months after clearance of maternal autoantibodies, however deaths from hepatic failure have previously been reported.

### Pulmonary and Renal Manifestations

Pulmonary and renal involvements are rare in infants with NLS and their presence may be suggestive of infantile primary SLE [48]. Pulmonary manifestations are commonly presented as cough, tachypnea, hypoxemia, and a chest radiograph of interstitial lung infiltrates. The pathogenesis for lung involvement in NLS includes necrotizing pulmonary capillaritis, pneumonitis, and alveolar hemorrhage [49]. The common presenting renal manifestations are hematuria, hypertension, and edema related to glomerulonephritis and congenital nephrotic syndrome [50]. However, nephritis and nephritic presentations suggest the diagnosis of infantile lupus and not NLS. This is possibly related to absence of antibody deposition in the fetal kidney due to absence of renal antigens during fetal life [51].

### Endocrine Manifestations

Thyroid and adrenal dysfunctions are the most common endocrine sequelae of neonatal lupus. Since thyroid disease represents a prevalence of 14% to 20% in women who have SLE and Sjogren syndrome [52], assessment of sick infants who have NLS should include evaluation for thyroid dysfunction and maternally derived blocking and stimulating thyroid antibodies. Women who have hypothyroidism and SSA/Ro antibodies have a nine fold increased risk for delivering a child who has CHB compared with women who have only SSA/Ro antibodies [53]. Transplacental passage of thyroid blocking or stimulating antibodies is associated with hypo or hyper thyroid disease of neonates [54].

Bilateral massive adrenal hemorrhage and adrenal insufficiency has been previously reported with transplacental acquired antiphospholipid antibodies [55].

## Musculoskeletal Manifestations

Rhizomelic chondrodysplasia punctata has been reported in infants born to mothers who had SLE antibodies, none of them had cataracts or defects in peroxisomal metabolism which is typical of the genetic forms of chondrodysplasia punctata [56]. They typically present with midfacial hypoplasia, shortening of the proximal limbs, and punctate calcifications of the epiphyses in any of the humerus, femur, tibia, tarsal bones, heels, phalanges, and vertebral spine. Rhizomelic chondrodysplasia punctata may be an isolated presentation or occur in association with NLS rash and CNS manifestations.

Similar to other NLS manifestation rhizomelic chondrodysplasia punctata occurs as a result of IgG–apoptotic cell complexes presented in the zones of newly forming fetal bones initiating an immune complex-mediated inflammation at growth plates [12].

## Neurologic Manifestations

Trans-placental passage of maternal auto-antibodies results in lenticulostriate vasculopathy and subsequent brain abnormalities as cerebral dysmaturation, cortical dysgenesis, ventriculomegaly, and dysgenesis of structures supplied by the lenticulostriate vasculature in infants with NLS [57-59].

Although most infants who have NLS are asymptomatic at birth, seizures, strabismus, opsochonus, truncal hypotonia, spastic paresis, myelopathies, cerebral haemorrhages, static encephalopathies, and developmental delay have been observed in infancy. Children born to women who have SLE and concurrent APL antibodies showed increased rate of learning disabilities [60]. Infants who have idiopathic lenticulostriate vasculopathies were more likely to have muscle tone abnormalities at 6 months of age and may have an increased risk of developing attention deficits, hyperactivity, obsession/compulsion, and tic disorders [61,62].

Radiologic evaluations have shown evidences of white matter disease, cerebral edema, hypomyelination, echogenic lenticulostriate vessels, basal ganglia calcifications, gangliothalamic vasculopathy, subependymal cysts, haemorrhages, and ventriculomegaly [57,63-65]. Less common radiological findings in infants who had NLS include thalamostriatal malformations, absent septum pellucidum, prominent cavum septum pellucidum, optic chiasm and optic nerve hypoplasia, and cortical dysgenesis. A statistically significant association has been observed between neonatal intraventricular hemorrhage and lenticulostriate vasculopathy in infants with NLS [66]. The prevalence of hydrocephalus and macrocephaly also is increased in infants born to mothers who have anti-SSA/Ro antibodies [63].

Although the relation between maternal autoantibodies and neonatal neurological diseases is not yet known to be true or confounded, clinical and experimental evidence support a true association. The known connection between autoantibodies, in the setting of SLE, Sjögren syndrome, and APL syndrome, with adult human CNS diseases like CNS vasculitis, white matter lesions, chorea, seizures, and cognitive dysfunction supports the association between neonatal CNS injury and maternal autoantibodies. Additionally, animal studies show that APL, anti-SSA/Ro, and anti-dsDNA antibodies mediate neurologic dysfunction, potentiate seizures, and lead to excitotoxic injury to the animal brain [67-73].

## Diagnosis

The diagnosis of NL is made when a fetus or newborn of a mother with anti-SSA/Ro and/or anti-SSB/La, or possibly anti-RNP, antibodies develops heart block and/or the typical rash or hepatic or hematologic manifestations in the absence of another explanation. Skin manifestation of NLS should be differentiated from various erythematous rashes seen in the neonatal period particularly erythema marginatum, tinea seborrheic dermatitis, ichthyosiform genodermatosis, erythema annulare centrifugum, familial annular erythema, erythema multiforme, infantile epidermodyplastic erythema, annular erythema of infancy, and erythema gyratum atrophicans [74]. However, skin rashes not related to NLS are not associated with maternal anti-SSA/Ro, anti-SSB/La antibodies or with congenital heart block. Congenital heart block related to NLS should be differentiated from other causes of CHB such as myocarditis, various structural cardiac defects, congenitally corrected transposition of the great arteries, and atrioventricular discordance [41]. Early presentation during fetal life and additional structural cardiac abnormalities such as VSD and endocardial fibroelastosis along with presence of antibodies to SSA/SSB favours the diagnosis of NLS.

## Prenatal screening

Prenatal screening for anti-SSA/Ro and anti-SSB/La antibodies, prior to conception or as early in pregnancy as possible, is warranted for women who are known to have lupus, Sjogren s yndrome, an undifferentiated autoimmune disease, or NL in a previous pregnancy. Neonatal lupus in an offspring can be the first sign that the mother has anti-SSA/Ro and anti-SSB/La antibodies.

Fetal congenital heart block occurs mostly during the period from 18 to 24 weeks gestation, less likely during the 26th through the 30th week, and rarely after 30 weeks of pregnancy. Normal sinus rhythm can progress to complete block in seven days during the initial high-risk period.

Complete heart block results in fetal bradycardia which can be detected by routine fetal auscultation, ultrasonography, or pulsed Doppler echocardiography [75,76]. Women who test positive for SSA/Ro and SSB/La autoantibodies should have a more intensive assessment for fetal heart block with frequent fetal echocardiographic testing during pregnancy. Although there are no formal guidelines for the type or the frequency of testing, performing weekly pulsed Doppler fetal echocardiography from the 18th through the 26th week of pregnancy and then every other week until 32 weeks has been strongly considered. Additional diagnostic modalities include fetal magnetocardiography and electrocardiography [77,78].

## Postnatal diagnosis

Newborns with heart block in absence of causal structural abnormalities should be testing for maternal anti-SSA/Ro antibodies because these antibodies account for 80 to 95 % of reported cases of CHB in the fetus and neonate [41,79].

Infants up to eight months of age with an annular or polycyclic rash and/or any degree of heart block should be tested for anti-SSA/Ro and anti-SSB/La antibodies.

Infants diagnosed with NL who has compatible clinical manifestations and detectable autoantibodies with no electrocardiographic evidence of heart block of any degree at birth, is at very low risk of subsequently developing conducting system disease however they should be followed for later development of cardiomyopathy.

## Management

### Skin disease

Treatment of skin manifestation is typically conservative with avoidance of sun or ultraviolet light exposure to prevent or minimize the rash and residual skin abnormalities. Topical corticosteroids have been previously evaluated, but the efficacy has not been established.

### Cardiac diseases

The clinical relevance of first degree heart block is unclear as progression from first degree block to more advanced heart block in untreated fetuses has not been documented. Second degree heart block may be reversible and may progress to complete heart block despite therapy [80,81]. Complete heart block is irreversible even with glucocorticoid therapy [76, 80].

**Prenatal treatment:** Fluorinated corticosteroids, as dexamethasone and betamethasone, and sympathomimetics have been used in mothers of affected fetuses to prevent in utero effusions, hydrops fetalis, and other complications of advanced heart block [80,82,83], however the efficacy and safety of antenatal steroid therapy has been questioned. Previous reports have shown that fetuses with second degree heart block treated with dexamethasone or betamethasone reverted to first degree block by birth, while those who were not treated progressed to complete heart block [80]. In a multicenter study of antenatal dexamethasone therapy, 100 % of fetuses with third degree block did not respond to therapy, 50 % of infants with second degree block remained in second degree block, 30 % reverted to normal sinus rhythm, and 20 % progressed to third degree heart block, while 100 % of fetuses with first degree block converted to normal sinus rhythm within one week [84]. In another multicenter prospective study, fetuses with first degree heart block, diagnosed by tissue velocity-based fetal kinetocardiogram, treated with antenatal dexamethasone had normalization of AV conduction in all affected fetuses within two weeks [85]. In a retrospective series of 37 patients with complete heart block, the one-year survival rate in the 21 patients treated with dexamethasone was 90 %, compared with a survival rate of 46 % in the 16 untreated patients [82].

Fluorinated glucocorticoids are also considered for signs of cardiomyopathy. However, the effectiveness of these agents in the treatment of endocardial fibroelastosis is unknown [41]. In a retrospective study for the use of glucocorticoids and IVIG (both in utero and after birth), a potential survival benefit was observed in cases with cardiomyopathy/endocardial fibroelastosis based upon comparison to historical control data [86].

Plasmapheresis and intrauterine placement of a fetal pacemaker also have been attempted [87,88]. Intrapartum IVIG (400 mg/kg given every three weeks from weeks 12 to 24) has also been used to prevent and treat CHB with limited success, but the safety profile maybe better than that of corticosteroids [89,90].

Hydroxychloroquine (400 mg orally once a day) inhibits ligation of endosomal Toll-like receptors. It is often used during pregnancies complicated by lupus and considered of minimal risk to the fetus and mother. It should be initiated between 6 and 10 weeks gestation in women who are not already on the medication. In a case-control study of mothers with SLE treated with hydroxychloroquine, the overall risk of cardiac lupus was decreased [91]. A subsequent retrospective study based upon data from neonatal lupus registries in the United States, France, and the United Kingdom supports the efficacy of

hydroxychloroquine in reducing the recurrence rate of cardiac-NL [92].

Accordingly, prenatal treatment with fluorinated glucocorticoids (oral dexamethasone 4 mg per day, or betamethasone 3 mg per day) is suggested for mothers of fetuses with second degree heart block, beginning as soon after detection and continuing through the end of pregnancy depending upon the response. Glucocorticoid therapy should be discontinued after one week of detection if heart block progresses to third degree block with no other signs of myocarditis. Most patients with third degree block will require cardiac pacing. Treatment of third degree block with glucocorticoids is generally not advised, unless there are other factors as suspected myocarditis and cardiomyopathy, although to date this has not been well evidenced [82,93]. Treatment of isolated first degree block is controversial, because of the risks of therapy, the evidence that first degree block can revert to normal sinus rhythm without therapy, and the absence of consistent evidence that untreated first degree block can progress to more advanced block [85,94]. Preemptive treatment with hydroxychloroquine in pregnant women who have previously given birth to a child with cardiac manifestations of neonatal lupus and who have anti-SSA/Ro antibodies has been shown to be promising.

**Postnatal treatment:** After delivery, infant electrocardiography should be obtained. When bradyarrhythmias or other arrhythmias are detected perinatally, infants should be monitored closely for progression of conduction abnormalities and cardiomyopathies. Treatment with sympathomimetic agents such as salbutamol and isoprenaline was proved, through case reports, to be effective prenatally in fetuses with congenital heart block [95] but not in postnatal management [96]. Post natal treatment with IVIG or glucocorticoids was found to be ineffective in neonates with CHB [97].

Infants born with congenital heart block may be indicated for permanent cardiac pacemaker insertion. Indications of cardiac pacing in cases of congenital heart block are summarized in (Table 2) [98,99].

Class	Indication
Class I (Pacing is indicated)	Congenital complete AV block with
	a. Ventricular rate less than 50 beats per minute.
	b. Wide QRS escape rhythm.
	c. Prolonged QTc interval.
	d. Complex ventricular ectopy.
	e. Ventricular dysfunction.
	f. Ventricular pause > 3 folds the cycle length of the underlying rhythm
Class IIa (Pacing is reasonable)	g. Associated congenital heart disease and a ventricular rate less than 70 beats per minute.
	Congenital complete A-V block beyond the first year of life with
	a. Average heart rate less than 50 beats per minute.
	b. Abrupt pauses in ventricular rate of 2 or 3 times the basic cycle length.
Class IIb (Pacing is considered)	c. Associated symptoms due to chronotropic incompetence.
	Congenital complete A-V block in asymptomatic children with an acceptable rate, narrow QRS complex, and normal ventricular function.
Class III (Pacing is not indicated)	Asymptomatic type I (Wenckebach) second-degree AV block.

**Table 2:** Indication of cardiac pacemaker in infants with congenital heart block [98-100].



Pacing devices are divided into either single (conventional right ventricular) or dual (combined right and left ventricular) pace makers. The use of dual pace maker in infants and children was associated with less frequent left ventricular modeling, dilatation, and asymmetrical hypertrophy [101]. Conventional right ventricular pacemaker was found to be associated with significant increase in chronotropic insufficiency, cardiomyopathy, and acute heart failure particularly in infants of mothers with lupus [102,103].

### Haematological diseases

Anaemia and thrombocytopenia are usually self-resolving and most infants do not need treatment and have spontaneous resolution of hematologic abnormalities with disappearance of maternal antibodies. Although irradiated blood products transfusion is indicated to control bleeding or to treat symptomatic anemia, they do not result in sustained counts when autoantibodies are present. In cases of fetal thrombocytopenia, postnatal management typically involves observation when platelet counts are greater than  $20 \times 10^3/\text{mL}$  ( $20 \times 10^9/\text{L}$ ) and there are no signs of bleeding.

Intravenous immunoglobulins (IVIG) at a dose of 1 g/kg/day for 1 or 2 days and corticosteroids at a dose of 1 to 2 mg/kg/day for 5 days are instituted in cases of persistent, severe hematologic manifestations.

### Hepatobiliary diseases

Corticosteroids should be initiated for severe or persistent moderate elevated transaminases at a dose of 1 to 2 mg/kg for 5 days or until an adequate response is achieved, followed by a slow wean. Transaminases should be monitored weekly during the corticosteroid wean, and worsening level should prompt escalation of corticosteroids therapy.

### Pulmonary and Renal

The available evidence for management of pulmonary and renal manifestations is very restricted to few case reports. Success has been reported with corticosteroids and immunosuppressive therapy [49].

### Other Systems

Musculoskeletal, endocrinal, and neurological diseases are managed according to the presenting manifestations. A multidisciplinary approach with involvement of other specialities is more beneficial for affected infants.

### Prognosis

The prognosis of neonatal lupus depends mainly on the presence or absence of cardiac involvement. The rash of neonatal lupus generally does not cause scarring and disappears within six to eight months. Although cardiac involvement is rare in patients who had no evidence of heart block or who had noncardiac manifestations of neonatal lupus at birth, infants with noncardiac manifestations of NL should at least have an ECG, and possibly an echocardiogram, since first degree block is clinically silent and can progress postnatally.

In cases with heart block, mortality varies with the time of presentation representing 43% when diagnosed in utero by fetal echocardiography [41]. In neonates with congenital NLS, complete CHB is associated with significant morbidity and mortality representing 20% cumulative probability of death at 3 years, and 65% of survivors require pacemakers [36]. In a prospective observational study of infants and children with isolated congenital

heart block, 67% were diagnosed before one year of age [104]. In the same study, authors noticed that 46% of infants with isolated congenital heart block secondary to maternal lupus required pacemaker in the first 24 months of life [104].

Data from Research Registry for Neonatal Lupus revealed an overall mortality of infants with congenital complete heart block, born to mothers with anti-SSA/Ro or anti-SSB/La antibodies, of 19%; 5% occurred in utero, 9% within the first three months of birth, 5% between the age of three months and three years, no deaths older than the age of three [42]. Of survivors, 63% ultimately required a pacemaker [42].

Previously reported fetal risk factors associated with increased mortality include early diagnosis (before 20 weeks gestational age), lower ventricular rate (less than 50 beats per minute), echocardiographic evidence of hydrops, echocardiographic evidence of endocardial fibroelastosis, and impaired left ventricular function at diagnosis [105,106].

Asymptomatic infants with complete heart block remain well until later childhood, adolescence, or adulthood. However, exercise limitation and even death are possible in the absence of pacing.

Children who have had NL may be at increased risk of developing an autoimmune and/or rheumatic disease including pauciarticular and polyarticular onset juvenile idiopathic arthritis, psoriasis, thyroid disease, iritis, type 1 diabetes mellitus, and nephrotic syndrome [107]. None of the children with neonatal disease, nor any of their unaffected siblings, developed systemic lupus erythematosus during at least eight years of follow-up [107].

### Summary

Neonatal lupus is a multisystem disease which affects mainly the cardiac, dermatologic, and hepatobiliary systems. It occurs in infants born to mothers with rheumatic conditions including, but not restricted to, systemic lupus erythematosus. Most clinical manifestations of NLS resolve spontaneously with vanishing of maternal auto-antibodies from the neonatal circulation except congenital complete heart block. Prenatal diagnosis and management are cornerstones in the care of infants with neonatal lupus to prevent permanent damage to the conducting system of the heart and later development of complete heart block. Congenital complete heart block is a poor prognostic marker in infants with neonatal lupus syndrome. Cardiac pacemaker, preferably the dual chamber pacemaker, is frequently indicated in infants with congenital complete heart block related to neonatal lupus.

### Competing Interests

The author declares no significant competing financial, professional or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

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