*Acad Med J 2025;5(Suppl 1):S89-S102.*
UDC: 616-002.52-053.31
https://www.doi.org/10.53582/AMJ255189z
*Review article*

# NEONATAL LUPUS SYNDROME – AN OVERVIEW OF THE PATHOGENESIS, CLINICAL FEATURES AND MANAGEMENT APPROACH

**Zdraveska Nikolina**

University Children's Hospital, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia
*email: n.zdraveska@medf.ukim.edu.mk*

**Abstract**

Neonatal lupus erythematosus (NLE) is a rare immune-mediated condition that affects newborns due to the transplacental transfer of maternal antibodies, specifically anti-Ro/SSA and/or anti-La/SSB. Seropositive mothers may have known or undiagnosed autoimmune diseases, and many of them remain asymptomatic.

NLE is associated with various phenotypic characteristics and can affect multiple organ systems, including the skin, heart, blood, and liver. The most severe manifestation of NLE is a complete atrioventricular block, which may occur *in utero* and is irreversible. Cutaneous manifestations resemble the rash seen in subacute lupus erythematosus and are generally benign and self-limiting, typically resolving completely within four to six months.

During the neonatal period, these rashes are frequently misdiagnosed and confused with other common erythematous conditions, particularly when the mother is asymptomatic.

Although NLE typically has a benign course, its clinical significance is highlighted by a tenfold increased risk of recurrence in subsequent pregnancies, as well as its association with more severe clinical outcomes. This article provides a comprehensive review of pathogenesis, clinical manifestations and management of NLE aiming to serve as a valuable reference for clinical practitioners in the field.

**Keywords:** neonatal lupus erythematosus, congenital heart block, cutaneous lupus syndrome, antibodies, autoimmune disease

## Introduction

Neonatal lupus erythematosus (NLE) is a distinct clinical condition caused by a passive transfer of maternal autoantibodies to the fetus. This rare acquired autoimmune disorder has an estimated incidence of 1 in 20,000 live births in the USA [1]. The maternal immunoglobulin G autoantibodies - including anti-Sjögren's syndrome A (Ro/SSA), anti-Sjögren's syndrome B (La/SSB), anti-U1 ribonuclear protein (U1-RNP), and antiphospholipid (APL) antibodies - cross the placenta during the second trimester of pregnancy and reach maternal concentrations in the fetus by approximately 30 weeks of gestation [2].

The presence of autoantibodies may lead to a range of fetal autoimmune manifestations due to the formation of complexes with apoptotic antigens in the skin, liver, or heart. The phagocytosis and opsonization of these complexes initiate a pro-inflammatory response, resulting in immune-mediated damage to fetal tissues [2,3].

Bridge and Foley first described neonatal lupus erythematosus in 1954 after they observed the transmission of lupus erythematosus factors from mothers to their infants. However, the precise pathogenetic mechanism still remains incompletely understood.

It is estimated that only 1-2% of infants born to mothers with positive autoantibodies develop neonatal lupus erythematosus, which is linked to the mother's disease activity during pregnancy. On the other hand, approximately half of the women with circulating autoantibodies whose children are affected by NLE remain asymptomatic. Nevertheless, these women may later develop rheumatologic disorders, particularly Sjögren syndrome, systemic lupus erythematosus (SLE), and, less frequently, mixed connective tissue diseases [3,4].

The clinical spectrum of NLE is quite variable and can include skin lesions, as well as cardiac, hematological, and hepatobiliary disorders [5]. While skin manifestations are common in NLE, they are often underestimated or misdiagnosed for various erythematous rashes seen in newborns, such as skin infections or eczema, particularly if the mother is asymptomatic.

This review aims to provide a comprehensive summary of the current understanding of NLE, offering clinicians a valuable reference tool for diagnostic and therapeutic guidance. It is based on a comprehensive systematic search of the PubMed and Embase databases for relevant articles published in English, utilizing various combinations of terms such as neonatal lupus erythematosus, neonatal lupus syndrome, transient autoimmunity, cardiac lupus, skin lesions, anti-Ro/SSA antibodies, anti-La/SSB antibodies, pregnancy screening, and treatment.

*Pathogenesis*

Neonatal lupus erythematosus is associated with Ro/SSA and La/SSB antibodies, regardless of the mother's autoimmune status. Seropositive mothers may have a previously diagnosed disease, like Sjögren's syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis, or undifferentiated connective tissue disease. Conversely, half of the women with circulating auto-antibodies are completely asymptomatic during pregnancy and discover their condition by the identification of fetal bradyarrhythmia or a skin rash in the neonate. However, they may develop some signs and symptoms consistent with an autoimmune disorder later in life, after a median of three years, and may request close monitoring after childbirth [2,6].

The prevalence of anti-Ro/SSA antibodies ranges from 0.2% to 0.72% among female blood donors [7]. It is approximately 0.86% in healthy females in the general population, potentially underestimating the true prevalence due to less reliable initial testing [8]. In patients with systemic lupus erythematosus (SLE), the estimated prevalence is around 40%, while in individuals with Sjögren's syndrome, it ranges from 60% to 100% [9].

The association between NLE and transplacental transfer of maternal auto-antibodies is well recognized. However, etiopathogenesis warrants further clarification, as it encompasses factors beyond the simple presence of antibodies in the fetal circulation, such as fetal genetic factors or other environmental stressors. This is evident, as the disease occurs in only 1 in 50 offspring of seropositive mothers despite the antibody titer levels [10].

The exact mechanism behind the injury is not fully understood. Current evidence suggests that heart block occurs due to damage to the conduction system during fetal development. The Ro/SSA antigen, which is intracellular, consists of two protein components: Ro52 and Ro60. These proteins can trigger the production of autoantibodies in the mother, leading to autoimmune injury and subsequent fibrosis of the atrioventricular (AV) node and its surrounding tissues [11].

Another proposed mechanism is molecular mimicry, where autoantibodies target and cross-react with L-type calcium channels. These channels are essential for the propagation of action potentials and conduction within the AV and sinoatrial nodes [11-13].

Numerous studies have examined the relationship between anti-Ro/SSA and anti-La/SSB antibodies and neonatal outcomes [14-16]. However, many of these studies have limitations, including insufficient participant numbers, narrow scopes, or limited endpoints.

Several investigations have identified a positive correlation between high levels of anti-Ro/SSA and anti-La/SSB antibodies in mothers and an increased incidence of congenital heart block (CHB) compared to those with lower levels [17-19]. Jaeggi *et al.* performed a study involving 186 infants exposed to maternal anti-Ro and anti-La antibodies, aiming to assess the risk of developing immune-mediated cardiac complications. The findings indicated that all cardiac complications were associated with moderate (≥50 U/ml; 15%) or high (≥100 U/ml; 85%) levels of maternal anti-Ro antibodies, regardless of the titers of anti-La antibodies. Additionally, infants exposed to high levels of anti-La/SSB were more likely to have noncardiac manifestations of NLE [19].

Another study showed an increased risk of cutaneous NLE in neonates of mothers with both anti-Ro/SSA and anti-La/SSB autoantibodies [14].

Sheng *et al.* conducted a systematic review and meta-analysis to estimate maternal and infant outcome rates for pregnant women with anti-Ro/SSA antibodies. The findings regarding fetal outcomes were as follows: the rates were 4% for perinatal death, 3% for intrauterine growth restriction, 6% for endocardial fibroelastosis, 6% for dilated cardiomyopathy, 7% for congenital heart block, 12% for recurrence of congenital heart block, 19% for cutaneous neonatal lupus erythematosus, 12% for hepatobiliary disease, and 16% for hematological manifestations [20].

However, the studies indicated considerable overlap in antibody titers between affected and unaffected cases, suggesting that high titers do not reliably predict clinical presentation or the development of CHB.

Also, NLE occurring due to maternal antibodies to other antigens, such as anti-U1 RNP antibodies in the absence of anti-Ro/SSA or anti-La/SSB, was described in some cases. All anti-U1RNP antibody-positive infants had classic cutaneous lesions of NLE but not CHB [21,22].

Several other factors likely contribute to the pathogenesis of congenital heart block, including variations in fetal HLA alleles. Specifically, HLA-DRB1*04 and HLA-Cw*05 have been identified as alleles associated with an increased risk of CHB, while HLA-Cw*06 appears to be a protective allele [23]. These associations have been suggested by studies conducted in various populations across Europe and Japan. Additionally, maternal myocardial cells have been discovered in the hearts of fetuses with CHB, indicating a potential role for maternal microchimerism. However, further research is needed to explore this phenomenon [24].

**Clinical presentation**

NLE presents mainly with cardiac, dermatologic, and hepatic manifestations and less commonly with hematologic, central nervous system, or splenic abnormalities. The symptoms may be present at birth or several weeks after birth. Table 1 summarizes the clinical manifestations of NLE.

**Table 1.** Clinical manifestations of neonatal lupus erythematosus

| |
|---|
| **Cutaneous manifestations**<br>Transient:<br>• annular and polymorphic erythematous plaques or targetoid plaques on the face, neck, and trunk<br>• periorbital "eye mask" or "raccoon eyes" sign<br>Sequels:<br>• Epidermal atrophy<br>• Telangiectasia<br>• Dyspigmentation<br>• Atrophic scarring |
| **Cardiac manifestations**<br>• Congenital AV block<br>• Sinus bradycardia<br>• Prolonged QT<br>• Myocarditis<br>• Endocarditis<br>• Fibroelastosis<br>• Dilated cardiomyopathy<br>• Valvular dysfunction<br>• Aortic dilatation and aneurysm |
| **Hematologic manifestations**<br>• Immune-cytopenia - anemia, thrombocytopenia, neutropenia<br>• Aplastic anemia |
| **Hepatobiliary manifestations**<br>• Neonatal cholestasis<br>• Mild elevation of serum transaminases<br>• Hepatomegaly<br>• Acute liver failure |
| **Neurologic manifestations**<br>• Hydrocephalus/macrocephaly<br>• CNS abnormality on imaging – white matter, basal ganglia calcifications, intracranial hemorrhage |
| **Other manifestations**<br>• Pulmonary (pneumonitis, alveolar hemorrhage, pulmonary hypertension)<br>• Pneumonitis<br>• Chondrodysplasia punctata<br>• Renal (hypertension, edemas, hematuria) |

*Cardiac manifestations*

The most severe and potentially life-threatening manifestation of NLE is an atrioventricular block caused by damage to the cardiac conduction system. This condition can be diagnosed prenatally, typically presenting as fetal bradycardia between 18 to 24 weeks of gestation [2,12].

Fetuses with first-degree atrioventricular (AV) block demonstrate a prolonged PR interval, accompanied by 1:1 AV conduction and a normal heart rate. Second-degree AV block is characterized by the nonconduction of at least one non-premature atrial impulse to the ventricles. In third-degree heart block (complete), there is a total dissociation between atrial and ventricular rates due to the absence of AV conduction. The atrial rate is generally normal, while the ventricular rate usually ranges between 50 and 80 beats per minute.

A complete (third-degree) atrioventricular (AV) block is generally irreversible, and the effectiveness of steroids in reducing mortality among these cases remains uncertain. In contrast, first- and second-degree AV block may fully resolve within the first few months after birth or may progress to complete block over time. The published data regarding second-degree AV block are inconsistent; treated and untreated cases have shown a range of outcomes, including progression to complete third-degree block, reversion to normal conduction, or persistence as second-degree AV block [12].

Sonesson *et al.* conducted a study involving 212 pregnancies at risk of fetal congenital heart block (CHB). The aim was to determine whether fetal AV block could be detected and treated before it progressed to a complete and irreversible state. Although the fetal AV interval was found to be a poor predictor of CHB progression, monitoring for CHB still enables the early detection of fetuses with second- or third-degree AV block, allowing prompt initiation of treatment and potentially better clinical outcome [25].

The neonatal presentation of CHB is significantly influenced by the impact of heart rate on cardiac output. The primary clinical finding in the newborn period is bradycardia, defined as a heart rate of less than 100 beats per minute. Other specific clinical signs may also be present, including pallor, intermittent gallops, murmurs, and signs of congestive heart failure.

Damage to the conduction tissue can occasionally result in transient sinus bradycardia, sinoatrial node dysfunction, QT interval prolongation, and Wolf-Parkinson-White syndrome[12].

The mortality risk of cardiac NLE ranges from 10% to 29%. Factors indicative of poor outcomes include fetal hydrops, cardiomyopathy, endocardial fibroelastosis, low heart rate, and prematurity [16,26,27].

*Cutaneous manifestations*

Cutaneous lesions are the most common manifestation of neonatal lupus erythematosus, appearing in approximately 40% of cases. These skin lesions may be present at birth or develop within the first 12 to 16 weeks after delivery. They closely resemble the rash seen in subacute cutaneous systemic lupus erythematosus, characterized by round, discoid, or elliptical erythematous patches or plaques, which may exhibit central clearing and could be accompanied by fine scaling (Figure 1). A hallmark feature of these lesions is the distinct periorbital involvement, often called the "eye mask" or "raccoon eyes" sign (Figure 2). Typically, neonatal lupus lesions are located on the face, scalp, neck, trunk, and extremities, and exposure to ultraviolet light - whether from sunlight or phototherapy - frequently triggers or exacerbates them [28,29].

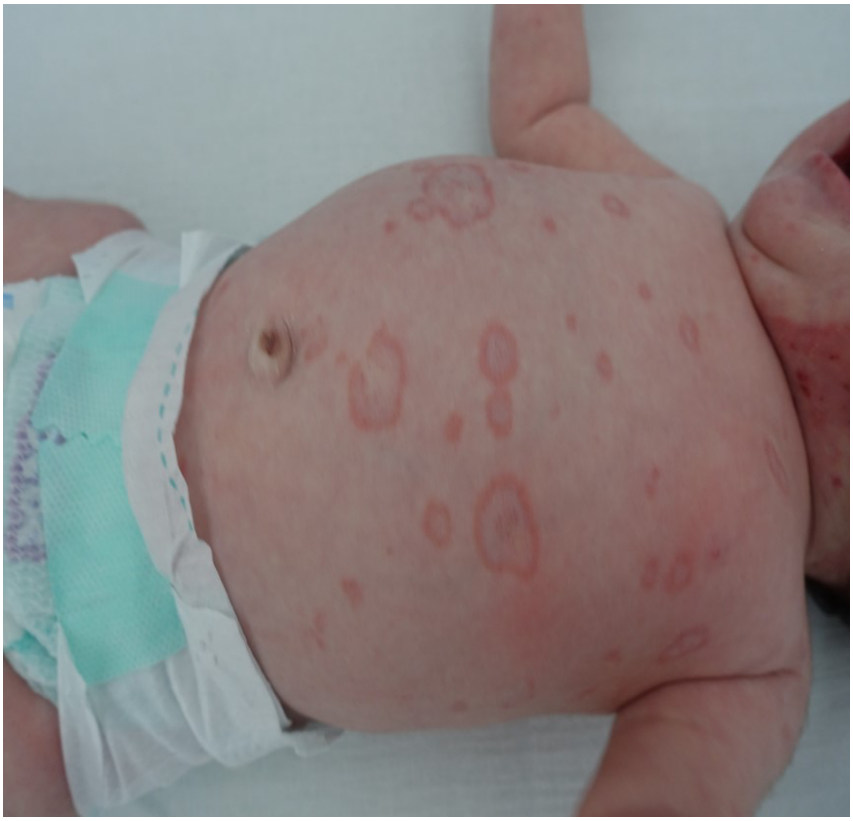

**Fig. 1.** Erythematous eruption with annular and discoid patches and central hypopigmentation

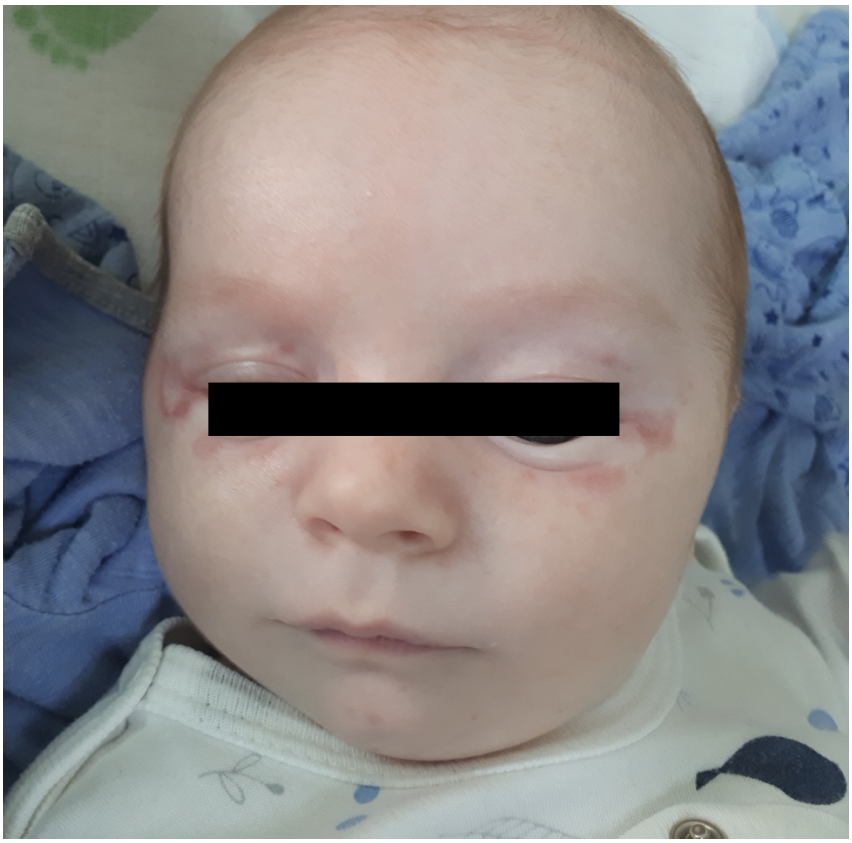

**Fig. 2.** The periocular rash signed as “raccoon-eye appearance”

While a skin biopsy is not required, histopathological analysis of the skin lesions typically shows features of epidermal necrosis, basal cell vacuolar degeneration at the dermo-epidermal interface, and changes in adnexal structures. Additionally, urticaria-like lesions may be observed, characterized by superficial and deep perivascular and periadnexal lymphocytic infiltrates [30].

In nearly all cases, the neonatal lupus rash tends to resolve within the first year, aligning with the clearance of maternal antibodies. Generally, the lesions heal without scarring; however, mild epidermal atrophy, telangiectasia, and dyspigmentation may persist, particularly if the lesions are highly inflammatory [31].

Although skin manifestations are characteristic, they are frequently misdiagnosed as birth trauma, fungal infection, or eczema, especially in newborns from asymptomatic mothers.

Cutaneous NLE should be distinguished from several erythematous rashes observed during the neonatal period, including annular urticaria, tinea corporis, eyelid telangiectasias, erythema multiforme, congenital rubella, and congenital syphilis [29]. The characteristics of NLE, neonatal annular erythema, and tinea are outlined in Table 2. These conditions can be differentiated by examining the mode of onset, progression, distribution, morphology of the skin lesions, associated features, and relevant family history [32].

**Table 2.** Disorders to consider in the differential diagnosis of neonatal lupus

| | **NLE** | **Annular erythema of infancy** | **Tinea corporis** |
|---|---|---|---|
| **Onset** | At birth or in the first few weeks of life | First few months of life | Very rare in neonates |
| **Site** | Face, scalp, neck, trunk | Face, trunk, extremities | Any site |
| **Morphology** | Erythematous, annular, polycyclic patches or plaques | annular and arcuate, erythematous plaque | Scaly, persistent, annular lesions |
| **Associated changes within lesions** | Central clearing, with or without fine scale | Slowly enlarging, scaling is absent | Progressive |
| **Histopathology** | Epidermal atrophy and a vacuolar interface dermatitis | Superficial and deep perivascular mononuclear infiltrate with eosinophils | Fungal hyphae in the str. corneum (Periodic Acid Schiff-PAS staining) |
| **Course of skin lesions** | Spontaneous resolution, sometimes with residual atrophy or telangiectasias | Cyclical eruption with complete resolution within 1 year. Resolution of individual lesions within a few days. | Progressive unless treated |
| **Diagnostic test** | SS-A and SS-B antibodies in the serum of the infant or the mother | Clinical suspicion | KOH examination of the scales |

*Annular erythema of infancy* is a benign condition marked by the cyclical appearance of ring-shaped, erythematous lesions that exhibit minimal scaling. These lesions typically resolve spontaneously within a few weeks and do not result in any long-term effects. The condition may have relapsing episodes until the child reaches one year of age. It has been postulated that annular erythema of infancy could be a hypersensitivity reaction to an unidentified antigen; however, the exact etiology remains unknown [32,33].

Although uncommon*, dermatophyte infections* can affect neonates. Several clinical forms of these infections may manifest in this age group, including tinea corporis, tinea capitis, tinea faciei, and onychomycosis. The associated skin lesions tend to be more inflammatory, and there may be a history of similar symptoms in other family members or in close contacts.

Individual patches of *seborrheic dermatitis* can resemble NLE due to their well-defined, scaly erythematous appearance. However, they can be differentiated by their yellow-red color and the type of scaling, which tends to be easily detachable and greasy. Additionally, seborrheic dermatitis is often associated with cradle cap.

Various *perinatal infections* may cause skin rashes, including congenital rubella, congenital syphilis, cytomegalovirus, and group B *Streptococcus*, which should be excluded.

*Atopic dermatitis* generally manifests later and presents as a more extensive rash, predominantly affecting the face, extremities, and intertriginous areas. It is characterized by itching and skin sensitivity. *Neonatal psoriasis* may mimic NLE but lacks the characteristic annular patterns. Both *Bloom syndrome* and *Rothmund-Thompson* syndrome are distinguished by the presence of a skin rash at birth.

The differential diagnosis for NLE also encompasses Langerhans cell histiocytosis, granuloma annulare, juvenile dermatomyositis, erythema multiforme, annular urticaria, neonatal acne, eyelid telangiectasias, and reactions to toxic exposures [29].

*Hepatobiliary manifestations*

Liver involvement has been rarely reported in case studies and might be underestimated. According to a national registry in the United States, estimated prevalence of hepatobiliary disease was around 10% of all cases of NLE [34]. However, findings from a multinational prospective study indicated that the true prevalence may be as high as 24% [14]. Hepatic manifestations can vary from mild and transient elevations of aminotransferases to cholestasis or even acute liver failure in neonates, resembling a neonatal hemochromatosis-like picture. The pathophysiology of liver disease related to NLE is not fully understood [35-37].

Earlier reports concerning NLE-associated liver disease suggested that liver injury might be secondary to hemodynamic compromise resulting from congenital heart block. However, more recent studies have identified a hepatitis profile distinct from congestive hepatopathy, based on the histological changes observed in liver biopsies from NLE patients[35]. These changes include non-specific giant cell hepatitis and ductal obstruction. As with the autoantibodies found in autoimmune hepatitis type 1, it remains uncertain whether the SSA/Ro and SSB/La autoantibodies play a direct pathogenic role in the liver injury associated with NLE[36].

*Hematologic manifestations*

Hematologic manifestations have been reported in some cases of NLE, including anemia, neutropenia, thrombocytopenia, and rarely, aplastic anemia [38-40].

In a prospective study, hematologic abnormalities were found in 27% of newborns born to mothers with anti-Ro/SSA or anti-La/SSB antibodies. Remarkably, there were no reported cases of neonatal sepsis among the neutropenic infants [14]. However, the prevalence of neutropenia in infants of anti-Ro/SSA-positive mothers is still uncertain, as healthy infants

typically do not undergo routine complete blood counts. The underlying mechanism of cytopenia is likely due to the suppressive effect of maternal antibodies on the bone marrow, rather than increased destruction of blood cells in the peripheral circulation.

*Pulmonary manifestations*

Pneumonitis, pleural effusion, necrotizing pulmonary capillaritis, and alveolar hemorrhage are all recognized clinical manifestations of pulmonary involvement in neonatal lupus erythematosus [14]. In a study by Pereira S. *et al*., severe pneumonitis was diagnosed in a neonate with a complete heart block who required a definitive pacemaker [41]. Furthermore, Maltret A. *et al.* detailed the clinical presentation, management, and outcomes of a series of four neonates who experienced reversible pulmonary hypertension associated with autoimmune congenital complete heart block [42].

*Neurologic manifestations*

Rare neurological abnormalities, such as macrocephaly and hydrocephalus, have been reported in association with anti-Ro/SSA antibodies; however, the exact causes remain unclear. In one study, 7 out of 87 infants exposed to maternal anti-Ro/SSA were found to have hydrocephalus, while 10 exhibited macrocephaly [43]. These findings have not been reported in other groups of children exposed to anti-Ro/SSA. Based on a systematic literature review, most neonates diagnosed with NLE and central nervous system involvement were identified through neuroimaging and were asymptomatic [44]. Other potential findings include vasculopathy in the gangliothalamic vasculature, ventriculomegaly, and vasculitis [45,46].

**Diagnosis and management**

The diagnosis of neonatal lupus erythematosus is established by fulfilling two primary criteria: 1) the presence of specific maternal antibodies, such as anti-Ro/SSA, anti-La/SSB, or potentially anti-ribonucleoprotein antibodies (U1-RNP), and 2) the identification of fetal or neonatal heart block, a characteristic neonatal skin rash, or hepatic or hematologic manifestations in the absence of any other explanation.

*Prenatal management*

Accurate prenatal diagnosis is essential for effective prenatal monitoring and therapy. Pregnant women with known autoimmune diseases should be referred to specialized tertiary care centers, where they can receive appropriate treatment aimed at achieving disease remission. Hydroxychloroquine, which has a favorable safety profile during pregnancy, is commonly prescribed by rheumatologists [12].

Several retrospective studies suggest that hydroxychloroquine reduces the overall risk of cardiac lupus and the likelihood of cardiac involvement in fetuses with a sibling who has a history of cardiac lupus. In the preconception period, hydroxychloroquine may be prescribed 2 to 8 weeks before the planned pregnancy, as evidence indicates that it can decrease the incidence of NLE, even in asymptomatic cases. Although there are no official guidelines from the American College of Rheumatology or the American College of Obstetricians and Gynecologists, most experts recommend administering hydroxychloroquine at a dosage of 5 mg/kg daily between the 6th and 10th weeks of gestation for seropositive women [47-49].

Fetal echocardiography is the most effective method for evaluating heart function. Serial fetal echocardiography examinations are recommended in all seropositive women between the 16th and 26th weeks of pregnancy [2].

If fetal heart block is suspected, close monitoring of the fetal cardiac conduction (atrioventricular) is essential. A progressive increase in the PR interval to over 150 ms indicates

the need for treatment with fluorinated steroids, such as dexamethasone or betamethasone, both of which can cross the placenta.

Dexamethasone can be administered orally at a dosage of 4–8 mg per day for 4 weeks. After this treatment period, it is crucial to reevaluate the atrioventricular interval and fetal development. If needed, dexamethasone dosage should be reduced after the first 2 weeks and discontinued if the AV interval decreases [47,50].

A β-sympathomimetics, such as terbutaline and salbutamol have favorable transplacental transfer. They can increase fetal heart rate and exert a positive inotropic effect on the fetal myocardium. These medications are usually administrated in combination with dexamethasone [51].

Intravenous immunoglobulin (IVIG) can reduce the transplacental autoantibody transfer, increase the release of anti-inflammatory factors, and have a promising role in the treatment of fetal cardiac disease, specifically when associated with cardiomyopathy. Brucato *et al*. reported two fetuses with complete heart block and severe myocarditis treated with IVIG 400 mg/kg/d for five days, resulting in prompt resolution of the echocardiographic indicators of myocarditis and notable clinical improvement [52].

Recently, the European Alliance of Associations for Rheumatology has issued guidelines for the care of patients with Sjogren's syndrome, including management of women of reproductive age and outlining the use of fluorinated steroids, IVIG, and plasma exchanges in the treatment of heart block [53].

*Neonatal management*

The management of neonatal NLE that affects the skin, blood, spleen, or liver is primarily supportive, as the condition is generally self-limiting and resolves spontaneously over time.

Treatment is often not necessary for cutaneous NLE since lesions typically heal without scarring. However, if intervention is needed, treatment may include mild topical corticosteroids and possibly, laser treatment for any residual telangiectasia. Avoidance of sun or ultraviolet light exposure to prevent or minimize the rash and residual skin abnormalities is recommended[12].

Symptomatic anemia or thrombocytopenia can be managed with blood and platelet transfusion. Also, glucocorticoids or intravenous immunoglobulin have been shown to be effective in certain circumstances.

Cardiac involvement is indicative of a poor prognosis especially when associated with ventricular rate <55 per minute, hydrops fetalis, cardiomegaly, atrioventricular valve regurgitation, or low aortic flow velocity. The insertion of a permanent pacemaker is a crucial treatment option for newborns with heart block [2,12].

**Prognosis**

The prognosis of NLE largely depends on the presence of cardiac involvement. The reported mortality rate is 10-29% in neonates with heart block, even with pacemaker implantation [12]. Furthermore, children who have had NLE may have an increased risk of developing an autoimmune or rheumatic disease; however, the existing literature presents conflicting results.

As clinical manifestations occur in early infancy, and only 10% of infants have persistent anti-SSA/Ro antibodies beyond 9 months of age, some authors suggest that follow-up until 6-9 months of age can ensure good clinical safety [54], while other recommend extended follow-up until adulthood [55].

**Conclusion**

Neonatal lupus erythematosus is a model of passively acquired autoimmune disease, where the fetus receives the pathogenic autoantibodies transplacentally. However, the specific underlying mechanisms are not fully understood, as the presence of maternal antibodies is not the only determinant of the development of NLE indicating that additional factors warrant further investigation. The identification of patients at risk for NLE and comprehensive screening of pregnant women with risk factors, accompanied by a multidisciplinary approach, is essential. This strategy facilitates maternal therapeutic interventions that may provide significant benefits.

*Conflict of interest statement.* None declared.

**References:**

1. Buyon JP, Clancy RM. Neonatal lupus syndromes. *Curr Opin Rheumatol*. 2003 Sep;15(5):535-41. doi: 10.1097/00002281-200309000-00003.
2. Vanoni F, Lava SAG, Fossali EF, Cavalli R, Simonetti GD, Bianchetti MG, Bozzini MA, Agostoni C, Milani GP. Neonatal Systemic Lupus Erythematosus Syndrome: a Comprehensive Review. *Clin Rev Allergy Immunol*. 2017; 53(3):469-476. doi: 10.1007/s12016-017-8653-0.
3. Izmirly PM, Halushka MK, Rosenberg AZ, Whelton S, Rais-Bahrami K, Nath DS, et al. Clinical and pathologic implications of extending the spectrum of maternal autoantibodies reactive with ribonucleoproteins associated with cutaneous and now cardiac neonatal lupus from SSA/Ro and SSB/La to U1RNP. *Autoimmun Rev*. 2017;16(9):980-3. doi:10.1016/j.autrev.2017.06.008.
4. Tran HB, Macardle PJ, Hiscock J, Cavill D, Bradley J, et al. Anti-La/SSB antibodies transported across the placenta bind apoptotic cells in fetal organs targeted in neonatal lupus. *Arthritis Rheum*. 2002;46(6):1572-9. doi:10.1002/art.10325.
5. Wisuthsarewong W, Soongswang J, Chantor R. Neonatal lupus erythematosus: clinical character, investigation, and outcome. *Pediatr Dermatol*. 2011;28(2):115–21. doi:10.1111/j.1525-1470.2010.01300.x.
6. Rivera TL, Izmirly PM, Birnbaum BK, et al. Disease progression in mothers of children enrolled in the Research Registry for Neonatal Lupus. *Ann Rheum Dis*. 2009;68(5):828. doi:10.1136/ard.2008.092822.
7. Fritzler MJ, Pauls JD, Kinsella TD, Bowen TJ. Antinuclear, anticytoplasmic, and anti-Sjogren's syndrome antigen A (SS-A/Ro) antibodies in female blood donors. *Clin Immunol Immunopathol*. 1985;36(1):120. doi:10.1016/0090-1229(85)90027-6.
8. Satoh M, Chan EK, Ho LA, et al. Prevalence and sociodemographic correlates of antinuclear antibodies in the United States. *Arthritis Rheum*. 2012;64(7):2319-27. doi:10.1002/art.34490.
9. Keogan M, Kearns G, Jefferies CA. Extractable nuclear antigens and SLE: specificity and role in disease pathogenesis. In: Lahita RG, Tsokos G, Buyon J, Koike T, editors. *Systemic Lupus Erythematosus*, 5th ed. San Diego: Academic Press; 2011. p. 259.
10. Buyon JP, Clancy RM, Friedman DM. Cardiac manifestations of neonatal lupus erythematosus: guidelines to management, integrating clues from the bench and bedside. *Nat Clin Pract Rheumatol*. 2009;5(3):139-48. doi:10.1038/ncprheum0999.
11. Izmirly PM, Buyon JP, Saxena A. Neonatal lupus: advances in understanding pathogenesis and identifying cardiac disease treatments. *Curr Opin Rheumatol*. 2012;24(5):466-72. doi:10.1097/BOR.0b013e328356a343.

12. Derdulska JM, Rudnicka L, Szykut-Badaczewska A, et al. Neonatal lupus erythematosus - practical guidelines. *J Perinat Med*. 2021;49(5):529-38. doi:10.1515/jpm-2020-0441.
13. Teixeira V, Gonçalo M. Neonatal lupus erythematosus – review of pathophysiology and clinical implications. *Acta Reumatol Port*. 2012;37(4):314-23.
14. Cimaz R, Spence DL, Hornberger L, Silverman ED. Incidence and spectrum of neonatal lupus erythematosus: a prospective study of infants born to mothers with anti-Ro autoantibodies. *J Pediatr*. 2003;142(5):678-83. doi:10.1067/mpd.2003.157.
15. Costedoat-Chalumeau N, Amoura Z, Lupoglazoff JM, et al. Outcome of pregnancies in patients with anti-SSA/Ro antibodies: a study of 165 pregnancies, with special focus on electrocardiographic variations in the children and comparison with a control group. *Arthritis Rheum*. 2004;50(10):3187-94. doi:10.1002/art.20513.
16. Izmirly PM, Saxena A, Kim MY, Wang D, Sahl SK, Llanos C, et al. Maternal and fetal factors associated with mortality and morbidity in a multi-racial/ethnic registry of anti-SSA/Ro-associated cardiac neonatal lupus. *Circulation*. 2011;124(18):1927-35. doi:10.1161/CIRCULATIONAHA.111.044807.
17. Buyon JP, Winchester RJ, Slade SG, et al. Identification of mothers at risk for congenital heart block and other neonatal lupus syndromes in their children. Comparison of enzyme-linked immunosorbent assay and immunoblot for measurement of anti-SS-A/Ro and anti-SS-B/La antibodies. *Arthritis Rheum*. 1993;36(9):1263-71. doi:10.1002/art.1780360907.
18. Gordon P, Khamashta MA, Rosenthal E, et al. Anti-52 kDa Ro, anti-60 kDa Ro, and anti-La antibody profiles in neonatal lupus. *J Rheumatol*. 2004;31(12):2480-4.
19. Jaeggi E, Laskin C, Hamilton R, et al. The importance of the level of maternal anti-Ro/SSA antibodies as a prognostic marker of the development of cardiac neonatal lupus erythematosus: a prospective study of 186 antibody-exposed fetuses and infants. *J Am Coll Cardiol*. 2010;55(25):2778-84. doi:10.1016/j.jacc.2010.02.044.
20. Sheng X, Song X, Xiong Y, Ren T, Chang X, Wu J, et al. Maternal and infant outcomes of pregnancy associated with anti-SSA/RO antibodies: a systematic review and meta-analysis. *Pediatr Rheumatol Online J*. 2023;21(1):22. doi:10.1186/s12969-023-00803-0.
21. Sheth AP, Esterly NB, Ratoosh SL, Smith JP, Hebert AA, Silverman E. U1RNP positive neonatal lupus erythematosus: association with anti-La antibodies? *Br J Dermatol*. 1995;132(4):520-6. doi:10.1111/j.1365-2133.1995.tb08705.x.
22. Dugan EM, Tunnessen WW, Honig PJ, Watson RM. U1RNP antibody-positive neonatal lupus. A report of two cases with immunogenetic studies. *Arch Dermatol*. 1992;128(11):1490-4. doi:10.1001/archderm.1992.01680230082020.
23. Sirén MK, Julkunen H, Kaaja R, et al. Role of HLA in congenital heart block: susceptibility alleles in children. *Lupus*. 1999;8(1):60-5. doi:10.1191/096120399678901412.
24. Stevens AM, Hermes HM, Lambert NC, Nelson JL, Meroni PL, Cimaz R. Maternal and sibling microchimerism in twins and triplets discordant for neonatal lupus syndrome-congenital heart block. *Rheumatology (Oxford)*. 2005;44(2):187-91. doi:10.1093/rheumatology/keh453.
25. Sonesson SE, Ambrosi A, Wahren-Herlenius M. Benefits of fetal echocardiographic surveillance in pregnancies at risk of congenital heart block: single-center study of 212 anti-Ro52-positive pregnancies. *Ultrasound Obstet Gynecol*. 2019;54(1):87-95. doi:10.1002/uog.19149.

26. Levesque K, Morel N, Maltret A, Baron G, Masseau A, Orquevaux P, et al. Description of 214 cases of autoimmune congenital heart block: Results of the French neonatal lupus syndrome. *Autoimmun Rev*. 2015;14(12):1154-60. doi:10.1016/j.autrev.2015.09.006.
27. Ho A, Gordon P, Rosenthal E, Simpson J, Miller O, Sharland G. Isolated complete heart block in the fetus. *Am J Cardiol*. 2015;116(1):142-7. doi:10.1016/j.amjcard.2015.04.053.
28. Neiman A, Lee L, Weston W, Buyon J. Cutaneous manifestations of neonatal lupus without heart block: characteristics of mothers and children enrolled in a national registry. *J Pediatr*. 2000;137(5):674-80. doi:10.1067/mpd.2000.106677.
29. Savino F, Viola S, Tarasco V, Locatelli E, Ricagni A, Coppo P. Neonatal lupus erythematosus: a cutaneous cases based update. *Ital J Pediatr*. 2016;42:1. doi:10.1186/s13052-016-0227-4.
30. Penate Y, Guillermo N, Rodríguez J, Hernández-Machín B, Montenegro T, et al. Histopathologic characteristics of neonatal cutaneous lupus erythematosus: description of five cases and literature review. *J Cutan Pathol*. 2009;36(7):660-7. doi:10.1111/j.1600-0560.2009.01217.x.
31. Levy R, Briggs L, Silverman E, Pope E, Lara-Corrales I. Cutaneous sequelae in neonatal lupus: a retrospective cohort study. *J Am Acad Dermatol*. 2020;83(2):440-6. doi:10.1016/j.jaad.2019.11.033.
32. Palit A, Inamadar AC. Annular, erythematous skin lesions in a neonate. *Indian Dermatol Online J*. 2012;3(1):45-7. doi:10.4103/2229-5178.93504.
33. Saha A, Seth J, Mukherjee S, Basu S. Annular erythema of infancy: a diagnostic challenge. *Indian J Pediatr Dermatol*. 2014;15:147.
34. Lee LA, Sokol RJ, Buyon JP. Hepatobiliary disease in neonatal lupus: prevalence and clinical characteristics in cases enrolled in a national registry. *Pediatrics*. 2002;109(1):e11. doi:10.1542/peds.109.1.e11.
35. Laxer RM, Roberts EA, Gross KR, et al. Liver disease in neonatal lupus erythematosus. *J Pediatr*. 1990;116(2):238–42. doi:10.1016/s0022-3476(05)82880-x.
36. Hon KL, Leung AK. Neonatal lupus erythematosus. *Autoimmune Dis*. 2012;2012:301274. doi:10.1155/2012/301274.
37. Khayat AA, Alkhaldi AJ. Neonatal lupus presenting with neonatal hemochromatosis-like liver disease that responded to steroids: a case report. *BMC Pediatr*. 2022;22(1):630. doi:10.1186/s12887-022-03682-x.
38. Kim KR, Yoon TY. A case of neonatal lupus erythematosus showing transient anemia and hepatitis. *Ann Dermatol*. 2009;21(3):315.
39. Kanagasegar S, Cimaz R, Kurien BT, et al. Neonatal lupus manifests as isolated neutropenia and mildly abnormal liver functions. *J Rheumatol*. 2002;29(1):187.
40. Wolach B, Choc L, Pomeranz A, et al. Aplastic anemia in neonatal lupus erythematosus. *Am J Dis Child*. 1993;147(8):941.
41. Pereira S, Flor-de-Lima F, Soares H, et al. Pulmonary involvement in neonatal lupus: a challenging diagnosis - case report and literature review. *Acta Reumatol Port*. 2018;43(3):230-4.
42. Maltret A, Morel N, Levy M, et al. Pulmonary hypertension associated with congenital heart block and neonatal lupus syndrome: A series of four cases. *Lupus*. 2021;30(2):307-14. doi:10.1177/0961203320973073.
43. Boros CA, Spence D, Blaser S, Silverman ED. Hydrocephalus and macrocephaly: new manifestations of neonatal lupus erythematosus. *Arthritis Rheum*. 1996;39(9):1594-6. doi:10.1002/art.1780390921.

44. Chen CC, Lin KL, Chen CL, et al. Central nervous system manifestations of neonatal lupus: a systematic review. *Lupus.* 2013; 22:1484.
45. Cabañas F, Pellicer A, Valverde E, Morales C, Quero J. Central nervous system vasculopathy in neonatal lupus erythematosus. *Pediatr Neurol*. 1996 Sep;15(2):124-6. doi: 10.1016/0887-8994(96)00159-2.
46. Saini AG, Sankhyan N, Bhattad S, Vyas S, Saikia B, Singhi P. CNS vasculitis and stroke in neonatal lupus erythematosus: a case report and review of literature. *Eur J Paediatr Neurol.* 2014 May;18(3):444-8. doi: 10.1016/j.ejpn.2014.01.007.
47. Clowse MEB, Eudy AM, Kiernan E, et al. The prevention, screening and treatment of congenital heart block from neonatal lupus: a survey of provider practices. *Rheumatology.* 2018; 57: v9–v17.
48. Izmirly PM, Costedoat-Chalumeau N, Pisoni CN, et al. Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro-antibody-associated cardiac manifestations of neonatal lupus. *Circulation* 2012; 126: 76–82.
49. Beksac MS, Donmez HG. Impact of hydroxychloroquine on the gestational outcomes of pregnant women with immune system problems that necessitate the use of the drug. *J Obstet Gynaecol Res* 2021; 47: 570–575.
50. Donofrio MT, Moon-Grady AJ, Hornberger LK, et al.; American Heart Association Adults With Congenital Heart Disease Joint Committee of the Council on Cardiovascular Disease in the Young and Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Council on Cardiovascular and Stroke Nursing. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. *Circulation*. 2014 May 27;129(21):2183-242. doi: 10.1161/01.cir.0000437597.44550.5d.
51. Saxena A, Izmirly PM, Mendez B, Buyon JP, Friedman DM. Prevention and treatment in utero of autoimmune-associated congenital heart block. *Cardiol Rev*. 2014 Nov-Dec;22(6):263-7. doi: 10.1097/CRD.0000000000000026.
52. Brucato A, Ramoni V, Gerosa M, Pisoni MP. Congenital fetal heart block: a potential therapeutic role for intravenous immunoglobulin. Author reply *Obstet Gynecol*. 2011;117:177. doi: 10.1097/AOG.0b013e3182042972.
53. Ramos-Casals M, Brito-Zerón P, Bombardieri S, et al. EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies. *Ann Rheum Dis* 2020; 79: 3–18.
54. Zuppa AA, Riccardi R, Frezza S, Gallini F, Luciano RM, Alighieri G, Romagnoli C, De Carolis S. Neonatal lupus: Follow-up in infants with anti-SSA/Ro antibodies and review of the literature. *Autoimmun Rev*. 2017 Apr;16(4):427-432. doi: 10.1016/j.autrev.2017.02.010.
55. Martin V, Lee LA, Askanase AD, Katholi M, Buyon JP. Long-term followup of children with neonatal lupus and their unaffected siblings. *Arthritis Rheum*. 2002 Sep;46(9):2377-83. doi: 10.1002/art.10638.