Elevate Series

REVIEW ARTICLE

Neonatal lupus erythematosus: an acquired autoimmune disease to be taken seriously

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ABSTRACT

Aim: This review aims to summarize the epidemiology, pathogenesis, clinical features, management, prognosis and regression of Neonatal lupus erythematosus (NLE) with a view to providing directions for standardized diagnosis, treatment and further research.

Methods: We conducted a comprehensive literature review of NLE. NLE-related peer-reviewed papers were searched through PubMed/Medline were searched up to November 2024.

Results: NLE is a rare acquired autoimmune disease (AD) linked to organ damage from maternal autoantibodies crossing the placenta to the foetus. However, not all mothers have ADs or associated antibodies. The disease involves autoantibody-induced inflammation, apoptosis, fibrosis, calcium channel dysregulation in cardiomyocytes, and increased interferon expression. NLE incidence shows no sex difference, but there is a differential distribution of clinical features across ethnic groups. The frequency of organ involvement in NLE patients is more common in the cutaneous and cardiac. NLE also affects the haematological and hepatobiliary systems, and some patients may experience neurological and endocrinological involvement. Steroids and immunoglobulins can aid in the recovery of some patients. Proper use of antimalarials during prenatal and gestational periods may prevent or improve the prognosis of patients with congenital heart block (CHB). Implantation of a pacemaker is effective in maintaining cardiac function in children with complete atrioventricular block. Symptoms associated with NLE may improve with antibody depletion, but some patients may experience sequelae such as irreversible CHB, neuropsychiatric disorders and developmental delays. Universal screening for autoantibodies to Sjögren syndrome A or B autoantigens should be offered to women of childbearing age experiencing desiccation syndrome. Antibody-positive individuals require appropriate reproductive counselling and advice, along with close foetal monitoring starting at 16 weeks of gestation and postnatal prognostic follow-up.

Conclusion: Epidemiologic investigations and clinical studies on NLE are currently inadequate, and large-scale epidemiologic investigations, prospective clinical studies, and basic research are needed in the future to improve the understanding of the disease and the standardization of its clinical management.

1. Introduction

Immunoglobulin G (IgG) from mothers with rheumatic/autoimmune disease (AD) can cross the placenta, affecting foetal and post-natal [1,2]. In 1954, Bridge and Foley [3] first reported that maternal 'lupus erythematosus factor' could be transmitted to newborns. The understanding of neonatal lupus erythematosus (NLE) has improved with more reported cases. NLE is now recognized as an acquired AD, a clinical syndrome with multiple organ involvement induced by maternal

IgG (mainly anti-SSA/Ro and anti-SSB/La antibodies) [4–6]. Most data on NLE come from observational studies and case reports, with few systematic summaries. The aim of this review is to summarize the epidemiology, pathogenesis, clinical features, management, prognosis and regression of NLE with a view to providing directions for standardized diagnosis, treatment and further research. For this purpose, we searched and screened the literature contained in databases such as PubMed/MEDLINE using the MeSH terms

neonatal lupus or congenital heart block. Focus on reviewing representative reports and high-quality research papers. The search was performed from database construction to November 2024.

2. Epidemiology

NLE incidence is approximately 2% among offspring of mothers who are positive for anti-SSA and anti-SSB antibodies, increasing to 18–20% in subsequent pregnancies. Nearly 5% of patients with NLE may develop systemic lupus erythematosus (SLE) during adolescence or early adulthood [7–9]. The male-to-female ratio of patients with NLE and cutaneous involvement ranges from 2:1 to 3:1 [7–11]. However, subsequent studies indicate no significant difference between males and females in NLE incidence [7–9,11–15]. Some prospective studies found CHB incidence in the offspring of women positive for anti-SSA/Ro with uninvolved previous pregnancies at approximately 2%. However, in subsequent pregnancies, CHB incidence in offspring increases 10-fold [7–9,11,16–18].

Studies from Europe and America report congenital heart block (CHB) in nearly 70% of patients with NLE patients [7–9,11,19,20]. In Asia, less than 30% have cardiac involvement, but cutaneous involvement is twice that of patients from other regions. Studies show that 80% of patients with NLE in Asia have cutaneous involvement, with CHB incidence between 8.9% and 23%. However, one Japanese study found that approximately 50% of newborns with mothers who are anti-SSA/Ro antibody-positive developed CHB [7–9,11,21]. In lower middle income regions, missed pre-natal cardiac NLE diagnosis may increase estimates of spontaneous foetal losses of unknown aetiology. This leads to fewer documented CHB cases, further reducing its reported prevalence. It is easy to speculate whether there are maternal and infants genetics or other factors involved. Overall, however, universal screening and epidemiologic investigations of autoantibodies and prevalence of NLE in offspring in high-risk populations are currently inadequate, which may contribute to the wide variation in the prevalence of NLE reported.

The most common autoantibody detected in patients and mothers is anti-SSA/Ro, followed by anti-SSB/La antibodies. A small percentage may have anti-U1RNP antibodies. Among pregnant women positive for these autoantibodies, 0.1–1.5% were healthy, while 90% had Sjögren's syndrome (SS), 20–30% had SLE, and 3% had rheumatoid arthritis (RA). Approximately 25% of mothers of patients with NLE

show no autoimmune disease-related symptoms at delivery, with 50% developing symptoms within 3 years. Notably, 10–15% of mothers are negative for serum circulating autoantibodies [7–9,11,22,23]. In the review by Brito-Zeron et al. [24], the existence of 'immunonegative' CHB was questioned, as the vast majority of CHB cases are diagnosed in children ≥15 years of age or in mothers who have not been systematically assayed for CHB-associated autoantibodies. This challenge is very reasonable. It is well known that NLE is a syndrome caused by the transfer of circulating autoantibodies from the mother to the foetus via the placenta. In fact, asymptomatic women are usually not tested for autoantibodies; additionally, negative results on circulating antibody assays need to take into account differences in laboratory sample quality control and sensitivity.

3. Pathogenesis

The widely accepted idea is that NLE is mediated by maternal autoantibodies transferred through the placenta, which explains that the human foetus produces only trace amounts of IgA and IgM but not IgG, which is of maternal origin. In the third trimester, due to its small size, maternal IgG passes easily through the placenta, resulting in foetal IgG levels approximately 10% higher than maternal levels at full-term. At physiological pH, neonatal FcRs ensure maternal IgG release into the foetal circulation via endocytosis [1,2,7–9,11,25]. The IgG antibodies inducing NLE include mainly anti-SSA/Ro and anti-SSB/La. These enter the foetal circulation through the placenta, specifically targeting foetal tissue antigens, forming antigen-antibody complexes and activating inflammatory reactions, causing foetal tissue damage. Anti-SSA/Ro antibody targets four miRNAs 45, 52, 54 and 60 kDa) but only used both anti-SSA/Ro52 and anti-SSA/Ro60 clinically. Anti-SSB/La primarily recognizes a 47kD cytoplasmic protein. Ro52 is more likely to induce NLE-associated phenotypes in animal models and functions as a ubiquitin E3 ligase, promoting inflammatory responses and cell death. Additionally, it is a component of the TRIM21 receptor family, regulating T-cell activation and pro-inflammatory interleukin production [7–9,11,26–32].

Most mechanistic studies have focused on diseases with poor prognosis in patients with NLE and CHB. Anti-SSA/Ro antibodies are linked to an increased CHB risk in NLE [7–9,11,33–35]. High anti-SSB/La antibody levels may correlate with non-cardiac features [7,11,36]. Anti-SSA/Ro antibodies bind to foetal cardiomyocytes, inhibiting apoptotic cell clearance during foetal heart development, resulting in foetal or neonatal arrhyth-

mias and structural cardiac. Additionally, antigen-antibody complex generation enhances Toll-like receptor signalling, triggers macrophage activation and fibrogenic factor secretion, and is associated with myocardial fibrosis development. At 18–26 weeks of gestation, type A or B autoantigens translocate to cardiomyocyte surfaces. Maternal IgG antibodies then enter foetal circulation, binding to these antigens and causing atrioventricular node injury. The cross-reactivity between cardiomyocyte L- and T-type calcium channels and autoantibodies disrupt cardiomyocyte calcium homeostasis and affect action potential conduction [7,11,24,32,37]. Related study shows that only foetuses exposed to high doses of maternal Anti-SSA/Ro antibodies are at risk for antibody-mediated heart disease [38,39]. Edgar Jaeggi et al. [38]used solid-phase enzyme-linked immunosorbent assay for maternal 60-kd Ro and 52-kd Ro proteins and found that only the offspring of mothers with Anti-SSA/Ro antibodies titres greater than 50 units/ml developed cardiac neonatal lupus. They then used chemiluminescent immunoassay and multiplex bead-based immunoassay to similarly confirm the association between high titres of Anti-SSA/Ro antibodies and the development of cardiac neonatal lupus [35]. Anti-U1RNP antibodies, associated with U1 spliceosome RNA, are linked to CHB development. When patients with CHB lack anti-SSA/Ro and anti-SSB/La antibodies and structural aetiology, testing for maternal anti-U1RNP antibody is advisable [29,32], and antibody titres may correlate with CHB development in patients with NLE. Mothers with high autoantibody titres face greater CHB risk in offspring than those with low titres [24,32]. The risk of NLE with CHB significantly increases when both anti-SSA/Ro and anti-SSB/La antibodies are positive [24]. CHB probability increases with the presence of anti-SSA/Ro, anti-SSB/La and anti-U1RNP antibodies [40].

Numerous studies suggest type I interferons (IFN) may be essential in CHB development. Neonates positive for both anti-SSA/Ro and anti-SSB/La antibodies exhibit increased expression of plasma IFN regulatory genes and IFNα [41,42]. Type I IFN activates tissue-resident, infiltrates macrophages and upregulates Ro52 expression, accelerating apoptosis and inducing a localized inflammatory response in the foetal heart [43,44]. Additionally, type I IFN directly contributes to arrhythmogenic effect [45–47].

Genetic factors may also contribute to NLE development. However, a multi-ancestral cohort study on anti-SSA/Ro antibody-positive found no association between SLE-associated genes and NLE outcome risk [48].

4. Clinical features and management of NLE

Clinical manifestations associated with NLE may appear at birth or within the first few weeks, usually before 4–6 weeks [10,13,15,49,50]. NLE often presents reversible symptoms of generalized multi-organ involvement and resolves as antibodies diminish, often within 6–12 months [51]. Cutaneous involvement is prevalent, followed by haematological, hepatobiliary and cardiac involvement; neurological and endocrinological involvement may occur in some patients [13,51,52].

4.1. Cutaneous

Cutaneous lesions are common in NLE, resembling those in children and adolescents with SLE. Relevant studies show varying rates of cutaneous involvement among ethnic groups, with Asians having the highest, up to 45.2%, overall and approaching 80% in some regions [15,22,52]. These usually appear at birth (20%) or within weeks (80%), with a cephalofacial distribution being the most common (up to 95%), followed by the trunk and extremities, respectively. Some patients may develop generalized cutaneous involvement. Ultraviolet exposure accelerates cutaneous lesions onset and progression [4,13,53,54]. Lesions primarily appear as macular rings or oval erythema with protruding edges, occasionally as papular or plaque-like lesions, some with central hyaline or fine-scaled lesions. Most lesions are usually 1 cm in diameter, with some fusing to form patchy erythema [50,55–57]. A small percentage of patients with NLE may present with oral mucosal lesions, mainly oral ulcers [58,59]. Cutaneous lesions typically resolve within six months in most patients and within one year in all patients [4,13,60]. Histological examination reveals granular IgG deposits at the dermal-epidermal junction and vesicular changes at the interface and skin adnexal structures [56].

Cutaneous lesions in NLE usually improve as antibodies deplete. Sunlight avoidance are the main treatment [61,62]. Topical steroids effectively treat cutaneous lesions in NLE but may not be necessary in all cases [58,62,63]. There have also been reports of reduced cutaneous rash in infants born to mothers taking hydroxychloroquine (HCQ) [64]. Some patients with NLE may experience long-term cutaneous damage, including capillary dilatation, hyperpigmentation and atrophic scars [63,65–67]. Cutaneous sequelae may be associated with photodamage, topical steroid use, immune complex deposition, etc. [65]. Patients with NLE who develop dilated capillaries can be treated with laser therapy. In conclusion, patients with NLE and cutaneous lesions require long-term follow-up

with timely symptomatic interventions to minimize sequelae.

4.2. Haematological

NLE patients often experience isolated decreases in specific blood cell lineages, with anaemia being the most common, followed by thrombocytopenia and neutropenia. A small number of infants may present with pancytopenia resembling aplastic anaemia. However, precise estimates of prevalence are challenging since otherwise well newborns do not routinely undergo complete blood count testing. In contrast to the mechanism of lymphopenia in SLE, neutropenia in NLE is associated with the direct destruction of anti-SSA/Ro antibodies [68]. Zuppa AA et al. [51] found that clinical and laboratory monitoring of newborns born to anti-SSA/Ro antibody-positive mothers should be performed at 3 months of age, which is the time when infants have a high prevalence of haematologic and liver test abnormalities. Haematological symptoms usually resolve spontaneously, while symptomatic anaemia and thrombocytopenia may require blood transfusions [13,69,70]. Steroids/immunoglobulin therapy yields better results in some patients [7,71]. It's worth noting that pancytopenia in NLE patients needs to be differentiated from familial hemophagocytic lymphohistiocytosis/aplastic anaemia, etc. [72–74]. Pancytopenia in NLE patients is usually transient, and some symptomatic children improve with transfusion therapy [51].

4.3. Cardiac

Cardiac involvement is common in patients with NLE, with rates varying by ethnicity, reaching approaching 70% in Europe and the Americas [19,20] and less than 30% in Asia [15,52]. This involvement includes chronic CHB, arrhythmias and myocarditis. Studies indicate patients with NLE have a higher incidence of structural heart defects than normal newborns [7,14,15]. However, a clear causal relationship and the exact mechanism remain unknown despite the absence of high-quality clinical studies on NLE and congenital cardiac structural defects.

The riskiest manifestation of cardiac involvement in NLE is CHB, occurring at a high rate, with a 15–20% risk of death from complete atrioventricular block (CAVB) [20,75]. It is believed that 60–90% of CHB cases are due to maternal antibodies entering the foetal circulation, unrelated to heart structural abnormalities [76]. CHB typically develops between the 18th and 26th weeks of gestation, less commonly after 26-30 weeks. Foetuses with severe CHB may exhibit bradycardia in utero, with a normal atrial and ventricular rate (40 –80/min [24,31,77,78]. Some newborns with severe CHB may develop myocardial dysfunction, possibly due to endocardial elastic fibre hyperplasia and myocardial fibrosis or associated with arrhythmia-induced cardiac dysfunction [24,31,77,78]. A related study confirmed that steroids and immunoglobulins completely improved biventricular dysfunction in NLE patients without arrhythmias [79]. A long-term follow-up study of 239 patients with NLE and cardiac involvement found that 2.4% developed cardiac insufficiency by age 1, 14.8% between ages 1 and 17, and 28.1% after age 17. Additionally, 43.8% of children with cardiac insufficiency by age 1 persisted until ages 1 to 17 [80]. Therefore, long-term follow-up is essential for patients with cardiac involvement.

CHB caused by NLE requires a wide range of perinatal and postnatal interventions. CHB induced by anti-SSA/Ro and anti-SSB/La antibodies is common and irreversible, causing a severe burden on patients and their families. In this population, anti-SSA/Ro antibody positivity ranged from 0.5% to 2.7%, and anti-SSB/La antibody positivity was 0.2% [81–83]. Currently there is wide variation in the timing of foetal cardiac monitoring in pregnant women with autoantibodies against SSA/Ro [84]. Mothers with autoimmune diseases, especially those positive for anti-SSA/Ro and anti-SSB/La antibody antibodies, should receive counselling about CHB risk during prenatal care. Per Canadian Rheumatology Association Recommendations, women with SLE should be tested for these antibodies before and during the first three months of pregnancy for timely monitoring and prophylactic treatment [85]. Regular ultrasonic cardiogram (UCG) monitoring is required to detect abnormalities, such as CHB, guiding delivery timing and treatment initiation. Foetal arrhythmias can be detected by UCG starting at 16–17 weeks of gestation, prompting regular screening of high-risk foetuses from the 16th week. Since few CHB cases are detected post-birth, monitoring during the first month after birth is also required for such patients [22,24,86,87]. Foetal heart rate and rhythm is effective in identifying atrioventricular block in the foetus and may reduce the need for serial echocardiograms, according to new research [34].

Studies have shown that the rational use of HCQ, an antimalarial drug, reduces cardiac involvement risk in children with NLE by 98.7%, possibly due to its cardioprotective effect in inhibiting toll-like receptor signalling [11]. HCQ significantly reduces the recurrence rate of CHB in women who previously delivered an affected infant, with a protective effect exceeding 50% [18,88]. The 2020 American College of Rheumatology Reproductive Health Management Guidelines for

Rheumatoid and Musculoskeletal Diseases recommend HCQ treatment for all pregnant women positive for anti-SSA/Ro-and/or anti-SSB/La antibodies to reduce CHB risk [89]. Currently, dexamethasone and/or IVIG are commonly used to treat II and III foetal atrioventricular blocks [84,90]. However, Previous studies have shown conflicting results regarding the effectiveness of fluorinated steroid betamethasone and immunoglobulin in preventing cardiac involvement in patients with NLE [24,35,78,86,91]. The 2020 American College of Rheumatology Guidelines for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases recommend 4 mg/day oral dexamethasone for pregnant women positive for anti-SSA/Ro and/or anti-SSB/La antibodies, with UCG suggesting CHB presence in the foetus [89]. Plasmapheresis may reverse and improve CHB but may be ineffective for CAVB [92].

Pacemaker implantation is an effective treatment option for patients with CAVB. Most require a pacemaker within one year of birth to maintain cardiac function [35,93–95]. After 9 years of follow-up, the survival of patients with CHB, although pacemaker implantation, can also induce abnormal electrical activation patterns [95,96].

4.4. Hepatobiliary

Hepatobiliary involvement in patients with NLE is mainly characterized by hepatomegaly, elevated transaminases, cholestasis, feeding intolerance and rarely, splenomegaly and peritoneal effusion [14,51,52,54,97–99]. This involvement is self-limiting, usually resolving within 6 months [14,54,70]. Manifestations associated with hepatobiliary involvement in NLE are often detected through laboratory tests. Relevant studies have shown that patients with NLE and hepatobiliary involvement often present with feeding intolerance and diarrhoea as the first manifestations, which may be attributed to lupus antibody-induced vascular inflammation throughout the hepatobiliary [14]. Therefore, offspring of mothers with AD or NLE-related antibodies who develop hepatobiliary involvement, such as feeding intolerance, after birth should be promptly examined and treated symptomatically. Some studies have suggested that steroids and immunoglobulins may effectively treat liver symptoms in patients with NLE [7]. However, this remains a subject for further research.

4.5. Neurological

Neurological involvement due to NLE is often overlooked but not uncommon. Central nervous system (CNS) involvement in patients with NLE can manifest as benign macrocephaly, seizures, cerebral haemorrhage and spinal cord lesions [13,49,100–103]. NLE-induced neurological involvement is usually asymptomatic and typically resolves without adverse sequelae once the antibodies subside. Intracranial haemorrhage may also be associated with antibody-induced systemic vasculitis. Lupus-associated antibodies can affect blood vessels throughout the body, often resulting in thrombosis, vasospasm, aneurysms and haemorrhage in the CNS [104,105]. Aseptic meningitis has also been reported in NLE, usually presenting with fever as the first symptom. CNS involvement may not be obvious, and brain magnetic resonance imaging findings may show irregular enhancement or no abnormalities. Hydrocephalus may occur in a small number of patients, and the diagnosis can be clarified through cerebrospinal fluid (CSF) analysis [13,49,69]. Steroids and immunoglobulins may be effective against aseptic meningitis [13].

Some studies have evaluated neurodevelopmental outcomes in patients with NLE. A prospective study from the United States [9] showed that 40% of children exposed to maternal autoantibodies developed neuropsychiatric disorders, significantly higher than the 27% in the control group. However, there were no significant differences between the two groups in the prevalence of depression, anxiety, developmental delays, learning, hearing and speech problems. In a related study, patients with CAVB associated with anti-SSA/Ro antibody positivity were followed up over an extended period, and neurodevelopmental assessment was performed using the Griffiths Developmental Assessment Scale and the Wechsler Intelligence Scale for Children. The intellectual level of the patients was normal, except for one patient with a learning disability [106]. However, it has also been shown that some patients with NLE and CNS involvement experience seizures and varying degrees of growth retardation, which usually improves with rehabilitation therapy [13,70]. Few relevant studies have addressed neurodevelopmental outcomes in NLE, and it is not yet completely clear whether there is a direct causal relationship between long-term neurodevelopmental delays or adverse neurological events and NLE in patients with NLE.

4.6. Endocrinological

A variety of endocrine glands, including the pancreas and thyroid, can be affected by ADs, and endocrine gland damage is also present in patients with NLE [13,107]. A retrospective study from China [13] found that 9 of 39 patients with NLE had different types of endocrinological impairments, among which abnormal

pancreatic function was the most common. This was mainly characterized by hyperinsulinemia with hypoglycaemia, hypothyroidism, hypoadrenocorticism and lysineurine-protein intolerance. Nine patients with endocrinological involvement tested positive for anti-SSA/Ro antibodies. Endocrinological involvement due to NLE is often transient and does not require special management; however, close monitoring of the patient's blood glucose level is required for hyperinsulinemia with hypoglycaemia. If necessary, exogenous glucose supplementation is required to avoid the organ damage caused by hypoglycaemia.

5. Prognosis

The effect of maternal ADs on offspring has been a focal point and hot topic in current research. Offspring of mothers with ADs have a significantly increased risk of developing ADs and neurodevelopmental disorders [71,108–110]. Therefore, long-term follow-up for patients with NLE is necessary. Less than 5% of patients with NLE may progress to SLE during adolescence or early adulthood [7,8]. Besides SLE, patients with NLE also have a significantly increased risk of developing other types of ADs in the future [71,111]. A long-term follow-up study of patients with NLE ($n=49$) and their unaffected siblings ($n=45$) found that six children previously diagnosed with NLE eventually received a definitive diagnosis of Ads. These included two cases of juvenile rheumatoid arthritis, one case of Hashimoto's thyroiditis, one case of psoriasis and iritis, one case of diabetes and psoriasis, and one case of congenital hypothyroidism and nephrotic syndrome [111].

A small percentage of offspring from mothers with ADs have varying degrees of neuropsychiatric disorders and developmental delays [9,13,70,109,110]. Offspring of mothers with SLE are more likely to have neurodevelopmental disorders, possibly related to foetal exposure to autoantibodies and steroids [102,109,110,112]. However, steroids are degraded and inactivated as they pass through the placenta, with only 10% reaching the foetus. Further studies are needed to determine whether these factors are associated with an increased neurodevelopmental risk in offspring. A related study demonstrated that a subpopulation of anti-dsDNA antibodies, called anti-N-methyl-D-aspartate-receptor antibodies, induces apoptosis in foetal neurons, which is associated with the development of neuropsychiatric disorders [113]. Although many studies have shown that mothers with ADs have a significantly increased risk of ADs and neurodevelopmental disorders in their offspring, some

studies have not found this phenomenon. However, these studies did not investigate the mechanism linking NLE to neurodevelopmental issues. Furthermore, selective reporting by families and care providers may introduce bias, affecting the perceived prevalence of this association. Future controlled, prospective, large-scale clinical follow-up studies are required.

6. Conclusion

Epidemiologic descriptions and surveys on the type, frequency and severity of clinical presentations in NLE patients are scarce. NLE presents with reversible symptoms of multiple organ involvement associated with maternal autoantibodies, often involving the cutaneous, cardiac, haematological and hepatobiliary in a small percentage of patients, as well as neurological and endocrinological involvement. There were no significant differences in sex prevalence; however, organ involvement varied according to race. The main mechanisms involved in the development of NLE are fetotransmitted antibody-induced inflammation, apoptosis, fibrosis, an imbalance in calcium channel homeostasis in cardiomyocytes and increased IFN expression. Genetics may also play a role in the development of NLE. Maternal and infant genetic factors may confound the NLE and outcomes association, but such studies are rare, and this will be a key area for future research.

Steroids and immunoglobulins have therapeutic effects in some patients; however, some controversy remains. The appropriate use of HCQ during the prenatal and gestational periods may prevent or improve the prognosis of patients with NLE and CHB. Patients with NLE have an increased incidence of ADs, and some may experience CHB, neuropsychiatric disorders, and developmental delays. Pregnant mothers who test positive for these antibodies should be provided with reproductive counselling, long-term management and follow-up. Most studies on NLE are retrospective descriptive studies or case reports/series; controlled, prospective, large-scale clinical prospective studies are needed in the future.

Author contributions

CRediT: **Wenqiang Sun**: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing; **Changchang Fu**: Data curation, Investigation, Writing – original draft; **Xinyun Jin**: Data curation, Investigation; **Changda Lei**: Data curation, Investigation; **Xueping Zhu**: Conceptualization, Funding acquisition, Investigation, Methodology, Writing – review & editing.

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Data availability statement

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References

[1] Holt PG, Jones CA. The development of the immune system during pregnancy and early life. Allergy. 2000;55(8):688–697. doi: 10.1034/j.1398-9995.2000.00118.x.

[2] Ygberg S, Nilsson A. The developing immune system—from foetus to toddler. Acta Paediatr. 2012;101(2):120–127. doi: 10.1111/j.1651-2227.2011.02494.x.

[3] Bridge RG, Foley FE. Placental transmission of the lupus erythematosus factor. Am J Med Sci. 1954;227(1):1–8. doi: 10.1097/00000441-195401000-00001.

[4] Diaz-Frias J, Badri T. Neonatal lupus erythematosus. Treasure Island (FL): StatPearls Publishing;2023.

[5] Yokogawa N, Sumitomo N, Miura M, et al. Neonatal lupus erythematosus. Nihon Rinsho Meneki Gakkai Kaishi. 2017;40(2):124–130. doi: 10.2177/jsci.40.124.

[6] Brucato A, Cimaz R, Stramba-Badiale M. Neonatal lupus. Clin Rev Allergy Immunol. 2002;23(3):279–299. doi: 10.1385/CRIAI:23:3:279.

[7] Yang X. Clinical features, autoantibodies, and outcome of neonatal lupus erythematosus. Fetal Pediatr Pathol. 2022;41(3):436–442. doi: 10.1080/15513815.2020.1836097.

[8] Lee LA. Neonatal lupus: clinical features and management. Paediatr Drugs. 2004;6(2):71–78. doi: 10.2165/00148581-200406020-00001.

[9] Askanase AD, Izmirly PM, Katholi M, et al. Frequency of neuro-psychiatric dysfunction in anti-SSA/SSB exposed children with and without neonatal lupus. Lupus. 2010;19(3):300–306. doi: 10.1177/0961203309354542.

[10] Weston WL, Morelli JG, Lee LA. The clinical spectrum of anti-ro-positive cutaneous neonatal lupus erythematosus. J Am Acad Dermatol. 1999;40(5 Pt 1):675–681. doi: 10.1016/s0190-9622(99)70146-5.

[11] Barsalou J, Jaeggi E, Laskin CA, et al. Prenatal exposure to antimalarials decreases the risk of cardiac but not non-cardiac neonatal lupus: a single-centre cohort study. Rheumatology (Oxford). 2017;56(9):1552–1559. doi: 10.1093/rheumatology/kex191.

[12] Dorner T, Feist E, Chaoui R, et al. Enhanced frequency of autoimmune congenital heart block in female offspring. Rheumatology. 1999;38(4):380–382. doi: 10.1093/rheumatology/38.4.380.

[13] Sun W, Ding L, Li M, et al. Neurological and endocrinological involvement in neonatal lupus erythematosus: a retrospective study at a tertiary hospital in eastern China. Clin Rheumatol. 2023;42(9):2461–2468. doi: 10.1007/s10067-023-06622-8.

[14] Fu C, Sun W, Peng H, et al. Neonatal lupus erythematosus as a rare trigger of gastrointestinal involvement in neonates. Sci Rep. 2024;14(1):3791. doi: 10.1038/s41598-024-54091-z.

[15] Li YQ, Wang Q, Luo Y, et al. Neonatal lupus erythematosus: a review of 123 cases in China. Int J Rheum Dis. 2015;18(7):761–767. doi: 10.1111/1756-185X.12652.

[16] Brucato A, Frassi M, Franceschini F, et al. Risk of congenital complete heart block in newborns of mothers with anti-Ro/SSA antibodies detected by counterimmunoelectrophoresis: a prospective study of 100 women. Arthritis Rheum. 2001;44(8):1832–1835. doi: 10.1002/1529-0131(200108)44:8<1832::AID-ART320>3.0.CO;2-C.

[17] 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):3187–3194. doi: 10.1002/art.20554.

[18] 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(1):76–82. doi: 10.1161/CIRCULATIONAHA.111.089268.

[19] Levesque K, Morel N, Maltret A, et al. Description of 214 cases of autoimmune congenital heart block: results of the French neonatal lupus syndrome. Autoimmun Rev. 2015;14(12):1154–1160. doi: 10.1016/j.autrev.2015.08.005.

[20] Ho A, Gordon P, Rosenthal E, et al. Isolated complete heart block in the fetus. Am J Cardiol. 2015;116(1):142–147. doi: 10.1016/j.amjcard.2015.03.051.

[21] Miyagawa S. Neonatal lupus erythematosus: a review of the racial differences and similarities in clinical, serological and immunogenetic features of Japanese versus Caucasian patients. J Dermatol. 2005;32(7):514–522. doi: 10.1111/j.1346-8138.2005.tb00793.x.

[22] Erden A, Fanouriakis A, Kiliç L, et al. Geoepidemiology and clinical characteristics of neonatal lupus erythematosus: a systematic literature review of individual patients' data. Turk J Med Sci. 2020;50(1):281–290. doi: 10.3906/sag-1910-39.

[23] Jaeggi ET, Hornberger LK, Smallhorn JF, et al. Prenatal diagnosis of complete atrioventricular block associated with structural heart disease: combined experience of two tertiary care centers and review of the literature. Ultrasound Obstet Gynecol. 2005;26(1):16–21. doi: 10.1002/uog.1919.

[24] Brito-Zerón P, Izmirly PM, Ramos-Casals M, et al. The clinical spectrum of autoimmune congenital heart block. Nat Rev Rheumatol. 2015;11(5):301–312. doi: 10.1038/nrrheum.2015.29.

[25] Lozano NA, Lozano A, Marini V, et al. Expression of FcRN receptor in placental tissue and its relationship with IgG levels in term and preterm newborns. Am J Reprod Immunol. 2018;80(3):e12972. doi: 10.1111/aji.12972.

[26] Miranda-Carús M-E, Askanase AD, Clancy RM, et al. Anti-SSA/Ro and anti-SSB/La autoantibodies bind the surface of apoptotic fetal cardiocytes and promote secretion of TNF-alpha by macrophages. J Immunol. 2000;165(9):5345–5351. doi: 10.4049/jimmunol.165.9.5345.

[27] Pisetsky DS. Antinuclear antibody testing—misunderstood or misbegotten? Nat Rev Rheumatol. 2017;13(8):495–502. doi: 10.1038/nrrheum.2017.74.

[28] Marks SD, Tullus K. Autoantibodies in systemic lupus erythematosus. Pediatr Nephrol. 2012;27(10):1855–1868. doi: 10.1007/s00467-011-2078-4.

[29] Izmirly PM, Halushka MK, Rosenberg AZ, 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):980–983. doi: 10.1016/j.autrev.2017.07.013.

[30] Izmirly PM, Rivera TL, Buyon JP. Neonatal lupus syndromes. Rheum Dis Clin North Am. 2007;33(2):267–285, vi. doi: 10.1016/j.rdc.2007.02.005.

[31] Ambrosi A, Sonesson SE, Wahren-Herlenius M. Molecular mechanisms of congenital heart block. Exp Cell Res. 2014;325(1):2–9. doi: 10.1016/j.yexcr.2014.01.003.

[32] Izmirly P, Saxena A, Buyon JP. Progress in the pathogenesis and treatment of cardiac manifestations of neonatal lupus. Curr Opin Rheumatol. 2017;29(5):467–472. doi: 10.1097/BOR.0000000000000414.

[33] Gryka-Marton M, Szukiewicz D, Teliga-Czajkowska J, et al. An overview of neonatal lupus with anti-Ro characteristics. Int J Mol Sci. 2021;22(17):9281. doi: 10.3390/ijms22179281.

[34] Buyon JP, Masson M, Izmirly CG, et al. Prospective evaluation of high titer autoantibodies and fetal home monitoring in the detection of atrioventricular block among anti-SSA/Ro pregnancies. Arthritis Rheumatol. 2024;76(3):411–420. doi: 10.1002/art.42733.

[35] Jaeggi E, Kulasingam V, Chen J, et al. Maternal anti-Ro antibody titers obtained with commercially available immunoassays are strongly associated with immune-mediated fetal heart disease. Arthritis Rheumatol. 2023;75(9):1556–1565. doi: 10.1002/art.42513.

[36] Anuwutnavin S, Chuenchitkultavorn V, Nitiyarom R, et al. Prenatal predisposing factors associated with neonatal lupus erythematosus. Lupus. 2022;31(1):77–88. doi: 10.1177/09612033211066455.

[37] Meisgen S, Hedlund M, Ambrosi A, et al. Auxilin is a novel susceptibility gene for congenital heart block which directly impacts fetal heart function. Ann Rheum Dis. 2022;81(8):1151–1161. doi: 10.1136/annrheumdis-2021-221714.

[38] 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(24):2778–2784. doi: 10.1016/j.jacc.2010.02.042.

[39] Kaizer AM, Lindblade C, Clancy R, et al. Reducing the burden of surveillance in pregnant women with no history of fetal atrioventricular block using the negative predictive value of anti-Ro/SSA antibody titers. Am J Obstet Gynecol. 2022;227(5):761. doi: 10.1016/j.ajog.2022.05.071.

[40] Gleicher N, Elkayam U. Preventing congenital neonatal heart block in offspring of mothers with anti-SSA/Ro and SSB/La antibodies: a review of published literature and registered clinical trials. Autoimmun Rev. 2013;12(11):1039–1045. doi: 10.1016/j.autrev.2013.04.006.

[41] Ivanchenko M, Thorlacius GE, Hedlund M, et al. Natural killer cells and type II interferon in Ro/SSA and La/SSB autoantibody-exposed newborns at risk of congenital heart block. Ann Rheum Dis. 2021;80(2):194–202. doi: 10.1136/annrheumdis-2019-216786.

[42] Hedlund M, Thorlacius GE, Ivanchenko M, et al. Type I IFN system activation in newborns exposed to Ro/SSA and La/SSB autoantibodies in utero. RMD Open. 2020;6(1):e000989. doi: 10.1136/rmdopen-2019-000989.

[43] Suryawanshi H, Clancy R, Morozov P, et al. Cell atlas of the foetal human heart and implications for autoimmune-mediated congenital heart block. Cardiovasc Res. 2020;116(8):1446–1457. doi: 10.1093/cvr/cvz257.

[44] Strandberg L, Ambrosi A, Espinosa A, et al. Interferon-alpha induces up-regulation and nuclear translocation of the Ro52 autoantigen as detected by a panel of novel Ro52-specific monoclonal antibodies. J Clin Immunol. 2008;28(3):220–231. doi: 10.1007/s10875-007-9157-0.

[45] Parrens E, Chevalier JM, Rougier M, et al. Third degree atrio-ventricular block induced by interferon alpha. Report of a case. Arch Mal Coeur Vaiss. 1999;92(1):53–56.

[46] Rechciński T, Matusik D, Rudziński T, et al. Cardiotoxic properties of interferon: aggravation of atrio-ventricular block during treatment of chronic hepatitis c with peginterferon—a case report. Pol Arch Med Wewn. 2007;117(1-2):49–52. doi: 10.20452/pamw.75.

[47] Odashiro K, Hiramatsu S, Yanagi N, et al. Arrhythmogenic and inotropic effects of interferon investigated in perfused and in vivo rat hearts: influences of cardiac hypertrophy and isoproterenol. Circ J. 2002;66(12):1161–1167. doi: 10.1253/circj.66.1161.

[48] Misztal MC, Gold N, Cao J, et al. Genetics of neonatal lupus erythematosus risk and specific manifestations. J Rheumatol. 2024;52:52–57. doi: 10.3899/jrheum.2023-1036.

[49] Wisuthsarewong W, Soongswang J, Chantorn R. Neonatal lupus erythematosus: clinical character, investigation, and outcome. Pediatr Dermatol. 2011;28(2):115–121. doi: 10.1111/j.1525-1470.2011.01300.x.

[50] Neiman AR, Lee LA, Weston WL, et al. Cutaneous manifestations of neonatal lupus without heart block: characteristics of mothers and children enrolled in a national registry. J Pediatr. 2000;137(5):674–680. doi: 10.1067/mpd.2000.109108.

[51] Zuppa AA, Riccardi R, Frezza S, et al. Neonatal lupus: follow-up in infants with anti-SSA/Ro antibodies and review of the literature. Autoimmun Rev. 2017;16(4):427–432. doi: 10.1016/j.autrev.2017.02.010.

[52] Kobayashi R, Mii S, Nakano T, et al. Neonatal lupus erythematosus in Japan: a review of the literature. Autoimmun Rev. 2009;8(6):462–466. doi: 10.1016/j.autrev.2008.12.013.

[53] Zdraveska N, Kostovski A, Sofijanova A, et al. Neonatal lupus erythematosus—a rare syndrome of transient autoimmunity. Clin Case Rep. 2022;10(6):e6004. doi: 10.1002/ccr3.6004.

[54] Ma J, Li Z, Song H, et al. High-risk groups of neonatal lupus erythematosus in term infants: a birth cohort study. Eur J Pediatr. 2024;183(1):149–155. doi: 10.1007/s00431-023-05283-8.

[55] Kulkarni S, Adya KA, Janagond AB, et al. Coexistence of annular polycyclic, morpheaform and atrophic lesions in neonatal lupus erythematosus. BMJ Case Rep. 2022;15(10):e252434. doi: 10.1136/bcr-2022-252434.

[56] Baltaci M, Fritsch P. Histologic features of cutaneous lupus erythematosus. Autoimmun Rev. 2009;8(6):467–473. doi: 10.1016/j.autrev.2008.12.014.

[57] Fijalkowska A, Kadziela M, Zebrowska A. The spectrum of cutaneous manifestations in lupus erythematosus: a comprehensive review. J Clin Med. 2024;13(8):2419. doi: 10.3390/jcm13082419.

[58] Drohan A, Snyder A, Plante J, et al. Neonatal lupus erythematosus presenting as orolabial ulcerations: two cases and a review of the literature. Pediatr Dermatol. 2021;38(3):643–646. doi: 10.1111/pde.14555.

[59] Neel ML, Kern J, Ronis T. A 3-day-old girl referred from her pediatrician for oral ulcerations. Pediatrics. 2016;138(3):e20152043. doi: 10.1542/peds.2015-2043.

[60] Liszewska A, Wozniacka A. Neonatal lupus erythematosus—prevention is better than cure. Postep Dermatol Alergol. 2022;39(6):1021–1026. doi: 10.5114/ada.2022.122601.

[61] Walling HW, Sontheimer RD. Cutaneous lupus erythematosus: issues in diagnosis and treatment. Am J Clin Dermatol. 2009;10(6):365–381. doi: 10.2165/11310780-000000000-00000.

[62] Okon LG, Werth VP. Cutaneous lupus erythematosus: diagnosis and treatment. Best Pract Res Clin Rheumatol. 2013;27(3):391–404. doi: 10.1016/j.berh.2013.07.008.

[63] Sukumaran S, Singh D. Cutaneous neonatal lupus erythematosus: a case report. Cureus. 2022;14(2):e22279. doi: 10.7759/cureus.22279.

[64] Barsalou J, Costedoat-Chalumeau N, Berhanu A, et al. Effect of in utero hydroxychloroquine exposure on the development of cutaneous neonatal lupus erythematosus. Ann Rheum Dis. 2018;77(12):1742–1749. doi: 10.1136/annrheumdis-2018-213718.

[65] Levy R, Briggs L, Silverman E, et al. Cutaneous sequelae in neonatal lupus: a retrospective cohort study. J Am Acad Dermatol. 2020;83(2):440–446. doi: 10.1016/j.jaad.2019.09.083.

[66] Kleitsch J, Mazori DR, Derrick KM, et al. Periorbital hypopigmentation and telangiectasias: clues to diagnosing neonatal lupus in skin of color. Pediatr Dermatol. 2021;38 Suppl 2:135–136. doi: 10.1111/pde.14674.

[67] Guinovart RM, Vicente A, Rovira C, et al. Facial telangiectasia: an unusual manifestation of neonatal lupus erythematosus. Lupus. 2012;21(5):552–555. doi: 10.1177/0961203311430701.

[68] Hon KL, Leung AK. Neonatal lupus erythematosus. Autoimmune Dis. 2012;2012:301274. doi: 10.1155/2012/301274.

[69] Song JY, Park SE, Byun JH, et al. Neonatal lupus erythematosus as a rare cause of fever in young infants. J Clin Med. 2021;10(14):3195. doi: 10.3390/jcm10143195.

[70] Wang YA, Sibbald C, Moon AT. Retrospective, single-center case series of neonatal lupus. Pediatr Dermatol. 2020;37(3):484–489. doi: 10.1111/pde.14132.

[71] Vanoni F, Lava S, Fossali EF, et al. Neonatal systemic lupus erythematosus syndrome: a comprehensive review. Clin Rev Allergy Immunol. 2017;53(3):469–476. doi: 10.1007/s12016-017-8653-0.

[72] Wu Y, Sun X, Kang K, et al. Hemophagocytic lymphohistiocytosis: current treatment advances, emerging targeted therapy and underlying mechanisms. J Hematol Oncol. 2024;17(1):106. doi: 10.1186/s13045-024-01621-x.

[73] Wang P, Jiang W, Lai T, et al. Germline variants in acquired aplastic anemia: current knowledge and future perspectives. Haematologica. 2024;109(9):2778–2789. doi: 10.3324/haematol.2023.284312.

[74] Chew S, Kamangar M. Approach to pancytopenia: from blood tests to the bedside. Clin Med (Lond). 2024;24(5):100235. doi: 10.1016/j.clinme.2024.100235.

[75] Sheng X, Song X, Xiong Y, 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.

[76] Friedman DM, Rupel A, Buyon JP. Epidemiology, etiology, detection, and treatment of autoantibody-associated congenital heart block in neonatal lupus. Curr Rheumatol Rep. 2007;9(2):101–108. doi: 10.1007/s11926-007-0003-4.

[77] Gordon PA. Congenital heart block: clinical features and therapeutic approaches. Lupus. 2007;16(8):642–646. doi: 10.1177/0961203307079041.

[78] Martin TA. Congenital heart block: current thoughts on management, morphologic spectrum, and role of intervention. Cardiol Young. 2014;24 Suppl 2:41–46. doi: 10.1017/S1047951114001358.

[79] Jain S, Spadafora R, Maxwell S, et al. A case of neonatal lupus presenting with myocardial dysfunction in the absence of congenital heart block (CHB): clinical management and brief literature review of neonatal cardiac lupus. Pediatr Cardiol. 2023;44(3):736–739. doi: 10.1007/s00246-022-03056-y.

[80] Saxena A, Izmirly PM, Bomar RP, et al. Factors associated with long-term cardiac dysfunction in neonatal lupus. Ann Rheum Dis. 2020;79(2):217–224. doi: 10.1136/annrheumdis-2019-215900.

[81] Satoh M, Chan EK, Ho LA, et al. Prevalence and socio-demographic correlates of antinuclear antibodies in the united states. Arthritis Rheum. 2012;64(7):2319–2327. doi: 10.1002/art.34380.

[82] Guo YP, Wang CG, Liu X, et al. The prevalence of anti-nuclear antibodies in the general population of china: a cross-sectional study. Curr Ther Res Clin Exp. 2014;76:116–119. doi: 10.1016/j.curtheres.2014.06.004.

[83] Hayashi N, Koshiba M, Nishimura K, et al. Prevalence of disease-specific antinuclear antibodies in general population: estimates from annual physical examinations of residents of a small town over a 5-year period. Mod Rheumatol. 2008;18(2):153–160. doi: 10.1007/s10165-008-0028-1.

[84] Howley LW, Eyerly-Webb SA, Killen S, et al. Variation in prenatal surveillance and management of anti-SSA/Ro autoantibody positive pregnancies. J Matern Fetal Neonatal Med. 2024;37(1):2323623. doi: 10.1080/14767058.2024.2323623.

[85] Keeling SO, Alabdurubalnabi Z, Avina-Zubieta A, et al. Canadian rheumatology association recommendations for the assessment and monitoring of systemic lupus erythematosus. J Rheumatol. 2018;45(10):1426–1439. doi: 10.3899/jrheum.171459.

[86] Saxena A, Izmirly PM, Mendez B, et al. Prevention and treatment in utero of autoimmune-associated congenital heart block. Cardiol Rev. 2014;22(6):263–267. doi: 10.1097/CRD.0000000000000026.

[87] Klein-Gitelman MS. Neonatal lupus: what we have learned and current approaches to care. Curr Rheumatol Rep. 2016;18(9):60. doi: 10.1007/s11926-016-0610-z.

[88] Izmirly P, Kim M, Friedman DM, et al. Hydroxychloroquine to prevent recurrent congenital heart block in fetuses of anti-SSA/Ro-positive mothers. J Am Coll Cardiol. 2020;76(3):292–302. doi: 10.1016/j.jacc.2020.05.045.

[89] Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. Arthritis Care Res (Hoboken). 2020;72(4):461–488. doi: 10.1002/acr.24130.

[90] Mawad W, Hornberger L, Cuneo B, et al. Outcome of antibody-mediated fetal heart disease with standardized anti-inflammatory transplacental treatment. J Am Heart Assoc. 2022;11(3):e23000. doi: 10.1161/JAHA.121.023000.

[91] Izmirly PM, Saxena A, Sahl SK, et al. Assessment of flu-orinated steroids to avert progression and mortality in anti-SSA/Ro-associated cardiac injury limited to the fe-tal conduction system. Ann Rheum Dis. 2016;75(6):1161–1165. doi: 10.1136/annrheumdis-2015-208311.

[92] Tonello M, Ruffatti A, Marson P, et al. Plasma exchange effectively removes 52- and 60-kda anti-Ro/SSA and anti-La/SSB antibodies in pregnant women with con-genital heart block. Transfusion. 2015;55(7):1782–1786. doi: 10.1111/trf.13046.

[93] DE Caluwé EVA, VAN DE Bruaene A, Willems RIK, et al. Long-term follow-up of children with heart block born from mothers with systemic lupus erythematosus: a retrospective study from the database pediatric and congenital heart disease in University Hospitals Leuven. Pacing Clin Electrophysiol. 2016;39(9):935–943. doi: 10.1111/pace.12909.

[94] Moak JP, Barron KS, Hougen TJ, et al. Congenital heart block: development of late-onset cardiomyopathy, a previously underappreciated sequela. J Am Coll Cardiol. 2001;37(1):238–242. doi: 10.1016/s0735-1097(00)01048-2.

[95] Eliasson H, Sonesson SE, Salomonsson S, et al. Outcome in young patients with isolated complete atrioventricular block and permanent pacemaker treat-ment: a nationwide study of 127 patients. Heart Rhythm. 2015;12(11):2278–2284. doi: 10.1016/j.hrthm.2015.06.028.

[96] Brito-Zerón P, Izmirly PM, Ramos-Casals M, et al. Autoimmune congenital heart block: complex and un-usual situations. Lupus. 2016;25(2):116–128. doi: 10.1177/0961203315624024.

[97] Lee LA. Maternal autoantibodies and pregnancy–II: the neonatal lupus syndrome. Baillieres Clin Rheumatol. 1990;4(1):69–84. doi: 10.1016/s0950-3579(05)80244-4.

[98] Cimaz R, Spence DL, Hornberger L, et al. Incidence and spectrum of neonatal lupus erythematosus: a pro-spective study of infants born to mothers with anti-ro autoantibodies. J Pediatr. 2003;142(6):678–683. doi: 10.1067/mpd.2003.233.

[99] Morel N, Georgin-Lavialle S, Levesque K, et al. Neonatal lupus syndrome: literature review. Rev Med Interne. 2015;36(3):159–166. doi: 10.1016/j.revmed.2014.07.013.

[100] Diaz T, Dominguez D, Jaeggi E, et al. Ethnicity and neonatal lupus erythematosus manifestations risk in a large multiethnic cohort. J Rheumatol. 2021;48(9):1417–1421. doi: 10.3899/jrheum.201338.

[101] Boros CA, Spence D, Blaser S, et al. Hydrocephalus and macrocephaly: new manifestations of neonatal lupus erythematosus. Arthritis Rheum. 2007;57(2):261–266. doi: 10.1002/art.22543.

[102] Chen CC, Lin KL, Chen CL, et al. Central nervous sys-tem manifestations of neonatal lupus: a systematic review. Lupus. 2013;22(14):1484–1488. doi: 10.1177/0961203313509294.

[103] Sun W, Jin X, Li Y, et al. Neonatal lupus erythematosus presenting with effusions: a 13-year retrospective study. Clin Rheumatol. 2024;43(9):2927–2932. doi: 10.1007/s10067-024-07060-w.

[104] Elefante E, Bond M, Monti S, et al. One year in review 2018: systemic vasculitis. Clin Exp Rheumatol. 2018;36 Suppl 111(2):12–32.

[105] Zhang S, Yuan D, Tan G. Neurological involvement in primary systemic vasculitis. Front Neurol. 2019;10:430. doi: 10.3389/fneur.2019.00430.

[106] Brucato A, Astori MG, Cimaz R, et al. Normal neuropsy-chological development in children with congenital complete heart block who may or may not be ex-posed to high-dose dexamethasone in utero. Ann Rheum Dis. 2006;65(11):1422–1426. doi: 10.1136/ard.2005.049866.

[107] Munoz C, Isenberg DA. Review of major endocrine ab-normalities in patients with systemic lupus erythema-tosus. Clin Exp Rheumatol. 2019;37(5):791–796.

[108] Couture J, Bernatsky S, Scott S, et al. Brief report: risk of childhood rheumatic and nonrheumatic autoim-mune diseases in children born to women with sys-temic lupus erythematosus. Arthritis Rheumatol. 2018;70(11):1796–1800. doi: 10.1002/art.40570.

[109] Vinet E, Pineau CA, Clarke AE, et al. Increased risk of autism spectrum disorders in children born to women with systemic lupus erythematosus: results

from a large population-based cohort. Arthritis Rheumatol. 2015;67(12):3201–3208. doi: 10.1002/art.39320.

[110] Yousef YF, van Royen-Kerkhof A, Derksen R, et al. The development of offspring from mothers with systemic lupus erythematosus. A systematic review. Autoimmun Rev. 2017;16(7):701–711. doi: 10.1016/j.autrev.2017.05.005.

[111] Martin V, Lee LA, Askanase AD, et al. Long-term follow-up of children with neonatal lupus and their unaf-fected siblings. Arthritis Rheum. 2002;46(9):2377–2383. doi: 10.1002/art.10638.

[112] Wojcik S, Bernatsky S, Platt RW, et al. Risk of autism spectrum disorders in children born to mothers with rheumatoid arthritis: a systematic literature review. Arthritis Care Res (Hoboken). 2017;69(12):1926–1931. doi: 10.1002/acr.23235.

[113] Vinet E, Bernatsky S. Outcomes in children born to women with rheumatic diseases. Rheum Dis Clin North Am. 2017;43(2):263–273. doi: 10.1016/j.rdc.2016.12.006.