Prenat Cardio 2019
DOI: https://doi.org/10.5114/pcard.2019.91001
Received: 26.08.2019
Accepted: 8.11.2019

Prenatal Cardiology
www.termedia.pl/Journal/Prenatal_Cardiology

Review paper

Management in maternal autoantibody-mediated clinical foetal myocardial disease

Julia Murlewska[1,2], Krzysztof Preis[2,3], Maciej Słodki[1,2,4], Iwona Strzelecka[1,5], Elżbieta Smolewska[6], Maria Respondek-Liberska[1,5]

[1]Department of Prenatal Cardiology, Polish Mother's Memorial Hospital Research Centre, Lodz, Poland
[2]Board of the Polish Prenatal Cardiology Society, Poland
[3]Department of Obstetrics & Gynaecology, Medical University of Gdansk, Poland
[4]Institute of Health Sciences, The State School of Higher Professional Education in Plock, Poland
[5]Department for Foetal Malformations and Diagnoses & Prevention, Medical University of Lodz, Poland
[6]Department of Paediatric Rheumatology, Institute of Paediatrics, Medical University of Lodz, Poland

Abstract

Our group presents our reflections, based on the current literature, concerning the obstetric and rheumatologic management of the foetus identified with clinical myocardial disease mediated by maternal autoantibodies (MAb). The European League Against Rheumatism (EULAR) have recommended the use of hydroxychloroquine (HCQ) during asymptomatic lupus pregnancies since 2007. Foetal echocardiography is indicated if there is suspected foetal dysrhythmia or myocarditis, especially in the involvement of positive maternal anti-Ro/SSA or anti-La/SSB antibodies weekly from 16 weeks of gestation upwards. The obstetric management should be guided by the degree of cardiac failure on foetal echocardiography. Foetal therapy with steroids, intravenous immunoglobulin (IVIG), and plasmapheresis should be reasonably introduced in the lowest effective doses for the shortest duration of time. The aim of the management should be to reverse incomplete heart block and other MAb-mediated foetal myocardial disease, presumably induced due to ongoing inflammation. In irreversible cases the treatment should be stopped, due to its possible maternal side effects. Delivery of the affected newborn should be performed in a tertiary centre, and pacemaker implantation might be an option for neonates.

Key words: foetal echocardiography, congenital heart block, foetal lupus syndrome, foetal myocarditis, foetal cardiomyopathy.

Corresponding author:
Dr. Julia Murlewska
Department of Prenatal Cardiology
Polish Mother's Memorial Hospital Research Centre
Lodz, Poland
e-mail: juliamurlewska.jm@gmail.com

Introduction

Connective tissue disease (CTD) is associated with a strong female predisposition and is often presented before or during reproductive years. Specialised issues in pregnancy management should be delivered in this patient group, which includes rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), systemic sclerosis (SSc), primary Sjogren's syndrome (PSS), and inflammatory

Table 1. Autoimmune connective tissue diseases (CTD)

Rheumatoid arthritis (RA)
Systemic lupus erythematosus (SLE)
Antiphospholipid syndrome (APS)
Systemic sclerosis (SSc)
Primary Sjogren's syndrome (PSS)
Inflammatory myositis

Table 2. Maternal laboratory investigations in foetal cardiac manifestations due to CTD

Anti-Ro/SSA (52 or 60 kD)
Anti-La/SSB (48 kD)

Table 3. Foetal echocardiography cardiac abnormalities that may suggest MAb-affected myocardial disease

Foetal heart rate abnormality, particularly bradycardia
Prolonged PR interval
Incomplete heart block
Congenital heart block
Myocarditis
Endocardial fibroelastosis
Cardiomyopathy
Decreased ventricular contractility
Increased cardiac size
Tricuspid regurgitation
Pericardial effusion
Ascites or hydrops

myositis (Table 1). In women with CTD early assessment of risk of pregnancy complications is very important. Detailed counselling concerning risk factors of poor pregnancy outcome, including consideration of relative contraindications to pregnancy (proper contraception) and appropriate planning for pregnancy, is required [1–10].

The best time for pregnancy initiation is during an inactive or stable phase of the disease. For decades, women with SLE were advised against pregnancy. High rates of poor outcome and risk for disease flare and lack of evidence for safe treatment proposals were established in pregnancy with lupus. Indeed, women with SLE/APS, RA, SSc have especially high rates of pregnancy complications, including: hypertensive disorders, including preeclampsia, intrauterine growth restriction (IUGR), foetal distress, foetal demise, placental insufficiency, caesarean deliveries, prematurity, premature rapture of membranes, and hospital admissions [2–10].

Pregnancy resulting in neonatal lupus syndrome (NL) with foetal cardiac manifestations, which represents passively acquired transplacental transfer of maternal anti-Ro/SSA (52 or 60 kD) or La/SSB (48 kD) antibodies (Table 2), may be the earliest signs of the disease in asymptomatic women [11–17]. Congenital heart block (CHB) is the most serious form of NL, affecting 2% of newborns of anti-Ro/La-positive women with CTD. The risk of CHB is increased when associated with maternal hypothyroidism or vitamin D deficiency and is 10-fold higher in women who have had a previously MAb-affected child [18–21]. Cardiac NL could also be demonstrated as more diffuse myocardial disease manifested as endocardial fibroelastosis (EFE), papillary muscle fibrosis, valvular disease calcifications of the atrial septum, mononuclear pancarditis, and cardiomyopathy (CM) with or without CHB [22, 23].

In case of foetal CHB it is worth remembering that, although very rare, causes other than maternal CTD may lead to CHB, which may require pacemaker implantation for the newborn baby. Left isomerism coexists more often with CHB. Logistic regression analysis confirmed that CHB associated with congenital heart defect (CHD) was the only one independent predictor of foetal death ($p < 0.001$) [24–31].

Management in asymptomatic women with autoimmune connective tissue diseases in pregnancies with foetal cardiac involvement

Any foetal heart rate abnormality, particularly bradycardia, should pay special attention and determine an urgent referral to a tertiary foetal cardiology centre. The detection of an early conduction defect such as prolonged PR interval should be importantly considered [32].

Indicated foetal echocardiography should be applied not only in foetal dysrhythmia, but also if there is suspected any foetal myocardial disease. Foetal cardiac abnormalities that may suggest maternal CTD are presented in Table 3.

Foetal CHB may be the first presentation of asymptomatic seropositive CTD in up to 50% of women [32]. Lopes et al. reported that late seroconversion of anti-Ro/La antibodies (MAb) is also possible in neonatal CHB. At the time of diagnosis of foetal CHB pregnant women were seronegative, but anti-Ro/anti-La antibodies were detected later, from one to eight years after the delivery in some cases [31].

In the involvement of positive maternal anti-Ro/SSA or anti-La/SSB antibodies titres should be checked every four weeks, and foetal echo is indicated weekly from 16 weeks of gestation upwards [33]. The obstetric management should be guided by the degree of cardiac failure noted on the echocardiography. An in utero environment with low-resistance circulatory pathways is preferred, as long as possible, to afford minimal work to maintain cardiac output and for the maturation of the lungs and other organs [34]. Laboratory tests for Rubella virus, Parvovirus, Coxackie virus, and Adenovirus, Cytomegalovirus should be implicated in foetal myocarditis [35].

In the recent analyses, registries, and national reviews 94.4% of CHBs were detected prenatally, there were no cases found before 18 weeks of gestation, and 90% were diagnosed before 30 weeks, with a median detection of 23 weeks [36].

Guidelines for the obstetric and rheumatologic management of the foetus identified with CHB have not been established; conversely, they are rather experimental [34, 36]. There-

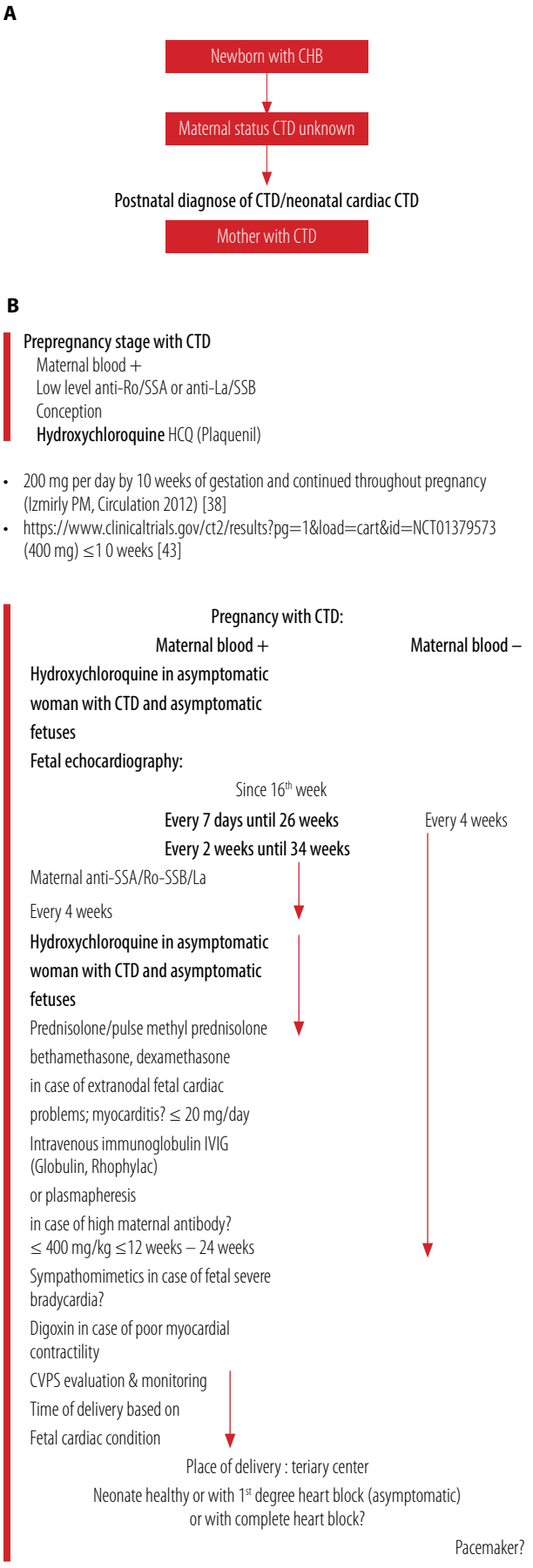

Figure 1. A – "Old way" of diagnosing maternal CTD. B – "New option" for women with CTD

Table 4. Foetal echocardiography parameters during monitoring in foetal cardiology centre

	ECHO 1	ECHO 2	ECHO X
Date of exam			
Gest age			
Foetal estimated weight			
Foetal heart rate			
Ventricular rate			
Atrial rate			
Increased echogenicity of the heart walls, valves			
Myocardial hypertrophy (M-mode SEP > 5 mm)			
Any signs of myocardial injury			
Hydrops, oedema, PE			
UMB A			
UMB vein			
HA/CA ratio			
LV SF			
RV SF			
Tricuspid V regur TR			
Mitral V regur MR			
CVPS			
Tei LV			
Tei RV			
TASPE			
MAPSE			
Atrioventricular conduction time PR interval (> 140–150 ms)			
SF shortening fraction < 28% = 2 SD below normal mean or qualitatively reduced systolic function			
Pharmacology treatment			

fore, our group decided to present our recommendations based on the current knowledge (Figure 1 and Table 4); however, it appears unlikely that appropriate treatment protocols to prevent CHB will be developed until the complicated pathophysiology of CHB is better understood and widely researched [20].

Hydroxychloroquine (HCQ) for CHB has been recommended by the European League Against Rheumatism EULAR during lupus pregnancies since 2007. HCQ has been shown to decrease the rate of neonatal cardiac involvement and reduce the risk of cardiac neonatal lupus in pregnant women who had foetal myocardial disease in a previous pregnancy [37–42] (Table 5).

There is only one registered non-randomised open-label study of hydroxychloroquine (Plaquenil) in the prevention of CHB, initiated in 2011 and still recruiting. Nineteen women

Table 5. Hydroxychloroquine (HCQ): Plaquenil (hydroxychloroquine sulphate) information

Dosage	• Lupus erythematosus: 200-400 mg daily, administered as a single daily dose or in two divided doses; doses above 400 mg a day are not recommended • The incidence of retinopathy has been reported to be higher when maintenance doses are exceeded • Corticosteroids may be used in conjunction with Plaquenil, and they can generally be decreased gradually in dosage
Side effects	• Cardiac disorders • Ear and labyrinth disorders • Eye disorders • Gastrointestinal disorders • General disorders and administration site conditions • Hepatobiliary disorders • Immune system disorders • Metabolism and nutrition disorders/musculoskeletal and connective tissue disorders • Nervous system disorders • Psychiatric disorders • Skin and subcutaneous tissue disorders • Use with caution in patients with gastrointestinal, neurological, or blood disorders, and in those with a sensitivity to quinine

meeting eligibility criteria: anti-Ro and/or anti-La Ab documented and with previous child with cardiac NL received 400 mg of Plaquenil per day, as soon as pregnancy was established. Mothers already on HCQ remained on 400 mg or were escalated to 400 mg if on 200 mg ≤10 weeks and might be followed with ≤ 20 mg of prednisone [43].

The study by Costedoat-Chalumeau et al. supported preliminary evidence for the safety of HCQ therapy during pregnancy. No visual, hearing, growth, or developmental abnormalities were reported in any of the children at the mean follow-up age of 26 months [44], although the potential effects of both retinal toxicity and ototoxicity have been reported in children [45–47].

From the evidence of foetal echocardiography, abnormalities such as : incomplete heart block, myocarditis, EFE, CM, decreased ventricular contractility, increased cardiac size, tricuspid regurgitation, pericardial effusion, ascites, or hydrops

Table 6. Steroids in prevention/treatment of foetal cardiac lupus

Prednisolone/pulse methyl prednisolone	• High doses can lead to higher maternal complications • Use lowest possible dose; pulse therapy can be used for acute flares
Fluorinated compounds: betamethasone, dexamethasone	• Some known association with impaired neuropsychological development of the child • Should be limited to one course for foetal lung maturation

Table 7. Side effects of steroids

Maternal side	Foetus side
• Infection • Osteoporosis • Osteonecrosis • Diabetes • Arterial hypertension	• Intrauterine growth restriction • Oligohydramnios • Adrenal suppression

therapy with steroids (dexamethasone, betamethasone, prednisolone, pulse methyl prednisolone) should be proposed. Steroids cross the placenta, and might be generally recommended in the lowest effective doses for the shortest duration of time, usually for several weeks (Table 6). Fluorinated steroids were effective at reversing incomplete heart block, presumably due to ongoing inflammation, but third-degree block with fibrosis of the conduction system is potentially irreversible. The maternal side effects of steroids are not trivial and may include infection, osteoporosis/osteonecrosis, diabetes, and arterial hypertension. Foetal risks include intrauterine growth restriction, oligohydramnios and adrenal suppression [33, 43, 48–57] (Tables 6, 7).

Many studies do not support the effectiveness of monotherapy with steroids (≤ 20 mg per day) for foetuses with CHB. Intravenous immunoglobulin (IVIG) (400 mg/kg IVIG) and plasmapheresis ≤ 12 weeks of pregnancy through 24 weeks could be considered as candidate agents to reverse the progression of incomplete CHB/myocarditis/CM in addition to FS and decrease higher titres of maternal anti-SSA/Ro-SSB/La antibodies ≥ 50 U/ml correlated with the increased foetal risk (Table 8). The contraindications of the use of IVIG are: prior serious reaction to use of IVIG infusion, known IgA deficiency, and intolerance of volume load, e.g. congestive heart failure, nephrotic syndrome [58–66].

Table 8. Intravenous immunoglobulin (IVIG) studies in cardiac NL prevention and treatment

IVIG to prevent cardiac NL in foetuses of anti-Ro positive mothers who had a previously affected child: prospective studies:	• 400 mg/kg every 3 weeks 12–24 weeks; cardiac NL developed in 15% American group and in 20% in European group (Friedman DM, Arthritis Rheum 2010 [58], Pisoni CN, Arthritis Rheum 2010 [65]) • 1 g/kg 14–18 weeks; 1 developed cardiac NL (Kaaja R, Arthritis Rheum 2003 [60])
IVIG in CHB + severe myocarditis	• 400 mg/kg/d, 5 days; resolution of echo signs of myocarditis/corresponding clinical improvement (Brucato A, Obstet Gynecol 2011 [66]) • 1 g/kg maternal IVIG/infant IVIG + corticosteroid therapy; 80% patients were alive at a median follow-up of 29 years, and none required cardiac transplantation/benefit of IVIG in foetal cardiomyopathy/EFE related to NL in combination with fluorinated steroids (Trucco SM, J Am Coll Cardiol 2011 [23])

The attempt to increase the foetal heart rate to treat CHB has been approached, but such a therapy with sympathomimetics does not restore coordination of AV conduction on which the heart is dependent for adequate filling [62].

Low-dose aspirin is recommended, particularly in SLE pregnancy with nephritis, or positive antiphospholipid antibodies (aPL) to limit preeclampsia risk factors. In women with SLE-associated APS or primary APS, combination treatment with aspirin and heparin is also recommended, to decrease the risk of adverse pregnancy outcomes [67, 68].

Supplementation with vitamin D (< 4000 IU/day) and folic acid should be offered. Measuring blood vitamin D levels should be considered after pregnancy is confirmed. Influenza vaccination should be repeated every year to limit the risk of flares in the pregnancy, and secondary protection should be offered to infants during the first months of life. Annual ophthalmologic examinations should be performed to rule out HCQ retinopathy [69–71].

The final decisions about the time and the mode of delivery in pregnancies with MAb-mediated foetal myocardial diseases should be managed with strict cooperation between the obstetrician, rheumatologist, and foetal cardiologist, based on the obstetric circumstances, maternal state of the disease, and haemodynamic foetal sufficiency. Achieving a term delivery is the priority issue because the continued therapy, even in a foetus with CHB, cardiovascular score ≤ 7, and hydrops might ensure a better prognosis for the full-term newborn's condition and for adequate pacemaker implantation. Anti-Ro/SSA or anti-La/SSB antibodies should be repeated after birth in the maternal serum and from the cord blood and in the newborn. Postnatal echocardiography and laboratory tests for Rubella virus, Parvovirus, Coxackie virus, Adenovirus, and Cytomegalovirus should be performed to exclude viral myocarditis, and targeted treatment must be coordinated [19, 30].

Conclusions

Foetal CHB may be the first presentation of asymptomatic CTD in up to 50% of women. All mothers of foetuses and infants with MAb-mediated myocardial disease should be echocardiographically screened. In the involvement of positive maternal anti-Ro/SSA or anti-La/SSB antibodies, foetal echo is indicated weekly from 16 weeks of gestation upwards. Polytherapy, rather than monotherapy with HCQ, steroids, IVIG, and plasmapheresis, to reverse the progression of the maternal autoantibody-mediated foetal cardiac disease, is recommended; however, appropriate treatment protocols cannot be developed because we are still waiting for the evidence-based results for their effectiveness. Similarly to the IVIG experience, HCQ data are inadequately small, and currently available evidence that these drugs reduce the risk of CHB appears insufficient. Our main goal, which is followed by contemporary progress in medicine and our knowledge is to prevent the occurrence of neonatal complete heart block and to diminish its consequences.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Cooper GS, Bynum MLK, Somers EC. Recent insights in the epidemiology of autoimmune diseases: improved prevalence estimates and understanding of clustering of diseases. J Autoimmun 2009; 33: 197-207.
2. Clowse MEB, Magder LS, Witter F, et al. Early risk factors for pregnancy loss in lupus. Obstet Gynecol 2006; 107: 293-299.
3. Clowse MEB, Jamison M, Myers E, James AH. A national study of the complications of lupus in pregnancy. Am J Obstet Gynecol 2008; 199: 127.
4. Nodler J, Moolamalla SR, Ledger EM, Nuwayhid BS, Mulla ZD. Elevated antiphospholipid antibody titers and adverse pregnancy outcomes: analysis of a population-based hospital dataset. BMC Pregnancy Childbirth 2009; 9: 11.
5. Chakravarty EF, Nelson L, Krishnan E. Obstetric hospitalizations in the United States for women with sysytemic lupus erythematosus and rheumatoid arthritis. Arthritis Rheum 2006; 54: 899-907.
6. Hughes GR. The antiphospholipid syndrome: ten years on. Lancet (London, England) 1993; 342: 341-344
7. Bharti B, Lee SJ, Lindsay SP, et al. Disease severity and pregnancy outcomes in women with rheumatoid arthritis: results from the ogranization of teratology information specialists autoimmune diseases in pregnancy project. J Rheumatol 2015; 42: 1376-1382.
8. Chakravarty EF, Khanna D, Chung L. Pregnancy outcomes in systemic sclerosis, primary pulmonary hypertension, and sickle cell disease. Obstet Gynecol 2008; 111: 927-934.
9. Knight CL, Nelson-Piercy C. Management of systemic lupus erythematosus during pregnancy: challenges and solutions. Open Access Rheumatol 2017; 9: 37-53.
10. Zmysłowska A, Smolewska E, Charubczyk A, Brózik H, Zielińska E. Toczeń rumieniowaty noworodków jako przykład biernej immunizacji płodu. Alergia Astma Immunologia 2001; 6: 164-168.
11. Shahne A, Patel R. The epidemiology of Sjogren's syndrome. Clin Epidemiol 2014; 6: 247-255.
12. Moak JP, Barron KS, Hougen TJ, Wiles HB, Balaji S, Sreeram N, et al. Congenital heart block: Development of late-onset cardiomyopathy, a previously underappreciated sequela. J Am Coll Cardiol 2001; 37: 238-342.
13. Nield LE, Silverman ED, Taylor GP, Smallhorn JF, Mullen JB, Silverman NH, et al. Maternal anti-Ro and antiLa antibody- associated endocardial fibroelastosis. Circulation 2002; 105: 843-848.
14. Jaeggi E, Laskin C, Hamilton R, Kingdom J, Silverman E. 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 Cardio 2010; 55: 2778-2784.
15. Both E. Neonatal lupus erythematosus. Clin Dermatol 2004; 22: 125-128
16. Brucato A, Frassi M, Franceschini F, Cimaz R, Faden D, Pisoni MP, 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: 1832-1835.
17. Lee L. The clinical spectrum of neonatal lupus. Arch Dermatol Res 2009; 301: 107-10
18. Spence D, Hornberger L, Hamilton R, Silverman ED. Increased risk of complete congenital heart block in infants born to women with hypothyroidism and anti-Ro and/or anti-La antibodies. J Rheumatol 2006; 33: 167-170.
19. Ambrosi A, Salomonsson S, Eliasson H, Zeffer E, Skog A, Dzikaite V, et al. Development of heart block in children of SSA/SSB-autoantibody-positive women is associated with maternal age and displays a season-of-birth pattern. Ann Rheum Dis 2012; 71: 334-340
20. Gleicher N, Elkayam U. Preventing congenital heart block in offspring of mothers with anti-SSA/Ro and SSB/La antibodies: a rewiew of published literature and registered clinical trials. Autoimmun Rev 2013; 12: 1039-1045.
21. Hassanaliilou T, Khalili L, Ghavanzadeh S, Shokri A, Poyahoo L, Bishak YK. Role of vitamin D deficiency in systemic lupus erythematosus incidence and aagravation. Auto Immun Highlights 2018; 9: 1.

22. Llanos C, Friedman DM, Saxena A, Izmirly PM, Tseng CE, Dische R. Anatomical and pathological findings in hearts from fetuses and infants with cardiac manifestations of neonatal lupus. Rheumatology (Oxford) 2012; 51: 1086-1092.
23. Trucco SM, Jaeggi E, Cuneo B, Moon-Grady AJ, Silverman E, Silverman N, Hornberger LK. Use of intravenous gamma globulin and corticosteroids in the treatment of maternal autoantibody-mediated cardiomyopathy. J Am Coll Cardiol 2011; 57: 715-723.
24. Respondek-Liberska M, Zarkowska A, Oszukowski P, Krasomski G, Wilczyński J, Gulczyńska E, et al. Perinatal management for complete heart block. Polski Przegląd Kardiologiczny 2007; 9: 423-427.
25. Respondek-Liberska M, Żarkowska A, Moll J, Sysa A. Neonatal follow-up of 45 fetuses with complete heart block (in Polish). Polski Przegląd Kardiologiczny 2008; 10: 207-211.
26. Respondek-Liberska M, Żarkowska A, Krekora M, Oszukowski P, Gulczyńska E, Moll J, et al. Fetal compaction cardiomyopathy and heart defect and complete heart block – report of two cases [in Polish]. Ultrasonography in Gyneclogy and Obststerics 2007; 3: 211-217.
27. Respondek M, Kalużyński A, Alwasiak J, Jaszewski P, Wilczyński J. Fetal endocarditis in left atrial isomerism – a case report. Ultrasound in Obstetrics and Gynecology 1993; 3: 45-47.
28. Michalak A, Witczak M, Kukawczyńska E, Niwald M, Respondek-Liberska M. Prenatally detected non-immune atrioventricular block and maternal arrhythmia – case presentation and literature review. Prenat Cardio 2016; 6: 90-95.
29. Suzin J, Respondek A, Respondek M, Bienkiewicz L, Armatys A. Wrodzony blok III stopnia rozpoznany prenatalnie. Polish Radiology Review/ Polski Przegląd Radiologiczny 1987; 1: 29-31.
30. Respondek M, Bratosiewicz J, Pertyński T, Liberski PP. Parvovirus particles in a fetal-heart with myocarditis: ultrastructural and immunohistochemical study. Arch Immunol Ther Exp (Warsz) 1997; 45: 465-470.
31. Lopes LM, Penha Tavares GM, Damiano AP, Borges Lopes MA, Aiello VD, Schultz R, et al. Perinatal outcome of fetal atrioventricular block. One-hundred-sixteen cases from a single institution. Circulation 2008; 118: 1268-1275.
32. 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: 1154-1160.
33. Izmirly PM, Saxena A, Sahl SK, Shah U, Friedman DM, Kim MY, et al. Assessment of fluorinated steroids to avert progression and mortality in anti-SSA/Ro-associated cardiac injury limited to the fetal conduction system. Ann Rheum Dis 2016; 75: 1161-1165.
34. Friedman D, Ducanson L, Glickstein J, Buyon J. A review of congenital heart block. Images Paediatr Cardiol 2003; 5: 36-48.
35. Donofrio MT, Moon-Grady AJ, Hornberger LK, Copel JA, Sklansky MS, Abuhamad A, 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 Anaesthesia, and Council on Cardiovascular and Stroke Nursing. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. Circulation 2014; 129: 2183-2242.
36. Brito-Zeron P, Izmirly PM, Ramos-Casals M, Buyon JP, Khamashta MA. The clinical spectrum of autoimmune congenital heart block. Nat Rev Rheumatol 2015; 11: 301-312.
37. Bertsias G, Ioannidis JP, Boletis J, Bombardieri S, Cervera R, Dostal C, et al. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. Ann Rheum Dis 2008; 67: 195-205
38. Izmirly PM, Costedoat-Chalumeau N, Pisoni CN, Khamashta MA, Kim MY, Saxena A, 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.
39. de Jesus GR, Mendoza-Pinto C, de Jesus NR, Dos Santos FC, Klumb EM, Carrasco MG, et al. Understanding and managing pregnancy in patients with lupus. Autoimmune Dis 2015; 2015: 943490.
40. Do SC, Druzin ML. Systemic lupus erythematosus in pregnancy: high risk, high reward. Curr Opin Obstet Gynecol 2019; 31: 120-126.
41. Tunks RD, Clowse MEB, Miller SG, Brancazio LR, Barker PCA. Maternal autoantibody levels in congenital heart block and potential prophylaxis with anti-inflammatory agents. Am J Obstet Gynecol 2013; 208: e1-e7.
42. Levy RA, Vilela VS, Cataldo MJ, Ramos RC, Duarte JL, Tura BR, et al. Hydroxychloroquine (HCQ) in lupus pregnancy: double-blind and placebo-controlled study. Lupus 2001; 10: 401-404
43. https://www.clinicaltrials.gov/ct2/results?pg=1&load=cart&id=NCT01379573
44. Costedoat-Chalumeau N, Amoura Z, Duhaut P, Huong DL, Sebbough D, Wechsler B, et al. Safety of hydroxychloroquine in pregnant patients with connective tissue diseases. Arthritis Rheum 2003; 48: 3207-3211.
45. Philips-Howard PA, Wood D. The safety of antimalarial drugs in pregnancy. Drug Sat 1996; 14: 131-45.
46. Roubenoff R, Hoyt J, Petri M, Hochberg MC, Hellmann DB. Effects of antinflammatory and immunosuppressive drugs on pregnancy and fertility. Semin Arthritis Rheum 1988; 18: 88-110.
47. Mata GJ, Naunton RF. Ototoxicity of chloroquine. Arch Otolaryngol 1968; 88: 370-372.
48. Buyon JP, Clancy RM. Maternal autoantibodies and congenital heart block: mediators, markers and therapeutic approach. Semin Arthritis Rheum 2003; 33: 140-154.
49. Buyon J, Hiebert R, Copel J, Craft J, Friedman D, Katholi M, et al. Autoimmune-associated congenital heart block: demographics, mortality, morbidity and recurrence rates obtained from a national neonatal lupus registry. J Am Coll Cardiol 1998; 31: 1658-1666.
50. Singh A, Chowdhary V. Pregnancy-related issues in women with systemic lupus erythematosus. Int J Rheum Dis 2015; 18: 172-181.
51. Friedman DM, Kim MY, Copel JA, Llanos C, Davis C, Buyon JP. Prospective evaluation of fetuses with autoimmune-associated congenital heart block followed in the PR Interval and Dexamethasone Evaluation (PRIDE) Study. Am J Cardiol 2009; 103: 1102-1106.
52. 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 multiracial/ethnic registry of anti-SSA/Po-associated cardiac neonatal lupus. Circulation 2011; 124: 1927-1935.
53. Benediktsson R, Calder AA, Edwards CR, Seckl JR. Placental 11 beta-hydroxysteroid dehydrogenase: a key regulator of fetal glucocorticoid exposure. Clin Endocrinol (Oxf) 1997; 46: 161-166.
54. Bramham K, Thomas M, Nelson-Piercy C, Khamashta M, Hunt BJ. First-trimester low-dose prednisolone in refractory antiphospholipid antibody-related pregnancy loss. Blood 2011; 117: 6948-6951.
55. Jaeggi ET, Fouron JC, Silverman ED, Ryan G, Smallhorn J, Hornberger LK. Transplacental fetal treatment improves the outcome of prenatally diagnosed complete atrioventricular block. Circulation 2004; 110: 1542-1548.
56. Theander E, Brucato A, Gudmundsson S, Salomonsson S, Wahren-Herlenius M, Manthorpe R. Primary Sjogren's syndrome-treatment of fetal incomplete atrioventricular block with dexamethasone. J Rheumatol 2001; 28: 373-376.
57. Rosenthal D, Druzin M, Chin C, Dubin A. A new therapeutic approach to the fetus with congenital complete heart block: preemptive, targeted therapy with dexamethasone. Obstet Gynecol 1998; 92: 689-691.
58. Friedman DM, Llanos C, Izmirly PM, Brock B, Byron J, Copel J, et al. Evaluation of fetuses in the preventive IVIG therapy for congenital heart block (PITCH) study. Arthritis Rheum 2010; 62: 1138-1146.
59. ClinicalTrials.gov: Identifier: NCT00460928. www.ClinicalTrials.gov.com [assessed: 14/07/2019]
60. Kaaja R, Julkuren H. Prevention of recurrence of congenital heart block with ontravenous immunoglobulin and corticosteroid therapy: comment

on the editorial by Buyon et al. Arthritis Rheum 2003; 48: 280-281. Author reply 281-2.
61. Routsias JG, Kyriakidis NC, Friedman DM, Llanos C, Clancy R, Moutsopoulos HM, et al. Association of the idiotypy: antidiotype antibody ratio with the efficiacy of intravenous immunoglobulin treatment for the prevention of recurrent autoimmune-associated congenital heart block. Arthitis Rheum 2011; 63: 2783-2789.
62. Lateef A, Petri M. Manging lupus during pregnancy. Best Pract Res Clin Rheumatol 2013; 27: 435-447.
63. Bramham K, Thomas M, Nelson-Piercy C, Khamashta M, Hunt BJ. First-trimester low-dose prednisolone in refractory antiphospholipid antibody-related pregnancy loss. Blood 2011; 117: 6948-6951.
64. Saleeb S, Copel J, Friedman D, Buyon JP. Comparison of treatment with fluorinated glucocorticoids to the natural history of autoantibody-associated congenital heart block: retrospective review of the Research Registry for Neonatal Lupus. Arthritis Rheum 1999; 42: 2335-2345.
65. Pisoni CN, Brucato A, Ruffatti A, Espinosa G, Cervera R, Belmonte-Serrano M. Failure of intravenous immunoglobulin to prevent congenital heart block. Findings of a multicenter, prespective, observational study. Arthritis Rheum 2010; 62: 1147-1152
66. Brucato A, Ramoni V, Gerosa M, Pisoni MP. Congenital fetal heart block: a potential therapeutic role for intravenous immunoglobulin. Obstet Gynecol 2011; 117: 177; author reply 177.
67. Andreoli L, Bertsias GK, Agmon-Levin N, Brown S, Cervera R, Costedoat-Chalumeau N, et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. Ann Rheum Dis 2017; 76: 476-485.
68. Mendel A, Bernatsky SB, Hanly JG, Urowitz MB, Clarke AE, Romero-Diaz J, et al. Low aspirin use and high prevalence of preeclampsia risk factors among pregnant women in a multinational SLE inception cohort. Annals of the Rheumatic Diseases 2019; 78: 1010-1012.
69. Thompson MG, Kwong JC, Regan AK, Katz MA, Drews SJ, Azziz-Baumgartner E, et al.; for the PREVENT Workgroup. Influenza vaccine effectiveness in preventing influenza-associated hospitalizations during pregnancy: a multi-country retrospective test negative design study, 2010-2016. Clin Infect Dis 2019; 68: 1444-1453.
70. https://www.lupus.org Help Us Solve The Cruel Mystery Lupus Foundation of America/ [access: 21.10.2019]
71. Marmor MF, Kellner U, Lai TYY, Melles RB, Mieler WF; for the American Academy of Opthalmology. Recommendations on Screening for Chloroquine and Hyrdoxychloroquine retinopathy (2016 Revision). American Academy of Opthalmology Statement. Opthalmology 2016; 123: 1386-1394.

Division of work:
Julia Murlewska (ORCID: 0000-0002-8266-4585): collection and/or assembly of data, data analysis and interpretation, writing the article
Krzysztof Preis (ORCID: 0000-0002-8097-3552): final approval
Maciej Słodki (ORCID: 0000-0002-0160-8013): critical revision, final approval
Iwona Strzelecka (ORCID: 0000-0003-3469-7064): critical revision, final approval
Elżbieta Smolewska (ORCID: 0000-0002-8421-0448): data analysis and interpretation, critical revision, final approval
Maria Respondek-Liberska (ORCID: 0000-0003-0238-2172): research concept and design, data analysis and interpretation, critical revision, final approval