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Review paper

Congenital heart block in fetuses of anti-SSA/SSB-positive mothers – treatment options, review 2021

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Abstract

Immune-mediated complete heart block (CHB) is one of the most common reasons of fetal bradycardia, burdened with high morbidity, fetal mortality rate up to 19%. Even 70% of survivors require pacemaker implantation after birth or in early childhood. The recurrence rate of CHB in a subsequent pregnancy reaches 19%. Rare incidence of disease in population, limited experience, lack of standard treatment protocols are main issues. This article is a clue to therapeutic indications and options, based on literature review covering years: 2000-2020.

Key words: fetal heart block, fetal therapy, immune-mediated heart block.

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Introduction

Among all cases of congenital heart block, third degree block occurs in 80% of cases; the other 20% are first and second degree blocks equally. In 50-55% of fetuses complete heart block (CHB) accompanies congenital heart defects (mainly left isomerism, corrected transposition of great arteries) because of structural abnormalities of the conductive system; not much can be done treatment wise because this kind of block will not respond to anti-inflammatory therapy.

Immune-mediated CHB with normal heart anatomy accounts for another 40% of cases, and in 5-10% the underlying cause remains unknown. In this paper we will focus only on autoimmune complete heart block, which is observed in approximately 2% of fetuses of anti-SSA/SSB-positive mothers. Up to one-third of women suffering from lupus erythematosus (LE), Sjogren's syndrome, undifferentiated connective tissue disease, previously asymptomatic, are diagnosed with fetal cardiac problems, which subsequently leads to diagnosis of maternal subclinical disease. The prevalence of 1 in 15-20,000 live births makes it a rare condition, small group of patients is the reason for mainly retrospective studies and difficulties in establishment of therapy consensus.

The recurrence rate for anti-SSA/SSB-positive mothers who previously had a CHB-affected child is as high as 19%. Pregnant women with high titres of SSA autoantibodies are considered at high risk [1]. CHB in pregnancies with low titres of anti-SSA or anti-SSB antibodies appear rarely.

A consequence of atrioventricular dissociation and the main diagnostic symptom is bradycardia, typically 50-70 bpm of ventricular escape rhythm, which presents most often around 16-29 weeks of gestation; however, autoantibodies can cross the placenta as early as at 11 weeks [2]. Inflammation and fibrosis of the atrioventricular (AV) node cause atrioventricular block (AVB) of various degrees; thus, thir de-

gree block is considered to be irreversible. The mortality rate reaches 19% (70% of deaths refer to the prenatal period) [3, 4]. Additional factors for bad prognosis are as follows: early diagnosis (< 20 weeks), hydrops fetalis, ventricular escape rhythm < 55 bpm, and poor left ventricular contractility [5]. Endocardial fibroelastosis (EFE), myocarditis, dilated cardiomyopathy, and valvar insufficiency may represent other manifestations of autoimmune disease.

Pregnancy surveillance

Screening for CHB in anti-SSA-positive pregnancy consists of weekly echocardiograms performed between 16 and 26 weeks of gestation. Measurement of atrioventricular intervals to determine first degree block may be done both by pulsed Doppler (PD) and tissue Doppler imaging (TDI), although cut-offs for these values depend on type and place of measurement as well as on gestational age [6]. Higher grades of block may be visualized both with M-mode and Doppler technique (Figure 1).

Studies show that AV prolongation measurement has little value for CHB prediction later in pregnancy [7]. Furthermore, complete heart block in majority of cases is not proceeded by first or second degree block and can develop rapidly (even within 24 hours) in anti-SSA-affected pregnancy.

This was confirmed in the PRIDE study by Friedman et al. in 2008 [8], which enrolled 127 anti-SSA-positive women, 95 of whom completed an evaluation based on weekly echocardiograms from 16 to 26 weeks of gestation and biweekly from 26 to 34 weeks. PR intervals were measured with a cut-off of 150 ms. The authors concluded that PR prolongation was rare and did not precede more advanced block, which may occur within one week of a normal echocardiogram.

Such potential for a rapid progression of lower degree block and/or de novo appearance of heart block creates a gap when even with the weekly monitoring mentioned above, emergent CHB still can be missed; this is important regarding treatment possibilities (see below) and imposes research on other diagnostic tools.

Fetal heart rate and rhythm monitoring (FHRM) is a self-evaluation method using a handheld Doppler, based on evaluation every 12 hours by pregnant women. If any abnormality in fetal heart rate is discovered, prompt detailed heart evaluation and therapy is offered. A prospective study by Cuneo et al. confirmed that FHRM can be used do catch atrioventricular block occurrence in a time frame allowing effective therapy. 87% of mothers who took part in the study completed the protocol. Three second or third degree blocks were discovered, and with therapy started in less than 12 hours second degree blocks were converted to sinus rhythm, and most importantly, no AVB was missed during the FHRM protocol [9, 10].

Prevention of CHB in subsequent pregnancies of anti-SSA-positive mothers

The risk of recurrence of CHB is about 19%. The role of macrophage toll-like receptors as factors contributing to immune-mediated CHB is currently emphasized. Therefore, a well-known medication acting as a toll-like receptor antagonist, hydroxychloroquine (HCQ), is tested for this purpose, with promising results so far. A multicentre, single-arm, 2-stage clinical trial by Izmirly et al. [11, 12] recruited anti-SSA-positive mothers who previously had a CHB-affected child (n = 19 stage 1, n = 35 stage 2), with HCQ implemented in early pregnancy (started before 10th week, 400 mg daily, maintained during pregnancy), which proved that HCQ can reduce the risk of block recurrence by over 50%.

The authors concluded that HCQ should be prescribed to prevent recurrence of CHB. (Preventive Approach to Congenital Heart Block with Hydroxychloroquine [PATCH]; NCT01379573). Hydroxychloroquine is well tolerated but po-

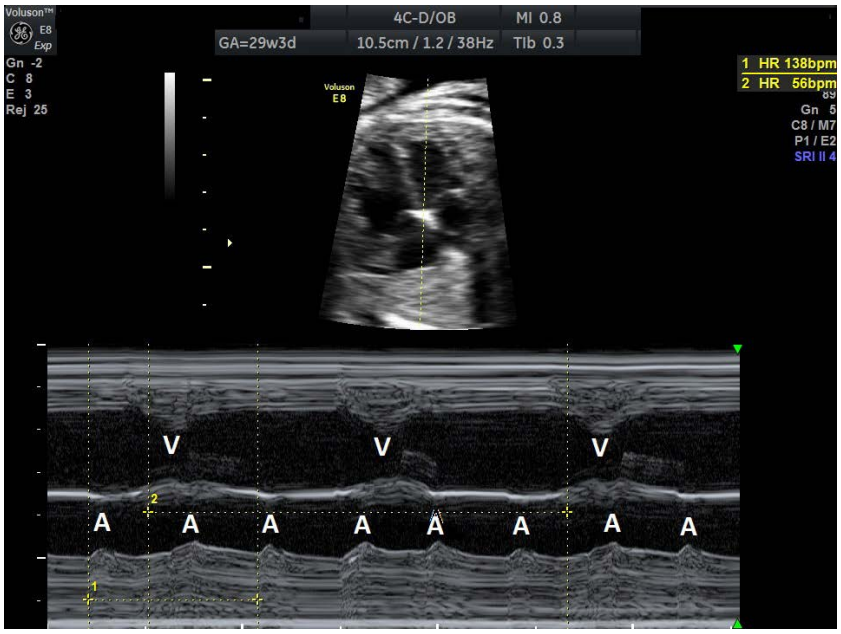

Figure 1. M-MODE tracing of fetal third degree AVB – atrial rate 138 pbm, ventricular rate 56 bpm

A – atrial contractions, V – ventricular contractions

Table 1. Complete heart block prophylaxis in anti-SSA/SSB-positive pregnancies

Method	Time of implementation	Purpose
Echocardiography	16-26 weeks of gestation, weekly assessment	• A-V time measurement (AVB I degree) • M-mode, Doppler (AVB II, III degree) • 2D echocardiography, colour Doppler (myocarditis, HF)
Fetal heart rate and rhythm monitoring (FHRM)	16-26 weeks of gestation, self-control every 12 hours	• decrease in FHR is followed by cardiology assessment and fast therapy if necessary
Pharmacotherapy – hydroxychloroquine (Plaquenil)	400 mg daily, started before 10th week of gestation, continued throughout pregnancy	• decrease of CHB recurrence rate

AVB – atrioventricular block, HF – heart failure, FHR – fetal heart rate, CHB – complete heart block.

tentially contributes to QT prolongation both in mother and in the fetus, especially when co-administered with other medications affecting QT interval (antihistamines etc.). ECG surveillance of the mother and magnetocardiography (not available in Poland) of the fetus play a role in QT-interval monitoring.

As mentioned above, considering the main role of anti-SSA/Ro antibodies in the pathogenesis of heart block [13-15], HCQ should be prescribed to pregnant women with high levels of anti-SSA. Low-titre anti-SSA- or anti-SSB-positive women qualify as a low-risk population, in whom therapy with HCQ requires further investigation and by now should be prescribed for other medical indications (e.g. active disease in the mother).

Preventive therapies in subsequent pregnancies of anti-SSA-positive mothers with immunoglobulins, plasmapheresis (to decrease serum autoantibody levels), and corticosteroids used in different combinations, presented over the years showed conflicting results [16, 17]. Adverse effects of these therapeutic strategies and lack of strong evidence for effectiveness do not support clinical recommendation. Table 1 presents summary of CHB prevention in anti-SSA affected pregnancy.

Beta-mimetics

Salbutamol (up to 3 × 10 mg daily) may be introduced when significant bradycardia (< 50-60 bpm) appears. The heart rate acceleration usually is not significant, we should rather say salbutamol prevents further reduction in ventricular rate, which allows prolongation of pregnancy. By increasing stroke volume, it prevents heart dysfunction as the fetal circulatory reserve is highly dependent on heart rate [18, 19]. However, no improvement in survival rates regarding this medication has been noted. Both before initiation and during treatment with salbutamol, levels of electrolytes and an ECG should be obtained.

Anti-inflammatory and immunomodulating therapy

Fluorinated steroids (oral dexamethasone 4-8 mg per day or betamethasone 3 mg per day) have the ability to cross the placenta, and their anti-inflammatory properties have undergone thorough investigation. Given the well-known side effects both to the mother (hypertension, diabetes) and the fetus (oligohydramnios, growth restriction) as well as divergent data regarding efficacy, especially when used alone, this treatment remains controversial. Meta-analyses suggest that steroids do not prevent AVB progression (all types of blocks analysed together), improve survival, or delay pacemaker implantation [20-24].

Intravenous immunoglobulins (IVIG) reduce the level of autoantibodies and increase the level of anti-inflammatory factors, often prescribed in combination with steroids. Although actual doses (and maximum doses) and duration of treatment are yet to be established, we know that IVIG crosses the placenta, especially in the third trimester, but no significant side effects to the fetus have been observed. Standard precautions when using IVIG in pregnant women (regarding volume overload, haemolysis, thromboembolic complication) should be applied.

An observational study by Cuneo et al. [25] points out that early detection (within 12 hours of AVB occurrence) and urgent treatment of second degree block with corticosteroids and/or IVIG (1 g/kg) may lead to regression or even reverse fetus back to a sinus rhythm. Moreover, in rare cases of acute third degree block, regression after combined therapy (IVIG + steroids) has been observed [26], but in general this type of block, because of irreversible fibrosis and calcification of the AV node, is considered permanent despite all treatment options [27].

Co-administration of steroids and IVIG (1 g/kg every 3 weeks) might be an option for immune-mediated cardiomyopathy/EFE [28], severe ventricular dysfunction, and hydrops fetalis, but the efficacy of this therapy is not proven [29].

Based on data published in recent years by prenatal centres, steroid therapy (±IVIG) in second degree heart block (regardless its duration) is used by most authors and so far cannot be disadvised despite the fact that not all cases will respond to the treatment and some cases will revert to sinus rhythm without medication [30-44]. Further investigation of this subject is necessary.

Tables 2 and 3 present the summary of the medications reported in fetal complete heart block.

Based on the data from Polish National Registry of Fetal Cardiac Anomalies in the years 2004-2017 (Figure 2), yearly we observed from one to 13 fetuses with complete heart block, in the majority with normal heart anatomy [45]. In our referral centre we have 1-4 such cases per year, and therefore, since 2007, we have developed also our institutional policy in perinatal care of fetuses with complete heart block and normal heart anatomy. This policy is very similar to the one presented above but with one major difference. In the case of fetal complete heart block, normal heart anatomy, normal fetal biometry, nor-

Table 2. Therapeutic options in fetal complete heart block and maternal positive serology for anti-SSA/SSB

Name of the medication	Goal of the treatment	References (name), year of publication
Steroids (dexamethasone, betamethasone)	anti-inflammatory	Michael, Use of antenatal fluorinated corticosteroids in management of congenital heart block: systematic review and meta-analysis 2019 [22] Ciardulli, Acta Obstet Genecol Scand 2018 [31] Donofrio, Circulation 2014 [32] Eliasson, Circulation 2011 [5] Friedman, Am J Cardiol 2009 [23] Fesslova, Cardiol Young 2009 [30]
Steroids + IVIG	anti-inflammatory, immunomodulating treatment: AVB II degree, emergent AVB III degree, hydrops fetalis, EFE, heart dysfunction	Cuneo, Am J Obstet Gynecol 2016 [25] Donofrio, Circulation 2014 [32] Trucco, J Am Coll Cardiol 2011 [28] Jaeggi, Clin Perinatol 2016 [18]
β-mimetics	increase in FHR	Jaeggi, Clin Perinatol 2016 [18] Donofrio, Circulation 2014 [32] Jaeggi, Circulation 2004 [19]

IVIG – intravenous immunoglobulins, AVB – atrioventricular block, EFE – endocardial fibroelastosis, FHR – fetal heart rate.

Table 3. Therapy options for immune-mediated complete heart block

Drug	Dosage	Indications	Expected effect	Side-effects
Dexamethasone Betamethasone	starting dose 4-8 mg daily, continuation 2-4 mg daily 3 mg daily	• first-degree block with signs of myocarditis (?) • second-degree block • emergent CHB • EFE • HF	prevention of progression to higher degree block, reversion of AVB	• hypertension • diabetes • osteoporosis • oligohydramnios • intrauterine grow restriction • adrenal insufficiency
IVIG	1 g per kg (max. dose?)	• second-degree block • emergent CHB • EFE • HF	prevention of progression to higher degree block, reversion of AVB	• volume overload • thromboembolic disorders • anaphylaxis • kidney failure
β-mimetics	max. dose 3 × 10 mg	• bradycardia < 55-60 bpm	prevention of further deceleration of FHR and HF	• tachycardia • hypokalaemia

IVIG – intravenous immunoglobulins, CHB – complete heart block, AVB – atrioventricular block, EFE – endocardial fibroelastosis, HF – heart failure, FHR – fetal heart rate.

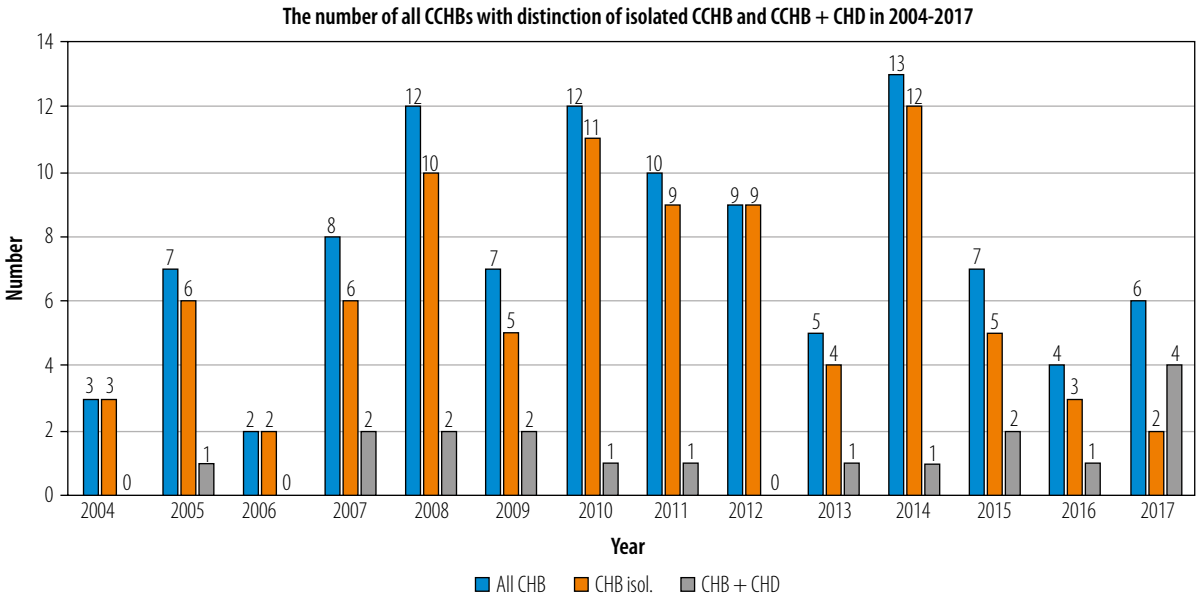

Figure 2. Number of fetuses diagnosed with complete heart block registered in the Polish database – orpkp.pl

Reprinted from: Kordjalik P. Analiza wybranych danych z Ogólnopolskiego Rejestru Patologii Kardiologicznych u Płodu z lat 2004–2017 [Selected data from the National Polish Registry of Fetal Cardiac Pathology]. Doctoral thesis. Polish Mother's Memorial Hospital Research Centre, Lodz 2018.

Table 4. Review of treatment recommendations for fetuses with immune-mediated complete heart block at the Department of Prenatal Cardiology

Year of recommendation	Prevention of recurrence of CHB in subsequent pregnancy	AVB I and II degree	AVB III degree	Severe bradycardia < 50-60 bpm	Cardiomyopathy, EFE, hydrops fetalis, heart failure
2007	steroids + IVIG	–	dexamethasone	salbutamol	digoxin
2019	HCQ IVIG plasmapheresis	steroids IVIG plasmapheresis	dexamethasone	salbutamol	steroids IVIG plasmapheresis
2021	HCQ	AVB I no treatment AVB II steroids + IVIG	–	salbutamol	steroids + IVIG digoxin

AVB – atrioventricular block, EFE – endocardial fibroelastosis, IVIG – intravenous immunoglobulins, HCQ – hydroxychloroquine

mal fetal placental thickness, and congestive heart failure (fetal heart cardiomegaly, tricuspid and mitral regurgitation, pericardial effusion, ascites, myocardial hypocontractility) we used also transplacental digoxin to prevent further deterioration and fetal demise. The treatment was carried out in hospital, with the first dose of digoxin at 0.5 mg and afterwards 0.25 mg every 8 hours administered intravenously for 3 days, followed by 0.25 mg every 8 hours orally until delivery/fetal demise. We had success in 2/3 of cases (there was one fetal demise at 32 weeks of gestation), and 2 live-born neonates; one of them required a pacemaker during the first week of postnatal life, and the other one was pacemaker free for 3 months. To observe any improvement in fetal echocardiography, usually 2-3 weeks of maternal transplacental treatment was required. The similar observations were reported by Eronen et al. in 2001 (from Helsinki) [46] and by Brackley et al. in 2000 (from Birmingham, UK) [47]. Also, such treatment in fetuses with complete heart block was recommended by two Japanese centres (Ishikawa et al. 1992 [48], Fukushige et al. 1998 [49]). Digoxin was used even in a twin pregnancy without any side effects (Czeszyńska et al. 1998 [50]).

Review of treatment recommendations for fetuses with immune-mediated complete heart block at the Department of Prenatal Cardiology is presented in Table 4.

Fetal pacing

To date, in utero pacing strategies have been unsuccessful because of the invasive techniques needed to deliver the systems and because of lead displacement issues. A study on a less invasive approach with micropacemaker device deployed in pericardial space is expected to start soon in Los Angeles [20] and hopefully will be an option for fetal hydrops and cases in which medication has failed. Similar devices are already successfully used in adults and on a smaller scale in paediatric patients.

The take-home messages are as follows:

- Hydroxychloroquine is used in the prevention of recurrence of CHB in anti-SSA-affected pregnancies and is effective when started before the 10th week of gestation.
- Treatment of first degree block is controversial because of rare progression to CHB and adverse effects of treatment.
- For second degree heart block, corticosteroids ±IVIG are recommended by most authors because of its progressive potential and documented cases of regression when treated early.
- Complete heart block is considered permanent. Due to irreversible fibrosis and calcification of the AV node there are no therapeutic options available. Only emergent CHB (within 12 hours of appearance), assuming inflammation as a potentially reversible state, may be an indication for treatment (steroids + IVIG).
- For EFE and severe heart dysfunction in the course of CHB, dexamethasone ±IVIG therapy may be offered.
- Severe fetal bradycardia (< 55-60 bpm) may be addressed with β-mimetics to maintain the ventricular rate within a safe range rather than increase it significantly, and to avoid heart failure.
- Delivery of a fetus with complete heart block should take place as late as possible (preferably after 37 weeks of gestation), in a tertiary centre, with paediatric cardiology and pacing facilities.

Conclusions

Fetal complete heart block, due to its high morbidity and mortality rate, remains a challenge. Treatment strategies vary among institutions and are strongly limited by the adverse effects of the medication used. Meticulous supervision of pregnancies at risk of AVB and with AVB is necessary, and management based on progression of the disease should be implemented.

Conflict of interest

The authors declare no conflict of interest.

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