Atrioventricular block during fetal life

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Lindsey E. Hunter [a], John M. Simpson [a],*

[a] Fetal Cardiology Unit, Department of Congenital Heart Disease, Evelina London Children's Hospital, London, UK

[a] Saudi Arabia

   Congenital complete atrioventricular (AV) block occurs in approximately 1 in 20,000 live births and is known to result in significant mortality and morbidity both during fetal life and postnatally. Complete AV block can occur as a result of an immune or a non-immune mediated process. Immune mediated AV block is a multifactorial disease, but is associated with the trans-placental passage of maternal autoantibodies (anti-Ro/SSA and/or anti-La/SSB). These autoantibodies attach to and subsequently damage the cardiomyocytes and conduction tissue in susceptible fetuses. In this report, we examine the evidence in reference to means of assessment, pathophysiology, and potential prenatal therapy of atrioventricular block.

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P.O. Box 2925 Riyadh – 11461KSA
Tel: +966 1 2520088 ext 40151
Fax: +966 1 2520718
Email: sha@sha.org.sa
URL: www.sha.org.sa

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Abbreviations

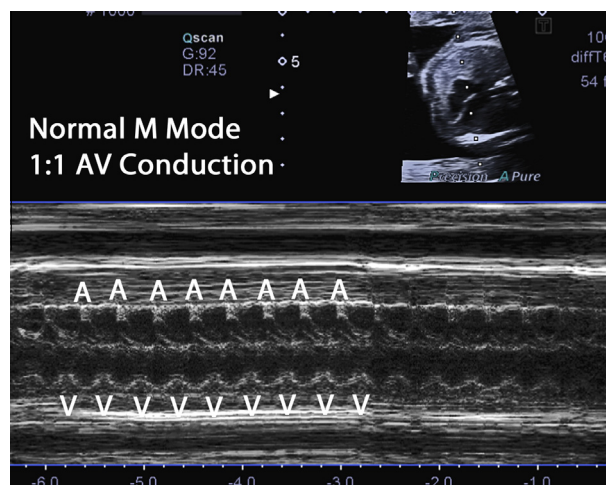|	
A	atrial
AA	ascending aorta
AV	atrioventricular
AVCTI	atrioventricular contraction time interval
CTD	connective tissue disease
ECG	electrocardiogram
EFE	endocardial fibroelastosis
IVC	inferior vena cava
IV	intravenous
LA	left atrium
LAI	left atrial isomerism
LV	left ventricle
LVOT	left ventricular outflow tract
MCG	magnetocardiography
MV	mitral valve
RA	right atrium
RPA	right pulmonary artery
SLE	systemic lupus erythematosis
SP	spine
SVC	superior vena cava
TV	tricuspid valve
V	ventricular
VSD	ventricular septal defect

Figure 1. Normal M mode. The cursor is aligned through the atrial and ventricular myocardium. This is a normal M mode recording demonstrating 1:1 AV conduction. AV, atrioventricular; A, atrial; V, ventricular.

Introduction

Congenital complete atrioventricular (AV) block is defined as the dissociation of atrial and ventricular contractions which occurs in approximately 1 in 20,000 live births [1–3]. This causes a significant drop in the ventricular rate which may cause fetal cardiac failure, including fetal hydrops. Complete AV block is associated with a risk of intrauterine or postnatal demise and the optimal prenatal therapy for affected fetuses has proven controversial. Congenital complete AV block may result from either an immune or non-immune mediated process. It can be associated with underlying structural heart disease or can develop in association with a multifactorial, autoimmune process, associated with the trans-placental transfer of maternal autoantibodies. These autoantibodies are directed against Ro/SSA and La/SSB antibodies expressed on the fetal cardiomyocytes of susceptible fetuses. Congenital complete AV block of either is associated with significant prenatal mortality and postnatal morbidity and thus remains an area of major clinical interest [1,4–8]. The aims of this report are to review atrioventricular block occurring during fetal life, with particular reference to means of assessment, causation and prenatal therapy.

Assessment of fetal atrioventricular block

Postnatally, the 12 lead electrocardiogram (ECG) recording is the gold standard for assessment and diagnosis of rhythm disturbance. During fetal life it is difficult to extract the fetal ECG because of the distance of the fetus to the maternal skin, possible insulating properties of vernix, and the small size of the fetus, all of which contribute to low voltages. Fetal movement, interference from the maternal heart rate and maternal muscular contraction further contribute to the difficulties in extracting a fetal ECG [9]. Despite these limitations, this method has been used to accurately record the fetal ECG. An alternative technique, fetal magnetocardiography (MCG) has been used to detect the magnetic fields caused by electrical signals in the fetal heart. This technique is used in a research setting and typically depends on a magnetically-shielded room to be feasible [10–12].

Thus, echocardiography remains the principal technique for assessing AV synchrony or arrhythmias in the fetus. Mechanical assessment by M mode infers electrical activity by demonstrating sequential contraction of the atrial and ventricular myocardium by aligning the cursor simultaneously through both myocardial walls [13] (Fig. 1). The M mode technique can be used to confirm normal sinus rhythm, tachycardia and fetal bradycardia, including complete AV block [14] (Fig. 2). Tissue Doppler and pulsed Doppler techniques are also widely employed [15–17].
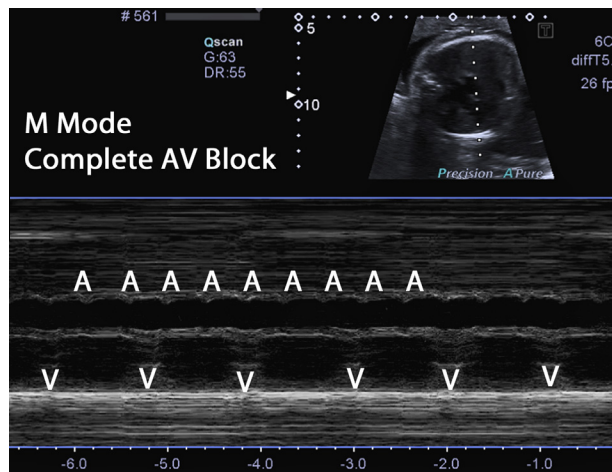
Figure 2. M mode – complete AV Block. This M mode recording demonstrates a slow ventricular rate and complete dissociation between atrial and ventricular contractions (CAVB). CAVB, complete atrioventricular block; A, atrial; V, ventricular.

Complete AV block can be easily detected using conventional M mode tracing, but measuring and determining the presence of lower grade AV block is challenging and Doppler methods are routinely incorporated to make this assessment. It should be noted that echocardiographic techniques cannot be used to measure time intervals such as the QT interval, which can be evaluated by magnetocardiography [12,18].

In an effort to detect lower grade AV block, attention has focused on the measurement of the mechanical PR interval by Doppler techniques, including pulsed wave (PW) Doppler or tissue Doppler. This is of particular interest in fetuses at an increased risk of developing heart block.
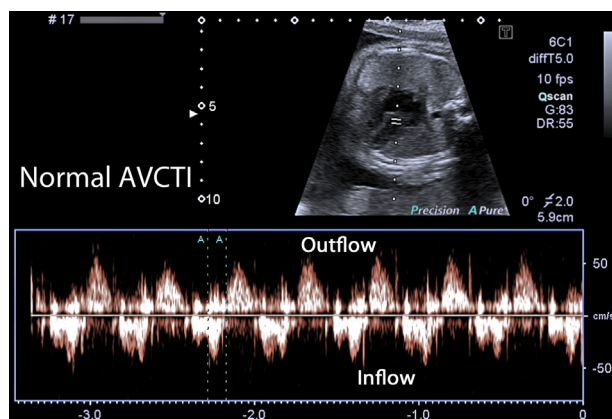

Figure 3. Normal AVCTI. The AVCTI is a reflection of the postnatal electrocardiographic PR interval. The cursor is aligned simultaneously through the mitral inflow and left ventricular outflow. The Doppler time interval between the onset of the A wave (atrial systole) and the onset of the ejection outflow Doppler (ventricular systole) is measured (ms). AVCTI, atrioventricular contraction time interval.

The time between atrial and ventricular systole is known as the atrioventricular contraction time interval (AVCTI) and is a mechanical representation of the traditional postnatal electrical PR interval (Fig. 3). Within the same cardiac cycle, the AVCTI is obtained by aligning the gated PW Doppler cursor simultaneously across an inflow and outflow, for example, left ventricular outflow tract (LVOT) and mitral valve. The Doppler time interval is measured between the onset of the A wave (atrial systole) and the onset of the ejection outflow Doppler (ventricular systole). Alternative methods involve aligning the Doppler cursor through a pulmonary vein and right pulmonary artery (RPA) or ascending aorta (AA) and superior vena cava (SVC), and measuring the time interval from the onset of the retrograde venous A wave to the onset of the outflow Doppler [11,19]. Although useful, AV time intervals are derived from flow and, as such, the accuracy of the measurements are influenced by myocardial intrinsic properties, ventricular loading conditions, fetal heart rate and the speed of pulse wave propagation [16]. Normative fetal mechanical PR interval reference ranges have been published. In addition, AVCTI values have been shown to be increasingly related to gestational age, and specifically, MV/LVOT time intervals are influenced independently by the fetal heart rate [16,20–23]. The various methods of assessing the AVCTI prenatally have been compared to the postnatal electrical PR interval. A study by Bergman et al. found the most accurate measurement when compared to the postnatal ECG was the AA/SVC technique [24]. Although AVCTIs are influenced by intrinsic myocardial properties, studies have confirmed that in the hands of experienced fetal echocardiographers there is minimal inter-operator variability [22]. It has been hypothesized that measuring the fetal mechanical PR interval by this method may allow for surveillance and early recognition of fetuses with lower degrees of AV block, and possible progression to complete AV block. However, this remains controversial [25].

Complete atrioventricular block associated with structural heart disease

Certain structural heart defects are known to predispose to the development of prenatal congenital complete AV block. The most frequent cardiac lesions associated with complete AV block are isomerism of the left atrial appendages (LAI) and discordant atrioventricular connections (Figs. 4 and 5). A retrospective study of 116 fetuses
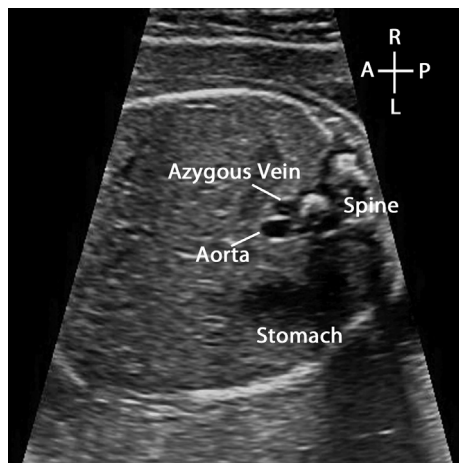
Figure 4. Left atrial isomerism – situs. This fetal echocardiographic image demonstrates cardiac situs in the presence of LAI. The spine lies posteriorly with one rib surrounding the fetal thorax. The stomach lies to the left. The aorta lies anteriorly and to the same side of the spine as the azygous vein. There is azygous continuation due to interruption of the IVC. LAI, left atrial isomerism; IVC, inferior vena cava.
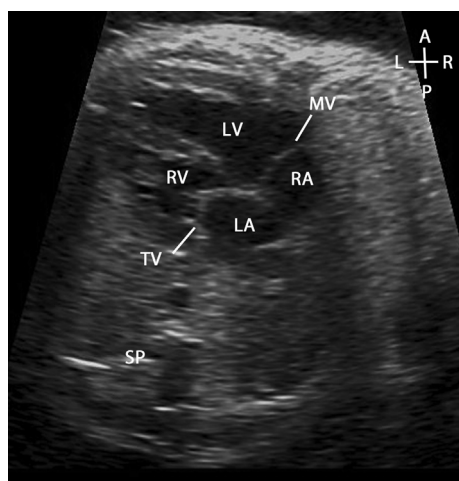

Figure 5. AV discordance. This demonstrates a traditional four chamber echocardiographic view of the fetal heart. There is reversal of normal AV valve offsetting, indicating AV discordance. AV, atrioventricular; VA ventriculoarterial.

diagnosed with complete AV block, detected an associated congenital structural heart defect in over 50%. Of these affected fetuses, greater than 60% were associated with LAI [26].

LAI is a multisystem disorder of visceral laterality, characterized by the presence of morphological, bilateral left atrial appendages. A spectrum of cardiac abnormalities can occur in association with LAI, for example, isolated interruption of the inferior vena cava (IVC) with azygous continuation to the SVC, defects of the atrioventricular junction and outflow tract abnormalities. Systemic manifestations may include abnormal pulmonary lobar morphology with bilateral left bronchial anatomy, abnormally positioned abdominal viscera including malrotation of the bowel, biliary atresia and polysplenia or, rarely, asplenia which may result in altered or suboptimal immune function. In normal cardiac situs, the sinus node is a morphologically right atrial structure. Thus, in a diagnosis of LAI, the sinus node by definition is abnormally positioned, hypoplastic or absent, often resulting in a sinus bradycardia or complete AV block. The combination of LAI and complete AV block prenatally has a very poor prognosis, particularly in the presence of fetal hydrops, with mortality rates by term reported as high as 100% [26]. This is a condition with very few therapeutic options and the prognosis does not seem to be improving with advances in fetal cardiology [4,6,8,27].

A diagnosis of discordant atrioventricular (AV) connections may be made during routine fetal echocardiography. The four chamber view of the heart is assessed in a cross sectional view through the fetal thorax. This traditional four chamber view demonstrates reversal of the normal pattern of offsetting of the atrioventricular valves (Fig. 5). Discordant AV connections can occur in isolation or with associated intra-cardiac defects, for example, ventricular septal defects (VSDs), and outflow tract obstruction. Morphologically, the atrial and inlet portion of the ventricular septum are maligned, disrupting the normal conduction axis, potentially leading to progressive AV block and subsequent complete AV block, pre or postnatally [28].

In addition to LAI and discordant AV connections, complete AV block can occur in association with more common structural heart defects, including tetralogy of Fallot, right ventricular hypoplasia, double inlet left ventricle, VSD, coarctation with VSD, and multiple rhabdomyomas [26].

Complete atrioventricular block with normal cardiac connections

In contrast to complete AV block associated with structural heart disease, immune mediated complete AV block most commonly occurs with a structurally normal heart. Functional abnormalities may coexist, including cardiomegaly, ventricular hypertrophy, impaired ventricular function, and atrioventricular valve regurgitation which can contribute to pericardial effusions and, in severe cases, fetal hydrops. Immune mediated

Table 1. Complete atrioventricular block.

Authors	Study design	Inclusion criteria	AV block	Treatment	Prenatal outcome	Postnatal outcome
Copel et al. [45]	Prospective	Antibody +ve $n = 5$	CAVB $n = 4$ Intermittent CAVB and second degree AV block $n = 1$	Dexamethasone $n = 4$ Dexamethasone $n = 1$	– –	CAVB $n = 4$ CAVB at term, reverted to second degree AV Block postnatally $n = 1$
Yamada et al. [51]	Prospective	Antibody +ve $n = 2$	CAVB $n = 1$	Prednisolone and Dexamethasone	–	CAVB $n = 1$
Friedman et al. [38] 'PRIDE'	Prospective, multicenter, observational	Antibody +ve $n = 98$ (pre study maternal steroids excluded)	CAVB $n = 1$ CAVB $n = 1$ CAVB $n = 1$	Dexamethasone Dexamethasone Dexamethasone	Fetal hydrops – TOP CAVB Fetal Hydrops – TOP	– CAVB Paced –
Jaeggi et al. [39] UOG	Case Study	Antibody +ve $n = 1$	CAVB at 21 weeks gestation	Dexamethasone	22 weeks second degree AV block 24 weeks First degree AV block 32 weeks CAVB and EFE	CAVB not paced
Jaeggi et al. [39] Circ	Retrospective	Antibody +ve $n = 33$	CAVB $n = 33$	Dexamethasone $n = 12$ Dexamethasone/β Stimulation $n = 8$ β Stimulation $n = 1$ Dexamethasone/IVIG $n = 1$	IUD $n = 1$ TOP/IUD $n = 2$ – –	CAVB $n = 11$ CAVB $n = 5$ IFD $n = 1$ CAVB/NND $n = 1$ CAVB $n = 1$
Jaeggi et al. [39] Circ	Retrospective	Antibody −ve $n = 4$	CAVB $n = 4$	No therapy $n = 2$ Dexamethasone/β Stimulation $n = 2$	– –	NND $n = 1$ CAVB $n = 1$ (paced) CAVB $n = 2$ (paced)
Sonesson et al. [40]	Prospective	Antibody +ve $n = 24$	CAVB $n = 1$ (preceded by first degree AV block)	Betamethasone $n = 1$	–	CAVB $n = 1$
Lopes et al. [26]	Retrospective	Antibody +ve $n = 42$ Antibody −ve $n = 15$	CAVB $n = 35$ CAVB (preceded by second degree AV block) $n = 9$	Dexamethasone ± β Stimulation $n = 4$ unspecified cases	IUD $n = 5$	Alive $n = 52$
Fesslova et al. [42]	Multicenter, retrospective	Antibody +ve $n = 28$	CAVB $n = 28$	Dexamethasone $n = 18$ Dexamethasone + β Stimulation $n = 2$ Isoproterenol $n = 1$ No therapy $n = 7$	IUD $n = 1$ – – IUD $n = 1$	CAVB $n = 17$ CAVB $n = 1$ NND $n = 1$ NND $n = 1$ CAVB $n = 6$
Eliasson et al. [47]	Multicenter, multinational, retrospective	$n = 175$ (80% Ro/La antibody +ve)	CAVB $n = 146$ CAVB (preceding second degree AV block) $n = 14$	Dexamethasone/ Betamethasone $n = 54$ No therapy $n = 92$ Dexamethasone/ Betamethasone $n = 6$ No therapy $n = 8$	TOP $n = 1$ IUD $n = 6$ (therapy) IUD $n = 9$ (no therapy) – –	NND $n = 3$ (therapy) $n = 7$ (no therapy) Alive at 1 month $n = 53$ (therapy) $n = 85$ (no therapy) 11 lost to f/u

Table 1. (*continued*)

Authors	Study design	Inclusion criteria	AV block	Treatment	Prenatal outcome	Postnatal outcome
Izmirly et al. [52]	Case controlled study	Antibody +ve $n = 201$ cardiac manifestations $n = 50$	Second degree AV block/ CAVB $n = 43$ (out of 50 with cardiac manifestations)	Dexamethasone/ betamethasone $n = 48$ of 50 hydroxychloroquine $n = 7$ of 50	–	No outcomes documented
Tunks et al. [55]	Retrospective	Antibody +ve $n = 33$	CAVB $n = 4$ (HCQ prophylaxis $n = 0$)	Dexamethasone $n = 4$	CAVB $n = 3$ CAVB preceded by 1st AV block $n = 1$	CAVB $n = 4$ (Paced $n = 3$)
Kaaja and Julkunen [57]	Prospective	Antibody +ve $n = 8$	CAVB $n = 1$ Sinus rhythm $n = 7$	IVIG IVIG/Steroids	– –	CAVB $n = 1$ Sinus rhythm $n = 7$
Pisoni et al. [58]	Multicenter, prospective, observational	Antibody +ve $n = 24$	Sinus rhythm $n = 24$	IVIG/Hydrocortisone prophylaxis $n = 15$ No prophylaxis $n = 9$	CAVB $n = 3$ (TOP $n = 2$) CAVB $n = 1$ (TOP)	Alive $n = 12$ CAVB $n = 1$ Alive $n = 8$
Friedman et al. [29]	Multicenter, prospective, open-label clinical trial	Antibody +ve $n = 20$	Sinus rhythm $n = 20$	IVIG prophylaxis $n = 20$	CAVB $n = 3$ ($n = 1$ preceded by 2nd AV block) Sinus rhythm $n = 17$	CAVB $n = 3$ (despite additional dexamethasone) Sinus rhythm $n = 17$
Jaeggi et al. [3]	Prospective	Antibody +ve $n = 40$	CAVB $n = 35$ (sinus rhythm $n = 3$)	Steroids ± Salbutamol ± IVIG $n = 25$ No therapy $n = 4$ Not documented $n = 6$	IUD $n = 1$ TOP $n = 2$ IUD $n = 1$ –	IFD $n = 2$, Alive $n = 22$ Alive $n = 1$ Alive $n = 6$

AV, atrioventricular; CAVB, complete; AV, block; TOP, termination of pregnancy; EFE, endocardial fibroelastosis; IUD, intrauterine demise; IFD, infant death; NND, neonatal death; f/u, follow up; IVIG, intravenous immunoglobulin.

congenital complete AV block is a passively acquired, autoimmune disease associated with the trans-placental passage of maternal autoantibodies to the developing fetus. In susceptible fetuses, the autoantibodies attach to the ribonucleotide proteins (antibodies) which are expressed on cardiomyocytes of the fetal myocardium, in particular: 52 kD Ro/SSA (Ro52); 60 kD Ro/SSA (Ro60) and 48 kD La/SSB (La48). This immune process results in inflammation of the fetal conduction tissue and myocardium with resultant progressive and irreversible fibrosis. In severe cases that result in intrauterine demise, post-mortem assessment has identified necrosis, fibrosis, and calcification of the fetal myocardium and conduction tissue [29]. Long QT syndrome may result in complete AV block within a structurally normal heart. The QT interval may be so prolonged that atrial depolarisation occurs during the refractory period of the ventricle so that the atrial impulse does not result in ventricular contraction. In this clinical situation parental ECGs may be helpful. In contrast to the PR interval, the QT interval cannot be measured by fetal echocardiography, but can be assessed by fetal MCG [12,18,30].

Anti-Ro/SSA and La/SSB antibodies are commonly associated with maternal connective tissue disease, but have been detected in the asymptomatic, general population. Within the population of women seropositive for anti-Ro/SSA or anti-La/SSB antibodies, it is estimated that only 2–3% of offspring will develop congenital AV block or abnormalities of the myocardium [9]. However, if a previous child has been affected the recurrence risk in subsequent pregnancies increases to 17–20% [1,31,32]. Thus, it can be hypothesized that the presence of autoantibodies may be associated with the disease process but is not the solitary causative factor resulting in irreversible damage to the fetal heart. There are as yet unrecognized factors which may contribute to the pathogenesis of immune mediated complete AV block, and

these may be genetic, maternal, fetal or external environmental factors. This hypothesis is corroborated by a study in which 85% of mothers with children with congenital complete AV block were asymptomatic for connective tissue disease prior to conception. In addition, 98% of the women in whom fetal complete AV block was detected had a previously healthy child with no evidence of a conduction disorder [3]. There are reports of delayed seroconversion in previously asymptomatic women several years after delivering a child affected by congenital complete AV block [26]. This highlights the importance of appropriate counselling of all women in whom a fetus is affected by complete AV block, including referral for assessment by specialists in connective tissue disease.

Treatment of complete AV block

Although complex, the pathophysiology of immune mediated congenital complete AV block involves an immune mediated inflammatory process which damages the conduction tissue and myocardium of the developing heart. In order to directly target and potentially halt this destructive process, anti-inflammatory medications and immune modulators have been utilized. Many studies are anecdotal, retrospective with small study numbers, and vary with respect to whether the aim is prevention of AV block in the fetus or treatment of the fetus who has developed signs of complete or lesser degrees of AV block. The most common therapies include maternal steroids, β stimulation with salbutamol, IV immunoglobulin and hydroxychloroquine. Other less common maternal therapies include: B cell depletion therapy [33], azathioprine [34], cyclophosphamide [35], and plasmapheresis [36,37], Treatment may be subdivided according to the degree of AV block, and may be classed as prophylactic or therapeutic.

Complete atrioventricular block

There is no robust evidence to suggest all cases of complete AV block are preceded by lower degrees of AV block. In the presence of lower degrees of AV block, progression to complete AV block can occur rapidly over a short period of time, often within days [25,38–40]. Once this immune reaction has occurred, complete AV block has not been reported to shown signs of reversibility or evidence of spontaneous reversion to sinus rhythm despite maternal medical therapy [38,41–43]. Prednisolone, betamethasone and dexamethasone have been used as therapy in many women with a positive antibody status. Dexamethasone, a fluorinated steroid, may act by reducing the maternal autoantibody load, but does not directly act to protect the fetal myocardium and conduction tissue from the destructive action of the autoantibodies [44]. However, maternal steroids have been associated with resolution of fetal hydrops when associated with complete AV block, which may be related to an acute inflammatory process resulting in a myocarditis [42,45]. Table 1 summarizes studies of the treatment and outcome of prenatally detected complete AV block.

The indications for treatment of complete AV block are controversial. Some data has suggested a beneficial effect of dexamethasone and salbutamol on outcome [43]. However, this paper used historic controls, and other groups have suggested that the apparent effect of therapy may be a time era effect [46]. Recently, a European multinational retrospective study confirmed that steroid therapy was used in 38% of affected cases but that this did not have a positive impact on intrauterine survival, postnatal survival or development of late cardiomyopathy [47]. Of mothers treated with steroids, 15% developed an adverse fetal or maternal side effect [47]. That study did not address the impact of additional therapy with β stimulation and confirmed that choice of therapy was more related to the institution than the condition of the fetus [43]. Groves et al. demonstrated that maternal salbutamol therapy increased the fetal ventricular rate and subsequently improved fetal myocardial function [48]. Conversely, other studies have suggested that β stimulation does not increase the fetal heart rate significantly but when the baseline fetal heart rate was lower than the controls there was no further reduction in the ventricular rate [43]. Use of maternal salbutamol has been associated with prolongation of gestation in affected fetuses [49].

Second degree AV block

Traditional M mode assessment may detect second degree AV block. In particular, type 2 second degree AV block can be detected by demonstrating two atrial contractions to every ventricular contraction with a fixed relationship between atrial and ventricular beats. However, differentiating second degree and complete AV block by M Mode assessment can be extremely difficult. Alternatively, Doppler techniques can be used to determine the time intervals between atrial and ventricular contractions including a Wenckebach pattern [50].

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Table 2. Second degree atrioventricular block.

Authors	Study design	Inclusion criteria	AV block	Treatment	Postnatal outcome
Copel et al. [45]	Prospective	Antibody +ve $n = 5$	Second degree AV block $n = 1$	Dexamethasone	Sinus rhythm $n = 1$
			Second degree AV block and intermittent CAVB $n = 1$	Dexamethasone	CAVB with subsequent second degree AV block (not paced) $n = 1$
Yamada et al. [51]	Prospective	Antibody +ve $n = 2$	Second degree AV block $n = 1$	Prednisolone and Dexamethasone	Second degree AV block at term $n = 1$
Sonesson et al. [40]	Prospective	Antibody +ve $n = 24$	Second degree AV block $n = 1$	Betamethasone	First degree AV block at term $n = 1$
Lopes et al. [26]	Retrospective	Antibody +ve $n = 42$ Antibody −ve $n = 15$	Second degree AV block $n = 22$	No therapy	Sinus rhythm $n = 4$ Second degree AV block $n = 9$ CAVB $n = 9$
Eliasson et al. [47]	Multicenter, retrospective	$n = 175$	Second degree AV block $n = 29$	Dexamethasone/ betamethasone $n = 13$ No therapy $n = 16$	Outcome see CAVB table[*]
Izmirly et al. [52]	Case controlled study	Antibody +ve $n = 201$ Cardiac Manifestations $n = 50$	Second degree AV block (or CAVB) $n = 43$ of 50	Dexamethasone $n = 26$ Betamethasone $n = 22$ Hydroxychloroquine $n = 7$	No outcomes documented[*]
Friedman et al. [29]	Multicenter, Prospective, Open-Label Clinical Trial	Antibody +ve $n = 20$	Second degree AV block $n = 1$	Prophylaxis IVIG/ hydrocortisone Treatment with dexamethasone	CAVB $n = 1$

AV, atrioventricular; SR, sinus rhythm; CAVB, complete atrioventricular block; IVIG, intravenous immunoglobulin.
[*] See CAVB Table.

In contrast to complete AV block, there is some evidence that second degree AV block may potentially be reversible (Table 2) and some cases of second degree AV block may not progress to complete AV block [40,45,51]. Lopes et al. retrospectively identified 22 fetuses affected by second degree AV block. None of the mothers received medical therapy and subsequently, nine fetuses remained in second degree AV block; four reverted to sinus rhythm, and a further nine progressed to complete AV block by term [26]. Other studies include very small numbers of fetuses affected by second degree AV block. Thus, the efficacy of maternal steroid therapy for the treatment of second degree AV block remains controversial [38,45,51–54]. Table 2 summarizes studies reviewing the treatment and outcomes of prenatally detected second degree AV block.

First degree AV block

It is reported that approximately 30% of women who are seropositive for anti-Ro/SSA 52 Kd exhibit transient first degree AV block in the fetus, without progression to higher degrees of AV block [40]. Screening high risk pregnancies by measuring the fetal AVCTI (mechanical PR interval) has been proposed to allow early recognition and potential intervention for first degree AV block. Normal ranges, using a variety of techniques have been published [11,22]. The fundamental clinical decision is whether treatment will be initiated following detection of prolongation of the AVCTI or whether the fetus will be observed to check that the AVCTI spontaneously normalizes. The approach in studies has varied between observation [40] and active therapy including dexamethasone, hydroxychloroquine and IV immunoglobulin [3,52,55]. Even the larger studies had a sample size of less than ten fetuses. Tunks et al. treated five antibody positive women, in whom the fetus demonstrated first degree AV block, with a combination of dexamethasone, IV immunoglobulin or hydroxychloroquine. Their results showed that one fetus progressed to complete AV block while the other four remained in first degree AV block or reverted to sinus rhythm [55]. Table 3 summarizes studies reviewing the treatment and outcomes of prenatally detected complete AV block.

Table 3. First degree atrioventricular block.

Authors	Study Design	Inclusion Criteria	AV Block	Treatment	Prenatal Outcome	Postnatal Outcome
Sonesson et al. [40]	Prospective	Antibody +ve $n = 24$	First degree AV block $n = 8$	Nil	–	Sinus rhythm $n = 5$ First degree AV block $n = 3$
			First degree AV block at 22 weeks gestation $n = 1$	Dexamethasone	Sinus rhythm within 2 days of therapy $n = 1$	Sinus rhythm $n = 1$
			Normal prenatal PR interval $n = 1$	–	–	First degree AV block (preterm 32 weeks) $n = 1$
Izmirly et al. [52]	Case control study	Antibody +ve $n = 201$ Cardiac manifestations $n = 50$	First degree AV block $n = 3$	Dexamethasone $n = 2$	Sinus rhythm $n = 2$	Sinus rhythm $n = 2$
				No therapy $n = 1$	–	First degree AV block $n = 1$
Tunks et al. [55]	Retrospective	Antibody +ve $n = 33$	First degree AV block $n = 5$	Dexamethasone $n = 1$ Dexamethasone/ IVIG $n = 1$	CAVB $n = 1$ Alternate first and second degree AV block $n = 1$	CAVB First degree AV block
				Hydroxychloroquine/ dexamethasone $n = 1$ Dexamethasone $n = 2$	First degree AV block $n = 1$ First degree AV block $n = 2$	Sinus rhythm or first degree AV block
Jaeggi et al. [3]	Prospective	Antibody +ve $n = 40$	First degree AV block $n = 2$	Steroids/IVIG $n = 1$ No therapy $n = 1$	– –	Alive Alive

AV, atrioventricular; IVIG, intravenous immunoglobulin; CAVB, complete atrioventricular block.

Prophylactic maternal therapy for complete AV block

Studies have been published on the use of therapies to prevent development of AV block in high risk pregnancies. The treatments used include hydroxychloroquine, IV immunoglobulin, plasmapheresis, azathioprine, and B cell depletion. Most data relates to the use of hydroxychloroquine and IV immunoglobulin. Hydroxychloroquine (Plaquenil) is an immune modulator with anti-inflammatory effects. A retrospective, case controlled study demonstrated a trend towards a lower incidence of rhythm or functional cardiac complications in fetuses exposed to hydroxychloroquine compared to those who were not. The study defined exposure to hydroxychloroquine as maternal therapy $\geqslant 200$ mg per day. This study did not reach statistical significance but the overall OR was 0.44 (95% CI 0.19–1.03; $p = 0.06$) [52]. This was corroborated by a single center, retrospective study by Tunks et al. ($n = 33$) [55], which suggested that exposure to hydroxychloroquine in the preconception phase or during pregnancy, may reduce the incidence of complete AV block in high risk fetuses. Of the fetuses who did not develop any degree of AV block ($n = 25$), thirteen were

exposed to hydroxychloroquine during the pregnancy. In the cohort of fetuses who developed AV block ($n = 8$) only one was exposed to hydroxychloroquine. All fetuses who developed complete AV block were treated with dexamethasone, but there was no reversion to lower degrees of AV block. A significant proportion of the mothers receiving hydroxychloroquine in this study was concurrently treated with low dose prednisolone, thus carrying implications for the interpretation of the results [55]. Both studies included women who were seropositive for anti-Ro/SSA or La/SSB, proven to be affected by systemic lupus erythematosus (SLE) or had a previous child affected by congenital complete AV block, thus representing a high risk population [52,55].

Murine models have hypothesized that IV immunoglobulin may prevent trans-placental passage of anti-Ro/SSA and anti-La/SSB antibodies by non-specifically blocking placental Fc receptors, and therefore preventing the detrimental antibody effects on the developing fetal myocardium [56]. Kaaja and Julkunen [57] prophylactically administered a combination of IV immunoglobulin and prednisolone to women ($n = 7$) in whom a previous pregnancy was affected by complete AV block. The fetuses of women treated with combina-

tion therapy remained in sinus rhythm at term. Conversely, the single fetus whose mother was administered IV immunoglobulin in isolation (patient declined prednisolone) developed complete AV block [57]. However, more recent prospective studies have not confirmed benefit. In a prospective, multicenter trial by Pisoni et al. [58] a cohort of antibody-positive women (n = 15) were treated prophylactically with hydrocortisone and IV immunoglobulin. In the treatment cohort, three fetuses developed complete AV block, and two out of the three pregnancies were interrupted. However, in the non-treatment cohort (n = 9) only one fetus developed complete AV block. They concluded that the dose and frequency of IV immunoglobulin was insufficient to prevent AV block in the fetus [58]. This was corroborated by a second multicenter, prospective study by Friedman et al. [29] who prescribed low dose immunoglobulin to mothers who were positive for anti-Ro/SSA antibodies. This failed to prevent the development of complete AV block in high-risk fetuses or reduce the level of maternal antibody titres. The trial was stopped early due to the development of complete AV block in three of the first 19 patients recruited. The study speculated that a higher dose of IV immunoglobulin might be more effective at preventing complete AV block [29]. These studies are summarized in Table 4.

In a further attempt to provide more accurate risk stratification for the development of congenital complete AV block, the assessment of plasma levels of maternal anti-Ro/SSA and anti-La/SSB have been studied. Jaeggi et al. [3] described an association between high levels of anti-Ro/SSA (>100U/ml) and the development of complete AV block [3]. No fetuses prenatally exposed to maternal anti-Ro/SSA levels <50 U/ml developed complete AV block. Levels of maternal anti-La/SSB showed no association with AV block. However, 57% of neonates with prenatal exposure to maternal anti-La/SSB levels ⩾100 U/ml developed signs of non-cardiac neonatal lupus [3]. These findings were not corroborated by Tunks et al. [55] whose study suggested there was no correlation between prenatal exposure to high levels of maternal anti-Ro/SSA antibody titres and the development of complete AV block. However, they suggested prenatal exposure to elevated levels of anti-La/SSB was pathognomonic of developing complete AV block [55]. It is difficult to compare these two studies as the demographics and inclusion criteria of the two studies vary significantly. Despite conflicting opinions, there are proposals that all

Table 4. Prophylaxis for AV block.

Authors	Study design	Inclusion Criteria	Prophylaxis	AV Block	Prenatal Outcome	Postnatal Outcome
Izmirly et al. [52]	Case controlled study	Antibody +ve n = 50	Dexamethasone n = 26 Betamethasone n = 22 Hydroxychloroquine n = 7	1st AV Block n = 3 2nd AV block (or CAVB) n = 43	–	No outcomes documented*
Tunks et al. [55]	Retrospective	Antibody +ve n = 33	Hydroxychloroquine or prednisolone n = 16	1st AV Block n = 1	–	Sinus rhythm n = 25 1st AV Block n = 1
			No therapy n = 17	CAVB n = 4 1st AV Block n = 3	–	CAVB n = 4 1st AV Block n = 3
Kaaja and Julkunen [57]	Prospective	Antibody +ve n = 8	IVIG n = 1 IVIG/Steroids n = 7	CAVB n = 1 Sinus rhythm n = 7	– –	CAVB n = 1 Sinus rhythm n = 7
Pisoni et al. [58]	Multicenter, prospective, observational	Antibody +ve n = 24	IVIG/Hydrocortisone prophylaxis n = 15 No prophylaxis n = 9	CAVB n = 3 CAVB n = 1	TOP n = 2 TOP n = 1	CAVB n = 1 Alive n = 12 Alive n = 8
Friedman et al. [29]	Multicenter, Prospective, Open–Label Clinical Trial	Antibody +ve n = 20	IVIG prophylaxis n = 20	CAVB n = 3 (n = 1 preceded by 2nd AV block) Sinus rhythm n = 17	– –	CAVB n = 3 (despite additional dexamethasone) Sinus rhythm n = 17

AV, atrioventricular; IVIG, intravenous immunoglobulin; CAVB, complete atrioventricular block; TOP, termination of pregnancy.
* See CAVB Table.

pregnant women should be screened in the first trimester for the presence of autoantibodies and with particular emphasis on anti-Ro/SSA and anti-LA/SSB levels [27].

Approach to management

Due to the low incidence of complete AV block in the general population, studies are mainly observational, retrospective and involve small cohorts of patients. The team from Toronto Sick Children's Hospital have published their guidance for the management of varying degrees of congenital AV block. In their protocol, Jaeggi et al. [43] advise no therapy in the presence of isolated first degree AV block, but in the presence of second degree AV block or complete AV block, a course of maternal steroids is recommended. If the fetal ventricular escape rate is ⩽55 bpm, supplementary maternal salbutamol therapy is considered. In the presence of isolated fetal myocardial endocardial fibroelastosis (EFE), maternal IV immunoglobulin is administered at two to three weekly intervals prenatally. Postnatally, the affected child would also be treated with a course of IV immunoglobulin [43].

Approach and policy at our centre

In our institution, Evelina London, we do not currently recommend cardiac referral of mothers with connective tissue disease (CTD) whose anti-Ro/La antibody status is negative, unless there is evidence of fetal heart block on the obstetric anomaly scan. Some mothers with CTD are referred with unknown antibody status. In this situation, anti-Ro/SSA and La/SSB titres are checked and, if negative, coupled with a normal echocardiogram, then no further cardiac review is undertaken. For mothers who are known to be anti-Ro and/or anti-La positive, fetal echocardiography is undertaken at 18–24 weeks gestational age, including 2D imaging to confirm structural normality, pulsed wave Doppler, color flow Doppler and M mode assessment to confirm AV synchrony. To identify first degree AV block, the AVCTI (ms) is measured by pulsed wave Doppler and compared to normative values. The presence of maternal anti-Ro/SSA and La/SSB antibodies is recorded in a bid to provide prognostication, and we recently introduced measurement of antibody titres. Tissue Doppler imaging is not routinely used in our assessment. In the presence of a structurally normal fetal heart and an AVCTI within normal limits for gestational age, two further assessments are arranged at regular intervals (Fig. 6). The detection of first degree AV block would warrant closer follow-up to assess for progression to higher degrees of AV block or reversion to a normal AVCTI. It is not our policy to treat isolated first degree AV block. Detection of second degree AV block would merit consideration of maternal dexamethasone therapy (4 mg daily initially, followed by a tapering regimen) to
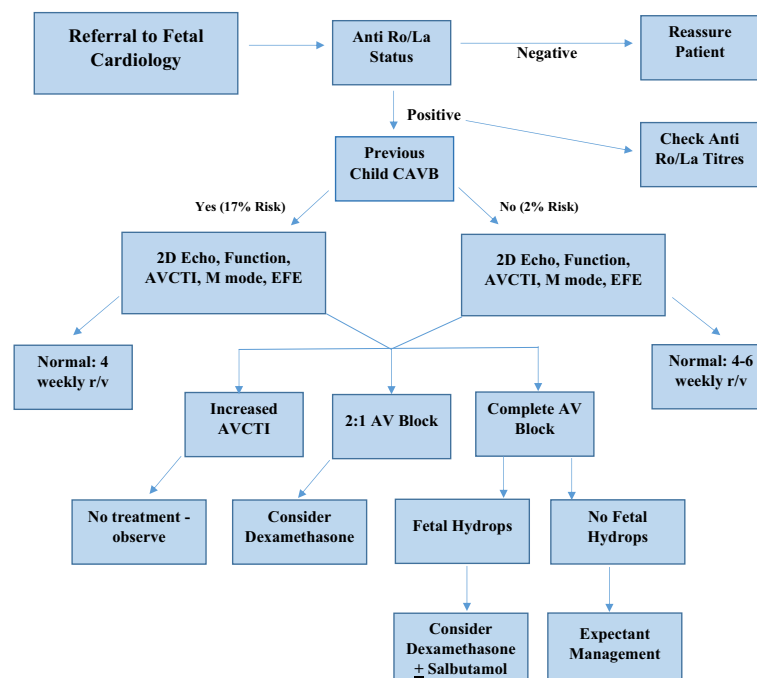

Figure 6. Fetal cardiology assessment of maternal autoimmune disease.

gauge whether this is associated with reversion to a lower degree of AV block. Depending on the fetal response, this dose is tapered with the aim of minimizing potential side effects of dexamethasone for the fetus and mother.

If there is complete AV block, then the decision to give therapy depends on additional findings. If there is no evidence of fetal hydrops, good ventricular function and no echogenicity of the ventricular myocardium, then our policy is for close review without initiation of therapy. If, however, there is hydrops, subjective evidence of reduced ventricular function and/or echogenicity of the myocardium (which may suggest endocardial fibroelastosis) then maternal dexamethasone would be seriously considered. Fetal hydrops would be an indication for active therapy which would include dexamethasone coupled with salbutamol, particularly if the fetal ventricular rate is very low. Slow release salbutamol is administered orally, with baseline monitoring of maternal electrolytes prior to therapy. Whether treatment is given or not, close fetal cardiological and obstetric review is warranted to monitor fetal cardiac function, fetal ventricular rate and signs of hydrops. Within our unit, we would not recommend extreme preterm delivery due to its association with poorer neonatal outcomes [59]. Each case is considered individually within our multidisciplinary team, ensuring delivery occurs at an optimal time, in an effort to minimize neonatal morbidity and mortality.

Treatment side effects

When considering prenatal therapy it is important to consider the risks and benefits for both the mother and the developing fetus. Some units have strongly advocated the use of dexamethasone, given the observation of better outcome [43]. Dexamethasone is associated with maternal complications such as hypertension, gestational diabetes and fetal complications, for example, oligohydramnios and detrimental effects on growth and development [42,47,60,61]. A single dose of steroids is commonly administered to promote lung maturation in the preterm infant with threatened preterm labor, but concerns have been raised regarding the effects of multiple steroid doses, in particular, the effect on the developing fetal brain. The National Institute of Health released a consensus statement, stating there are no substantiated reports of adverse effects from a single dose of prenatal steroids, but advised that multiple courses of steroids should only be

administered within clinical trials [61]. This was highlighted in the PRIDE study, which advised that the potential benefits of maternal steroid therapy must be carefully balanced against the potential detrimental effects on fetal growth [38]. Regarding neurodevelopment, Brucato et al. [62] retrospectively examined a cohort ($n = 16$) of infants with congenital complete AV block who had been exposed to high levels of dexamethasone in utero. They found no significant intellectual deficiencies in preschool or school age children [62]. As with dexamethasone therapy, maternal safety when prescribing salbutamol is fundamental. In our own unit, therefore, mothers are admitted for observation during initiation of salbutamol therapy and a baseline 12 lead ECG, plasma urea and electrolytes are undertaken. The ECG and electrolytes are assessed at regular intervals during the treatment period.

Fetal and neonatal outcome

When assessing the rate of intra-uterine death, the live birth rate and one year survival, studies have indicated no statistical difference between cohorts prenatally exposed to maternal dexamethasone when compared to those who received no prenatal therapy [26,47]. In one study, both cohorts had similar rates of fetal hydrops, fetal ventricular escape rates and ventricular dysfunction [47]. Risk factors predicting a poorer outcome in a fetus with congenital complete AV block have been identified. These include a ventricular escape rate ⩽50 bpm, gestation at diagnosis <20 weeks, fetal hydrops, and impaired left ventricular function [6]. In the presence of such risk factors, the risk of intrauterine death is 22%, and neonatal mortality 18% in comparison to 2% and 3%, respectively in the absence of any risk factors [47]. A report by Moak et al. [63] described 16 children with congenital complete AV block who developed late onset dilated left ventricular cardiomyopathy despite adequate pacing. Three quarters developed cardiac failure within the first two years of life, myocardial histology demonstrated fibrosis in eleven cases, and myocyte degeneration in two cases. This study highlights the importance of careful long term monitoring of cardiac function even in children receiving appropriate pacing for complete AV block [63].

In relation to fetal growth and development, a European study suggested that fetuses of mothers with anti-Ro/SSA 52 Kd antibodies and evidence of second degree AV block or complete AV block had a birth weight which was lower than those

with first degree AV block or normal conduction [64]. There was no statistical difference in the gestational age of both cohorts. In addition, the fetuses with second or complete AV block showed no evidence of catch up growth during early childhood. In contrast, those with first degree AV block or normal conduction demonstrated catch up growth within the first two months of life. None of the infants with a lower birth weight demonstrated any gross cognitive impairment [64].

In neonatal lupus syndrome, the autoimmune process not only affects the fetal conduction tissue, but also the myocardium, papillary muscles and valvular tissue, resulting in endocardial fibroelastosis (EFE). It should be noted that not all fetuses affected by immune mediated complete AV block have EFE and the converse is also true. Immunohistochemical staining of EFE in complete AV block demonstrates autoantibody deposition [65]. Previously, EFE in this condition was assumed to be a result of prolonged bradycardia in utero, but has now been described as a separate entity which may develop in both pre and postnatal periods. The postnatal prognosis must remain guarded due to the potential development of late congestive cardiac failure. Thus, neonatal lupus erythematosis can present as EFE or complete AV block, and these should probably be regarded as separate disease entities [65].

Future directions

New advances are being made in the form of in vitro studies. Preliminary studies have identified a potential protective mechanism in the form of β2-glycoprotein I. This glycoprotein is closely associated with anti-phospholipid antibodies, binding to Ro-60 on the surface of apoptotic cells. Further study is require to assess the efficacy of this potential therapy in a clinical setting [66–68].

Conclusion

The general consensus within the scientific and medical community is that the development of immune mediated complete AV block is a multifactorial, autoimmune process. Clinicians are in agreement that the presence of anti-Ro/SSA and La/SSB are contributing factors to the development of the disease but only as part of a more complex autoimmune process. Screening for prenatal complete AV block remains a challenge as the majority of women have no pre-existing clinical features of connective tissue disease or a previous child with complete AV block. In summary,

there is insufficient robust evidence to suggest that prophylactic maternal therapy alters the incidence or recurrence rate of congenital complete AV block in the high risk population [69]. Furthermore, despite an increased incidence of complete AV block in asymptomatic women, until more robust scientific evidence is available, most clinicians will continue to refer women with antibody positive connective tissue disease for fetal cardiology surveillance during the second trimester to monitor for the development and progression of AV block. A further understanding of the pathophysiology of complete AV block, in particular disease progression, will guide therapy for lower degrees of AV block, complete AV block and preconception therapy. This will allow clinicians to counsel parents more accurately and provide better prognostication. There is consensus that multicenter, prospective trials are required to answer these questions.

References

[1] Buyon JP, 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(7):1658–66.

[2] Michaëlsson M, Engle MA. Congenital complete heart block: an international study of the natural history. Cardiovasc Clin 1972;4(3):85–101.

[3] 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 Cardiol 2010;55(24):2778–84.

[4] Jaeggi ET, Hamilton RM, Silverman ED, Zamora SA, Hornberger LK. Outcome of children with fetal, neonatal or childhood diagnosis of isolated congenital atrioventricular block. A single institution's experience of 30 years. J Am Coll Cardiol 2002;39(1):130–7.

[5] Eronen M, Sirèn MK, Ekblad H, Tikanoja T, Julkunen H, Paavilainen T. Short- and long-term outcome of children with congenital complete heart block diagnosed in utero or as a newborn. Pediatrics 2000;106(1 Pt 1):86–91.

[6] Schmidt KG, Ulmer HE, Silverman NH, Kleinman CS, Copel JA. Perinatal outcome of fetal complete atrioventricular block: a multicenter experience. J Am Coll Cardiol 1991;17(6):1360–6.

[7] Izmirly PM, Saxena A, Kim MY, Wang D, Sahl SK, Llanos C, et al.. Maternal and fetal factors associated with mortality and morbidity in a multi-racial/ethnic registry of anti-SSA/Ro-associated cardiac neonatal lupus. Circulation 2011;124(18):1927–35.

[8] Berg C, Geipel A, Kohl T, Breuer J, Germer U, Krapp M, et al.. Atrioventricular block detected in fetal life: associated anomalies and potential prognostic markers. Ultrasound Obstet Gynecol 2005;26(1):4–15.

[9] Gardiner HM, Belmar C, Pasquini L, Seale A, Thomas M, Dennes W, et al.. Fetal ECG: a novel predictor of atrioventricular block in anti-Ro positive pregnancies. Heart 2007;93(11):1454–60.

[10] Horigome H, Takahashi MI, Asaka M, Shigemitsu S, Kandori A, Tsukada K. Magnetocardiographic determination of the developmental changes in PQ, QRS

and QT intervals in the foetus. Acta Paediatr 2000;89(1):64–7.

[11] Pasquini L, Seale AN, Belmar C, Oseku-Afful S, Thomas MJ, Taylor MJ, et al.. PR interval: a comparison of electrical and mechanical methods in the fetus. Early Hum Dev 2007;83(4):231–7.

[12] Strasburger JF, Cheulkar B, Wakai RT. Magnetocardiography for fetal arrhythmias. Heart Rhythm 2008;5(7):1073–6.

[13] Simpson JM. Fetal arrhythmias. Ultrasound Obstet Gynecol 2006;27(6):599–606.

[14] Allan LD, Anderson RH, Sullivan ID, Campbell S, Holt DW, Tynan M. Evaluation of fetal arrhythmias by echocardiography. Br Heart J 1983;50(3):240–5.

[15] Rein AJ, Mevorach D, Perles Z, Gavri S, Nadjari M, Nir A, et al.. Early diagnosis and treatment of atrioventricular block in the fetus exposed to maternal anti-SSA/Ro-SSB/La antibodies: a prospective, observational, fetal kinetocardiogram-based study. Circulation 2009;119(14):1867–72.

[16] Nii M, Shimizu M, Roman KS, Konstantinov I, Li J, Redington AN, et al.. Doppler tissue imaging in the assessment of atrioventricular conduction time: validation of a novel technique and comparison with electrophysiologic and pulsed wave Doppler-derived equivalents in an animal model. J Am Soc Echocardiogr 2006;19(3):314–21.

[17] Tutschek B, Schmidt KG. Pulsed-wave tissue Doppler echocardiography for the analysis of fetal cardiac arrhythmias. Ultrasound Obstet Gynecol 2011;38(4):406–12.

[18] Cuneo BF, Strasburger JF, Yu S, Horigome H, Hosono T, Kandori A, et al.. In utero diagnosis of long QT syndrome by magnetocardiography. Circulation 2013;128(20):2183–91.

[19] Nii M, Hamilton RM, Fenwick L, Kingdom JC, Roman KS, Jaeggi ET. Assessment of fetal atrioventricular time intervals by tissue Doppler and pulse Doppler echocardiography: normal values and correlation with fetal electrocardiography. Heart 2006;92(12):1831–7.

[20] Andelfinger G, Fouron JC, Sonesson SE, Proulx F. Reference values for time intervals between atrial and ventricular contractions of the fetal heart measured by two Doppler techniques. Am J Cardiol 2001;88(12):1433–6.

[21] Glickstein JS, Buyon J, Friedman D. Pulsed Doppler echocardiographic assessment of the fetal PR interval. Am J Cardiol 2000;86(2):236–9.

[22] Glickstein J, Buyon J, Kim M, Friedman D. PRIDE investigators. The fetal Doppler mechanical PR interval: a validation study. Fetal Diagn Ther 2004;19(1):31–4.

[23] Bergman G, Jacobsson LA, Wahren-Herlenius M, Sonesson SE. Doppler echocardiographic and electrocardiographic atrioventricular time intervals in newborn infants: evaluation of techniques for surveillance of fetuses at risk for congenital heart block. Ultrasound Obstet Gynecol 2006;28(1):57–62.

[24] Bergman G, Wahren-Herlenius M, Sonesson SE. Diagnostic precision of Doppler flow echocardiography in fetuses at risk for atrioventricular block. Ultrasound Obstet Gynecol 2010;36(5):561–6.

[25] Jaeggi ET, Silverman ED, Laskin C, Kingdom J, Golding F, Weber R. Prolongation of the atrioventricular conduction in fetuses exposed to maternal anti-Ro/SSA and anti-La/SSB antibodies did not predict progressive heart block. A prospective observational study on the effects of maternal antibodies on 165 fetuses. J Am Coll Cardiol 2011;57(13):1487–92.

[26] Lopes LM, Tavares GM, Damiano AP, 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(12):1268–75.

[27] Claus R, Hickstein H, Külz T, Lenschow U, Meiske D, Kotitschke A, et al.. Identification and management of fetuses at risk for, or affected by, congenital heart block associated with autoantibodies to SSA (Ro), SSB (La), or an HsEg5-like autoantigen. Rheumatol Int 2006;26(10):886–95.

[28] Anderson RH, Becker AE, Arnold R, Wilkinson JL. The conducting tissues in congenitally corrected transposition. Circulation 1974;50(5):911–23.

[29] Friedman DM, Llanos C, Izmirly PM, Brock B, Byron J, Copel J, et al.. Evaluation of fetuses in a study of intravenous immunoglobulin as preventive therapy for congenital heart block: Results of a multicenter, prospective, open-label clinical trial. Arthritis Rheum 2010;62(4):1138–46.

[30] Mitchell JL, Cuneo BF, Etheridge SP, Horigome H, Weng HY, Benson DW. Fetal heart rate predictors of long QT syndrome. Circulation 2012;126(23):2688–95.

[31] Julkunen H, Eronen M. The rate of recurrence of isolated congenital heart block: a population-based study. Arthritis Rheum 2001;44(2):487–8.

[32] Llanos C, Izmirly PM, Katholi M, Clancy RM, Friedman DM, Kim MY, et al.. Recurrence rates of cardiac manifestations associated with neonatal lupus and maternal/fetal risk factors. Arthritis Rheum 2009;60(10):3091–7.

[33] Nguyen TG, Ward CM, Morris JM. To B or not to B cells-mediate a healthy start to life. Clin Exp Immunol 2013;171(2):124–34.

[34] Yang CH, Chen JY, Lee SC, Luo SF. Successful preventive treatment of congenital heart block during pregnancy in a woman with systemic lupus erythematosus and anti-Sjögren's syndrome A/Ro antibody. J Microbiol Immunol Infect 2005;38(5):365–9.

[35] Aslan E, Tarim E, Kilicdag E, Simsek E. Sjögren's syndrome diagnosed in pregnancy: a case report. J Reprod Med 2005;50(1):67–70.

[36] Hickstein H, Külz T, Claus R, Stange J, Schmidt R. Autoimmune-associated congenital heart block: treatment of the mother with immunoadsorption. Ther Apher Dial 2005;9(2):148–53.

[37] Makino S, Yonemoto H, Itoh S, Takeda S. Effect of steroid administration and plasmapheresis to prevent fetal congenital heart block in patients with systemic lupus erythematosus and/or Sjögren's syndrome. Acta Obstet Gynecol Scand 2007;86(9):1145–6.

[38] Friedman DM, Kim MY, Copel JA, Davis C, Phoon CK, Glickstein JS, et al.. Utility of cardiac monitoring in fetuses at risk for congenital heart block: the PR Interval and Dexamethasone Evaluation (PRIDE) prospective study. Circulation 2008;117(4):485–93.

[39] Jaeggi ET, Silverman ED, Yoo SJ, Kingdom J. Is immune-mediated complete fetal atrioventricular block reversible by transplacental dexamethasone therapy? Ultrasound Obstet Gynecol 2004;23(6):602–5.

[40] Sonesson SE, Salomonsson S, Jacobsson LA, Bremme K, Wahren-Herlenius M. Signs of first-degree heart block occur in one-third of fetuses of pregnant women with anti-SSA/Ro 52-kd antibodies. Arthritis Rheum 2004;50(4):1253–61.

[41] 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(11):2335–45.

[42] Fesslova V, Vignati G, Brucato A, De Sanctis M, Butera G, Pisoni MP, et al.. The impact of treatment of the fetus by maternal therapy on the fetal and postnatal outcomes for fetuses diagnosed with isolated complete atrioventricular block. Cardiol Young 2009;19(3):282–90.

[43] Jaeggi ET, Fouron JC, Silverman ED, Ryan G, Smallhorn J, Hornberger LK. Transplacental fetal treatment improves the outcome of prenatally diagnosed complete atrioventricular block without structural heart disease. Circulation 2004;110(12):1542–8.

[44] Breur JM, Visser GH, Kruize AA, Stoutenbeek P, Meijboom EJ. Treatment of fetal heart block with

maternal steroid therapy: case report and review of the literature. Ultrasound Obstet Gynecol 2004;24(4):467–72.

[45] Copel JA, Buyon JP, Kleinman CS. Successful in utero therapy of fetal heart block. Am J Obstet Gynecol 1995;173(5):1384–90.

[46] Rosenthal E, Gordon PA, Simpson JM, Sharland GK. Letter regarding article by Jaeggi et al., "transplacental fetal treatment improves the outcome of prenatally diagnosed complete atrioventricular block without structural heart disease. Circulation 2005;111(18):e287–8 [author reply e-8].

[47] Eliasson H, Sonesson SE, Sharland G, Granath F, Simpson JM, Carvalho JS, et al.. Isolated atrioventricular block in the fetus: a retrospective, multinational, multicenter study of 175 patients. Circulation 2011;124(18):1919–26.

[48] Groves AM, Allan LD, Rosenthal E. Therapeutic trial of sympathomimetics in three cases of complete heart block in the fetus. Circulation 1995;92(12):3394–6.

[49] Sivarajah J, Huggon IC, Rosenthal E. Successful management of fetal hydrops due to congenitally complete atrioventricular block. Cardiol Young 2003;13(4):380–3.

[50] Swaminathan S, Parthiban A. Progressive fetal atrioventricular block in heterotaxy syndrome. Cardiol Young 2007;17(4):432–4.

[51] Yamada H, Kato EH, Ebina Y, Moriwaki M, Yamamoto R, Furuta I, et al.. Fetal treatment of congenital heart block ascribed to anti-SSA antibody: case reports with observation of cardiohemodynamics and review of the literature. Am J Reprod Immunol 1999;42(4):226–32.

[52] Izmirly PM, Kim MY, Llanos C, Le PU, Guerra MM, Askanase AD, et al.. Evaluation of the risk of anti-SSA/Ro-SSB/La antibody-associated cardiac manifestations of neonatal lupus in fetuses of mothers with systemic lupus erythematosus exposed to hydroxychloroquine. Ann Rheum Dis 2010;69(10):1827–30.

[53] Adams LL, Gungor S, Salim M, Harman CR, Baschat AA. Regression of fetal heart block and myocardial echogenicity with steroid therapy in maternal Sjögren's syndrome. Ultrasound Obstet Gynecol 2008;32(6):839–40.

[54] Buyon JP, Waltuck J, Kleinman C, Copel J. In utero identification and therapy of congenital heart block. Lupus 1995;4(2):116–21.

[55] Tunks RD, Clowse ME, Miller SG, Brancazio LR, Barker PC. Maternal autoantibody levels in congenital heart block and potential prophylaxis with antiinflammatory agents. Am J Obstet Gynecol 2013;208(1):64.e1–7.

[56] Tran HB, Cavill D, Buyon JP, Gordon TP. Intravenous immunoglobulin and placental transport of anti-Ro/La antibodies: comment on the letter by Kaaja and Julkunen. Arthritis Rheum 2004;50(1):337–8.

[57] Kaaja R, Julkunen H. Prevention of recurrence of congenital heart block with intravenous immunoglobulin and corticosteroid therapy: comment on the editorial by Buyon et al.. Arthritis Rheum 2003;48(1):280–1.

[58] Pisoni CN, Brucato A, Ruffatti A, Espinosa G, Cervera R, Belmonte-Serrano M, et al.. Failure of intravenous immunoglobulin to prevent congenital heart block: findings of a multicenter, prospective, observational study. Arthritis Rheum 2010;62(4):1147–52.

[59] Andrews RE, Simpson JM, Sharland GK, Sullivan ID, Yates RW. Outcome after preterm delivery of infants antenatally diagnosed with congenital heart disease. J Pediatr 2006;148(2):213–6.

[60] Bloom SL, Sheffield JS, McIntire DD, Leveno KJ. Antenatal dexamethasone and decreased birth weight. Obstet Gynecol 2001;97(4):485–90.

[61] National Institutes of Health Consensus Development Panel. Antenatal corticosteroids revisited: repeat courses – National Institutes of Health Consensus Development Conference Statement, August 17–18, 2000. Obstet Gynecol 2001;98(1):144–150.

[62] Brucato A, Astori MG, Cimaz R, Villa P, Li Destri M, Chimini L, et al.. Normal neuropsychological development in children with congenital complete heart block who may or may not be exposed to high-dose dexamethasone in utero. Ann Rheum Dis 2006;65(11):1422–6.

[63] 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(1):238–42.

[64] Skog A, Wahren-Herlenius M, Sundström B, Bremme K, Sonesson SE. Outcome and growth of infants fetally exposed to heart block-associated maternal anti-Ro52/SSA autoantibodies. Pediatrics 2008;121(4):e803–9.

[65] Nield LE, Silverman ED, Taylor GP, Smallhorn JF, Mullen JB, Silverman NH, et al.. Maternal anti-Ro and anti-La antibody-associated endocardial fibroelastosis. Circulation 2002;105(7):843–8.

[66] Clancy RM. When the levee doesn't break: a novel role of beta2-glycoprotein I to protect against congenital heart block. Arthritis Rheum 2009;60(3):636–8.

[67] Reed JH, Giannakopoulos B, Jackson MW, Krilis SA, Gordon TP. Ro 60 functions as a receptor for beta(2)-glycoprotein I on apoptotic cells. Arthritis Rheum 2009;60(3):860–9.

[68] Izmirly PM, Buyon JP, Saxena A. Neonatal lupus: advances in understanding pathogenesis and identifying treatments of cardiac disease. Curr Opin Rheumatol 2012;24(5):466–72.

[69] 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):1039–45.