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REVIEW

Diagnosis and Management of Fetal Autoimmune Atrioventricular Block

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Abstract: Autoimmune congenital atrioventricular block (CAVB) has been extensively studied in recent decades. The American Heart Association published guidelines for monitoring pregnant women with anti-Ro/Sjögren's syndrome antigen A (SSA) or anti-La/Sjögren's syndrome antigen B (SSB) autoantibodies, which are considered to increase the risk of CAVB. Information about the natural history of the disease *in utero* has contributed to the detection of fetuses with CAVB in the treatable stage. Hydroxychloroquine (HCQ) may be used to prevent CAVB. The lack of large randomized control trials is a major drawback to fully confirm the benefits of fluorinated steroids such as dexamethasone. Although, when combined with a β-sympathomimetic agent, the outcome of administering a fluorinated steroid in complete CAVB is still controversial. Novel treatments targeting the immunological process might prevent the recurrence of CAVB in pregnant women with previously affected children.

Keywords: autoimmune congenital heart block, anti-Ro, anti-La, fetal heart block, cardiomyopathy

Introduction

Ultrasonography has shown that intrauterine diagnosis of abnormal fetal rhythm is common nowadays. Fetal bradyarrhythmia is a type of arrhythmia that is diagnosed prenatally. According to the American College of Obstetricians and Gynecologists,[1] fetal bradycardia is defined as a sustained fetal heart rate <110 beats/min, and it is caused by fetal atrioventricular (AV) block, sinus bradycardia, and blocked atrial bigeminy or trigeminy.[2]

Congenital atrioventricular block (CAVB) occurs in approximately 1 in 20,000 births.[3] More than half of CAVB cases might be the result of structural congenital heart diseases (such as corrected transposition of the great artery and left atrial isomerism, a type of heterotaxy syndrome), which are non-immunological causes. However, another cause involves immunological processes, i.e., maternal autoantibodies enter the fetal circulation via the placenta.[4] Although CAVB is rare, it is associated with increased risk of intrauterine fetal death, neonatal morbidity, neonatal mortality, and long-term sequelae.[4]

The autoantibodies related to CAVB are anti-Ro/Sjögren's syndrome antigen A (SSA) and anti-La/Sjögren's syndrome antigen B (SSB). In pregnant women with these autoantibodies, the risk of the fetus developing CAVB is 2–5%, and this increases to 12–25% if the woman has had a previous child with CAVB.[5] Especially anti-Ro 52-kd antigen which has high specificity to damage the cardiomyocyte,[6] the risk of developing CAVB in fetus is one-third in this antibody-positive pregnant

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women.[7] Risk of developing CAVB increases significantly at a 9-fold in fetus born to women with autoantibodies and hypothyroidism.[8] The incidence of moderate or high autoantibody levels in the general population of pregnant women is 1.2%.[9] In a study of pregnant women who had autoantibodies, three-quarters had systemic lupus erythematosus (SLE) or Sjögren syndrome, while the remainder were asymptomatic carriers.[10] After the diagnosis of CAVB in the fetus of a previously healthy mother, the mother is usually diagnosed with an autoimmune disease.

Anti-Ro/SSA and anti-La/SSB autoantibodies are antinuclear antibodies that can cross the placenta from 12 weeks of gestation.[11] They can affect the fetal myocardium and AV conduction system, resulting in inflammation and fibrosis, which are mostly irreversible.[12] These autoantibodies can also be a cause of endocardial fibroelastosis. The key findings include bilateral ventricular dilatation, reduced ejection fraction, echogenic endocardium along the left ventricle including the mitral valve papillary muscles, and AV valve dysfunction.[13]

CAVB usually develops after 17 weeks of gestation, and it is frequently detected at 20–24 weeks of gestation, while about 20% of cases are diagnosed in the third trimester.[14] Uncommonly, CAVB initially presents in neonates.[14]

Types, Monitoring, and Diagnosis of CAVB

The degree of AV block can be categorized as first-degree, second-degree, and third-degree (complete) AV block. Fetuses with first-degree AV block have a prolongation of AV time, with 1:1 AV conduction, but a normal heart rate. There are two types of second-degree AV block: type 1 (Wenckebach type) and type 2 (Mobitz type). Type 1 usually involves an irregular heart rate, with AV time lengthening progressively until a signal is completely blocked, whereas type 2 involves a normal AV interval with a blocked signal, with 2:1 AV conduction, resulting in bradycardia. In complete AV block, the atrium and ventricle beat independently as a consequence of complete loss of the AV connection.

According to the American Heart Association, pregnant women with anti-Ro/SSA or anti-La/SSB autoantibodies should be referred for fetal echocardiography monitoring from 16–18 to 28 weeks of gestation with 1–2-week intervals.[15] Pulsed wave Doppler echocardiography is used to measure the fetal mechanical PR interval, which is the period from the beginning of the atrial contraction to the beginning of the ventricular contraction (AV time).[16] The measurement obtained from two-dimension ultrasonography and gated-pulsed sample volume placed to the area which can detect atrial systole and ventricular systole simultaneously,[17] such as the left ventricular inflow–outflow view, superior vena cava-aorta (SVC-Ao) view, and pulmonary artery–pulmonary vein (PA–PV) view. Figure 1, left ventricular inflow–outflow view from five-chamber view, the sample volume placed at the junction of mitral valve leaflet and left ventricular outflow tract.[17] SVC-Ao view was displayed in Figure 2, the measurement of mechanical PR interval starts from the beginning of atrial (A) wave of SVC to the onset of aortic ventricular outflow wave.[18] Figure 3, for PA-PV view the sample volume should place in fetal lung parenchyma near the left atrium to demonstrate pulsed waves from the PA–PV which are adjacent to each other in this area.[19] This interval is the time between onset atrial systole detected by an interrupted flow of the pulmonary vein and the sharp peak onset of pulmonary artery systole.[19] The normal PR interval in fetuses is 0.12 ± 0.02 second,[20] and the cut-off of 0.15 s has been widely used to diagnose first-degree AV block.[21] However, some researchers have suggested using a fetal kinetocardiogram to detect first-degree AV block early.[22] A ladder diagram-like fetal kinetocardiogram needs high-frame-rate 2D velocity images and software for analysis,[23] so this test might be not feasible in many centers.

The development of CAVB sometimes does not follow the normal disease progression and the duration of progression can sometimes be unpredictable. From a recent study, complete CAVB can be transition from normal sinus rhythm within 24 hours.[24] However, the PR Interval and Dexamethasone Evaluation (PRIDE) study recommended conducting intensive fetal cardiac scans for signs of cardiac damage, i.e., pericardial effusion, left ventricular enlargement or poor contraction, AV valve regurgitation or hydrops fetalis including assessing the mechanical PR interval from 16 to 24 weeks of gestation with a frequency not less than one week interval.[21] Another recommendation from a large observational study suggests PR interval is a weak predictor for complete CAVB. However, weekly cardiac scans between 18 to 24 weeks' gestation are still encouraged to aid timely detection of second-degree CAVB or complete CAVB for early treatment and potentially positive outcomes.[25] Although ambulatory monitoring of the fetal heart sound in autoantibody-positive

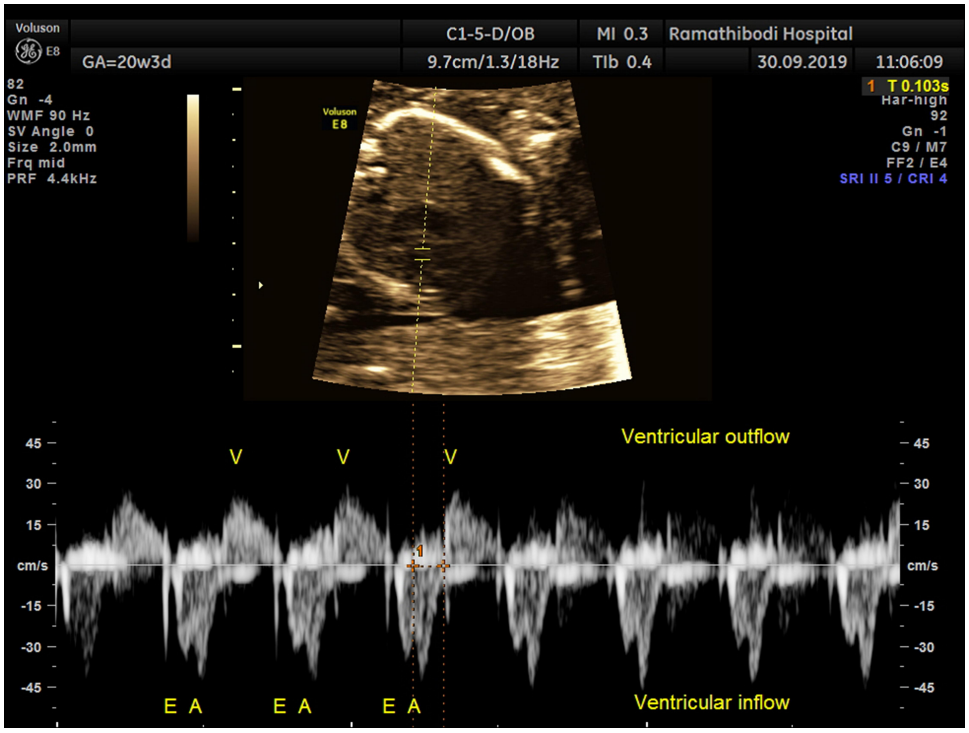

Figure 1 Pulsed wave Doppler image of mitral valve inflow–outflow view obtained from five-chamber view, time between atrial systole of mitral valve and onset of ventricular systole represents mechanical PR interval.

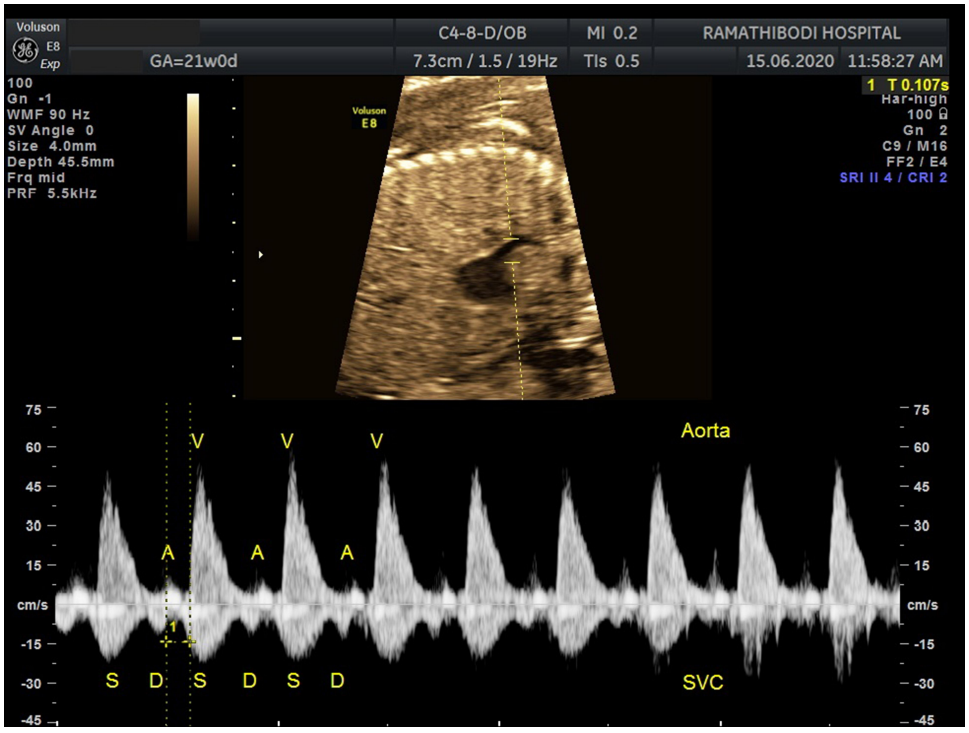

Figure 2 Pulsed wave Doppler image of superior vena cava-aorta (SVC-Ao) obtained from sagittal plane, time between SVC atrial wave onset and the beginning of aortic ejection flow represents mechanical PR interval.

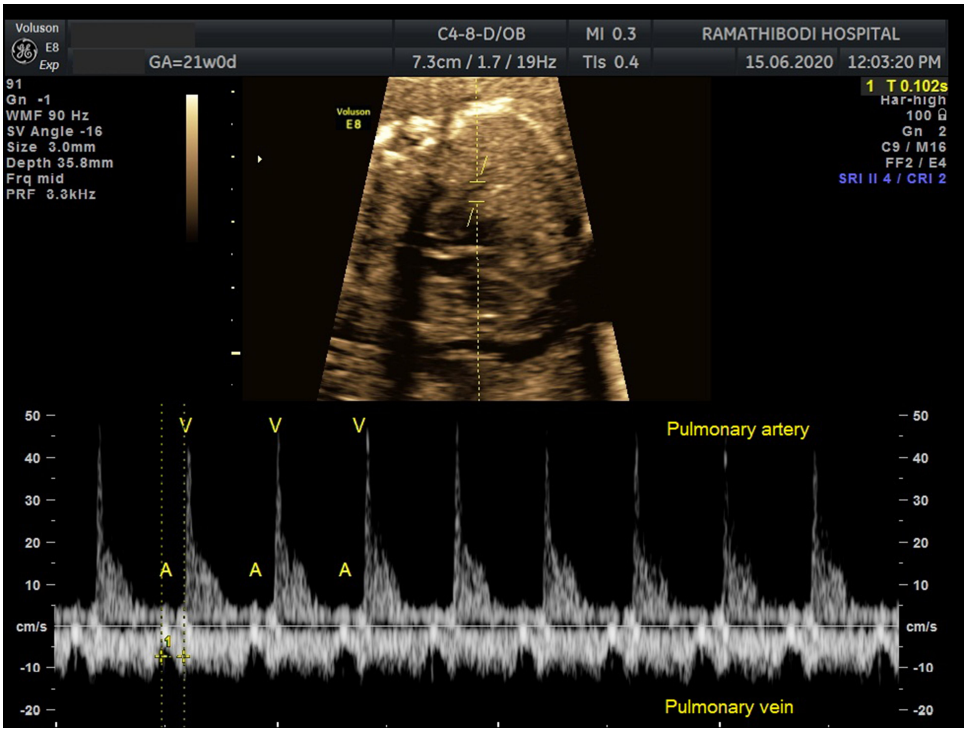

Figure 3 Pulsed wave Doppler image of pulmonary artery–pulmonary vein (PA–PV) view obtained from four-chamber view, mechanical PR interval was measured between onset of pulmonary vein atrial wave and onset of pulmonary artery ejection flow.

pregnancies can detect fetal arrhythmia and might improve detection of fetal CAVB,[26] this cannot totally replace echocardiography because some early signs, such as endocardial fibroelastosis, poor ventricular function or first-degree CAVB, can be missed.[25] Additionally, several studies have reported classifying the risk of CAVB based on the autoantibody level, with a high level (>50–100 U/mL) representing increased risk.[27,28]

Prevention and Treatment of CAVB

Recent data from a small observational cohort suggests hydroxychloroquine (HCQ) may prevent CAVB in fetus at risk from antibody-positive pregnant women[29] or recurrent CAVB in pregnant women with previously affected child.[30] But a prospective trial is needed to prove its effects. HCQ inhibits toll-like receptor signaling (which plays a critical role in the immune response), and it is prescribed for pregnancies involving a high risk of CAVB. For maternal advantages, the European League Against Rheumatism (EULAR) recommended HCQ for controlling disease activity and preventing flare-ups during pregnancy in SLE patients.[31]

Treatment of first-degree and second-degree AV block is controversial. The effect of fluorinated steroid on conversion from first-degree block to normal sinus rhythm cannot be ascertained based on current data.[21] In some centers, the fluorinated steroid is used to normalize AV conduction,[22,32] improve myocardial performance and prevention of complete CAVB.[33] A recent meta-analysis from retrospective studies failed to demonstrate the benefit of antenatal corticosteroid alone or combined with other medication to second-degree AV block in terms of disease progression, stable of disease at birth, postnatal pacing,[34,35] fetal survival,[34] and neonatal survival.[36] However, a fluorinated steroid is still encouraged until its benefit cannot be proved by a reliable study.[34]

The commonly used fluorinated steroid, dexamethasone, reduces the maternal autoantibody load. It can be administered orally or intravenously, and the regimen involves tapering. The initial dose is 4–8 mg/day for 2–4 weeks then 2 mg/day until delivery.[4,12,37] Side effects in the fetuses and the pregnant women are a major concern. A large randomized study showed that there was a higher rate of cerebral palsy after prolonged use of dexamethasone.[38] Other fetal side effects include fetal growth restriction and oligohydramnios, and maternal side effects include hypertension, diabetes mellitus, mood changes, and an increased risk of infection.[37] A large

randomized trial is needed to confirm the role of fluorinated steroids regarding the modification of the natural history of CAVB *in utero*.

In fetuses with complete CAVB and a heart rate <55 beats/min, β-sympathomimetic therapy combined with dexamethasone increased fetal heart rate[36] and reduced the morbidity and mortality.[39] Two widely used β2 adrenergic receptor agonists are oral salbutamol (10 mg every 8 h with a maximum dose of 30 mg/day) and terbutaline (2.5–7.5 mg every 4–6 h with a maximum dose of 30 mg/day), which increase the fetal ventricular rate by approximately 5–10 beats/min.[32] Maternal side effects include adrenergic nervous system stimulation, which can lead to tremors, palpitations, and sweating. Several retrospective studies demonstrated that a β2 adrenergic receptor agonist plus a fluoridated steroid had a positive inotropic effect on the fetal heart, reducing myocardial damage.[33,39]

Efficacy to increase heart rate and prevent heart failure of beta-sympathomimetic agents alone was documented in many case reports.[40–43] But data from other studies demonstrated inconsistent and insignificant effects for raising the fetal ventricular rate.[39,44] Furthermore, there are no studies demonstrating that the use of these medications can modify the survival of the fetuses.

IVIG and plasmapheresis aim to reduce the levels of circulating maternal autoantibodies, in order to minimize damage to the fetal heart. In a small non-randomized study, IVIG (400 mg/kg every 3 weeks from 12–24 weeks of gestation) have been shown to have potential roles in the prevention of the recurrence of CAVB among pregnant women who have had a previous child with CAVB.[12,45,46] Plasmapheresis and IVIG combined with a corticosteroid have been shown to revert second degree AVB to first degree AVB and stabilize the progression of complete AV block.[47,48] This combination can be used for treatment in fetuses with cardiomyopathy/endocardial fibroelastosis with or without complete AV block.[49] For invasive procedure, percutaneous implantation of a cardiac pacemaker was successfully placed *in utero* in experimental studies. Nevertheless, the procedure seriously jeopardized the fetus for intrauterine fetal demise.[50,51]

Delivery and Neonatal Outcomes of CAVB

Risk of intrauterine fetal demise is 22%[36] and neonatal mortality is 11–16%,[39,52] which are significantly increased due to CAVB. Infant death usually occurring in the first 3 months of life.[53] CAVB neonates who survive after the neonatal period have a good prognosis.[4] Preterm CAVB neonates have poorer outcomes than term CAVB neonates, so preterm delivery should only be performed when there are strong indications, such as non-reassuring fetal status (NRFS), severe fetal growth restriction, or hydrops fetalis.

Delivery is a critical period in pregnancies that are complicated with CAVB (especially for mothers with SLE) and these pregnancies require comprehensive maternal intrapartum management and fetal monitoring. In particular, for fetuses with second-degree or complete CAVB, monitoring the atrial heart rate and biophysical profile could help to confirm the healthy status of the fetus during labor.

Neonates with CAVB need specialized care by pediatric cardiologists and neonatologists. Evaluation of the heart rhythm and other signs of neonatal lupus are essential. About three-quarters of neonates with complete AV block required a pacemaker.[14] The severity of CAVB can progress after birth, so treatment is required in the neonatal period.[54]

Conclusion

The presence of anti-SSA/Ro or anti-SSB/La antibodies during pregnancy carries a significant risk for the fetus, and cases of CAVB require intensive antepartum, intrapartum, and neonatal management. To minimize the morbidity and mortality, understanding the natural history of the disease and knowing the current available therapeutic options are important. Many studies on the prevention and treatment of CAVB are being conducted. The knowledge in this field is continuously developing and continuous update is required.

Disclosure

The author reports no conflicts of interest for this work.

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