Fetal manifestations of maternal anti-Ro and La antibodies – more than complete heart block

Abstract

Complete heart block (CHB) is a potentially fatal condition occurring in approximately 1:10000 fetuses. Whilst it is well recognised that maternal anti-Ro and La antibodies are associated with fetal CHB, there are multiple other manifestations of fetal exposure to these autoantibodies which are not widely appreciated and rarely diagnosed. The importance of identifying affected fetuses lies in the significantly increased risk of recurrence in future pregnancies, and the potential for treatments which may modify this risk. This paper presents several cases to highlight the varying fetal presentations of maternal anti-Ro and La antibodies.

Keywords: anti-ro and la antibodies, complete heart block, fetal echocardiography.
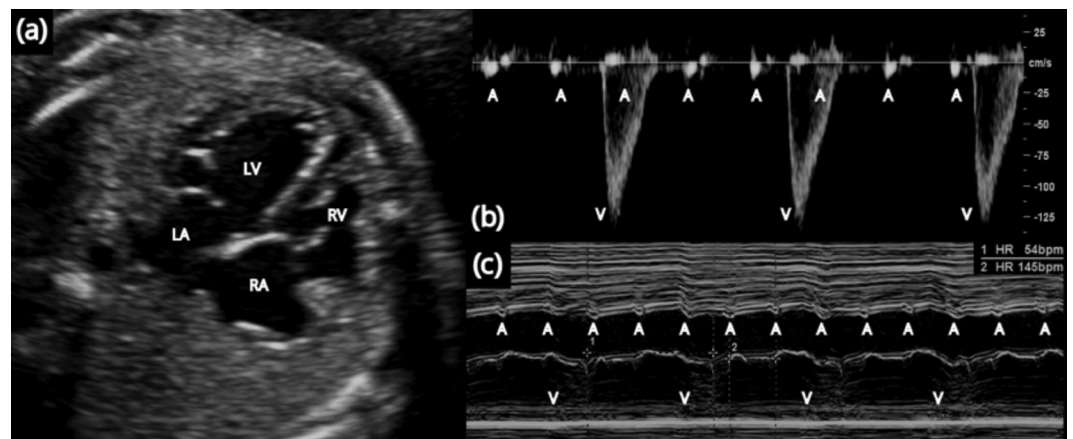
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Figure 1: (a) Four chamber view with normal appearing myocardium, borderline cardiomegaly. (b) SVC/Aortic Doppler demonstrating complete atrioventricular (AV) block with no relationship between A waves of SVC flow (A) and aortic flow (V). (c) Corresponding M-mode in complete AV block with atrial (A) and ventricular (V) contractions marked. LA = Left atrium, LV = Left ventricle, RA = Right atrium, RV = Right ventricle.

Introduction

Complete atrioventricular (AV) block (also known as complete heart block (CHB) or 3rd degree AV block) is a potentially fatal condition occurring in approximately 1:10000 fetuses. Whilst it is well recognised that maternal anti-Ro and La antibodies are associated with fetal CHB, there are multiple other manifestations of fetal exposure to these autoantibodies[1-7] which are not widely appreciated and rarely diagnosed. Maternal anti-Ro and La antibodies are present in systemic autoinflammatory disorders such as systemic lupus erythematosus (SLE) but are also naturally occuring during pregnancy and present at levels associated with CHB in approximately 1:100 pregnancies.[8] The importance of identifying affected fetuses lies in the significantly increased risk of recurrence in future pregnancies, and the potential for treatments which may modify this risk.[9] This paper presents several cases to highlight the varying fetal presentations of maternal anti-Ro and La antibodies.

Case 1

A Gravida 2 Parity 1 (G2P1) mother presented at 20/40 weeks gestation for routine morphology ultrasound scanning where her fetus was noted to be bradycardic with heart rate of 65 beats/minute and mild cardiomegaly. There were no fetal anomalies noted with normal growth for gestation, normal amniotic fluid level and no evidence of fetal hydrops.

The fetus was referred for fetal echocardiography which identified a structurally normal heart with no abnormally echogenic myocardium, no tricuspid or mitral valve regurgitation. M-mode assessment
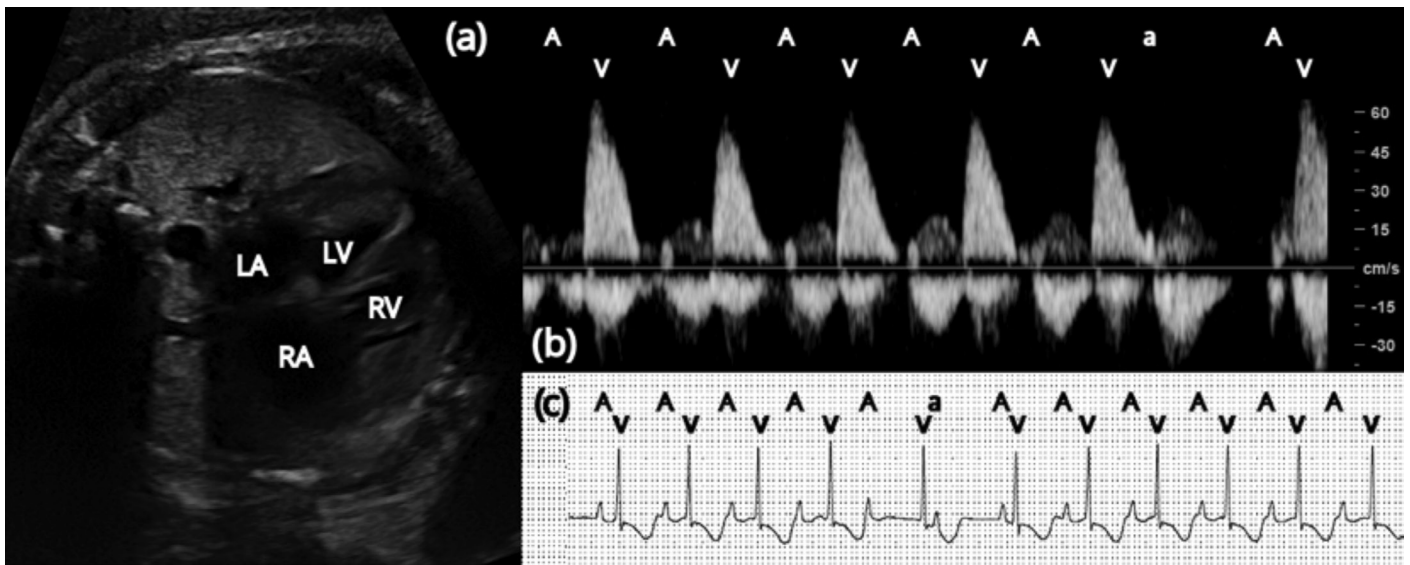
Figure 2: (a) Four chamber view demonstrating cardiomegaly and thickened ventricular myocardium bilaterally. (b) SVC/Aortic Doppler demonstrating Wenckebach conduction with increasing mechanical atrioventricular (AV) interval between A wave of SVC flow (A) and aortic flow (V). Note dropped atrial contraction (a) and shortened post block AV interval. (c) ECG post delivery confirming Wenckebach conduction. LA = Left atrium, LV = Left ventricle, RA = Right atrium, RV = Right ventricle.

through the atrial/ventricular myocardium simultaneously and Doppler assessment of superior vena cava (SVC)/Aortic flow confirmed the clinical diagnosis of CHB. See Figure 1. Maternal anti-Ro antibodies were strongly positive (weakly positive anti-La antibodies) with no clinical features to suggest maternal SLE.

The fetus was closely followed with repeat fetal echocardiography and maintained a heart rate between 55 and 65 beats/minute for the remainder of pregnancy. There was good ventricular systolic function and no sign of fetal hydrops. The fetus was born in good condition via elective caesarean section at 37/40 gestation due to a prior caesarean delivery and the difficulty of effective fetal monitoring during labour. A permanent pacemaker was inserted on day 5 of life as the baby had mild respiratory distress with a heart rate in the low 50's and difficulty establishing oral feeds (Class I indications for pacing in CHB – symptomatic bradycardia and heart rate < 55/minute in the infant.[10] Normal neonatal heart rate in the first week of life 90-165 beats/minute[11])

Further history at the time of initial fetal echocardiography noted that the mother's first pregnancy ended at 36/40 weeks gestation due to emergency caesarean delivery following rapid development of abdominal swelling and poor fetal movements. On ultrasound prior to delivery there was polyhydramnios with the fetus noted to have severe tricuspid valve regurgitation, a dilated right heart, small pleural and pericardial effusions, moderate ascites and poor biophysical profile score.

Following delivery her first child was ventilator dependent with severe tricuspid regurgitation due to a prolapsing anterior leaflet of the tricuspid valve. At surgery on day 6 of life the mechanism of the regurgitation was identified to be a flail segment of the anterior leaflet due to chordal rupture which was repaired with an excellent surgical result. The child is developing normally at 2 years of age with trivial tricuspid valve regurgitation and normal AV conduction.

Case 2

A G4P3 mother presented for ultrasound assessment of growth at 30/40 weeks gestation and was noted to have an irregular fetal heart rhythm. Ventricular ectopy was the reported diagnosis with an average heart rate of approximately 110 beats/minute. There was no fetal hydrops, normal biophysical profile score and normal amniotic fluid volume. There was a family history of supraventricular tachycardia in the family's first child without pre-excitation on his resting ECG.

A fetal echocardiogram was performed which confirmed a structurally normal heart with normal appearance of the myocardium and no AV valve regurgitation. The rhythm was identified to be predominantly sinus rhythm with frequent periods of Wenckebach (2nd degree AV block [Mobitz type I]) on SVC/Aortic Doppler flow assessment rather than the presumed ventricular ectopy. See Figure 2b. Approximately 1:10 beats were blocked followed by typical shortening of the post block AV interval. The overall heart rate varied between 105-130 beats/minute. Maternal anti-Ro antibodies were strongly positive (weakly positive anti-La antibodies) in a mother with no clinical features of SLE.

The fetus was followed closely with Doppler assessment of heart rate and fetal well-being scans. Repeat fetal echocardiography at 33/40 gestation showed generalised thickening of both left and right ventricular myocardium measuring up to 5.2 mm (normal in the second and third trimesters approximately 0.1 mm per week of gestation (See Figure 2a) and subjectively reduced myocardial contractility (fractional shortening 43%). There was borderline cardiomegaly. The fetal heart rate was approximately 105 beats/minute with up to 1:3 beats being blocked. Maternal dexamethasone was started 8mg daily for the first week and then reduced to 4mg daily.

At 34+5/40 weeks gestation the fetal rhythm had changed to have periods of apparent sinus rhythm along with intermittent AV block, at times 2:1 block for which the distinction between
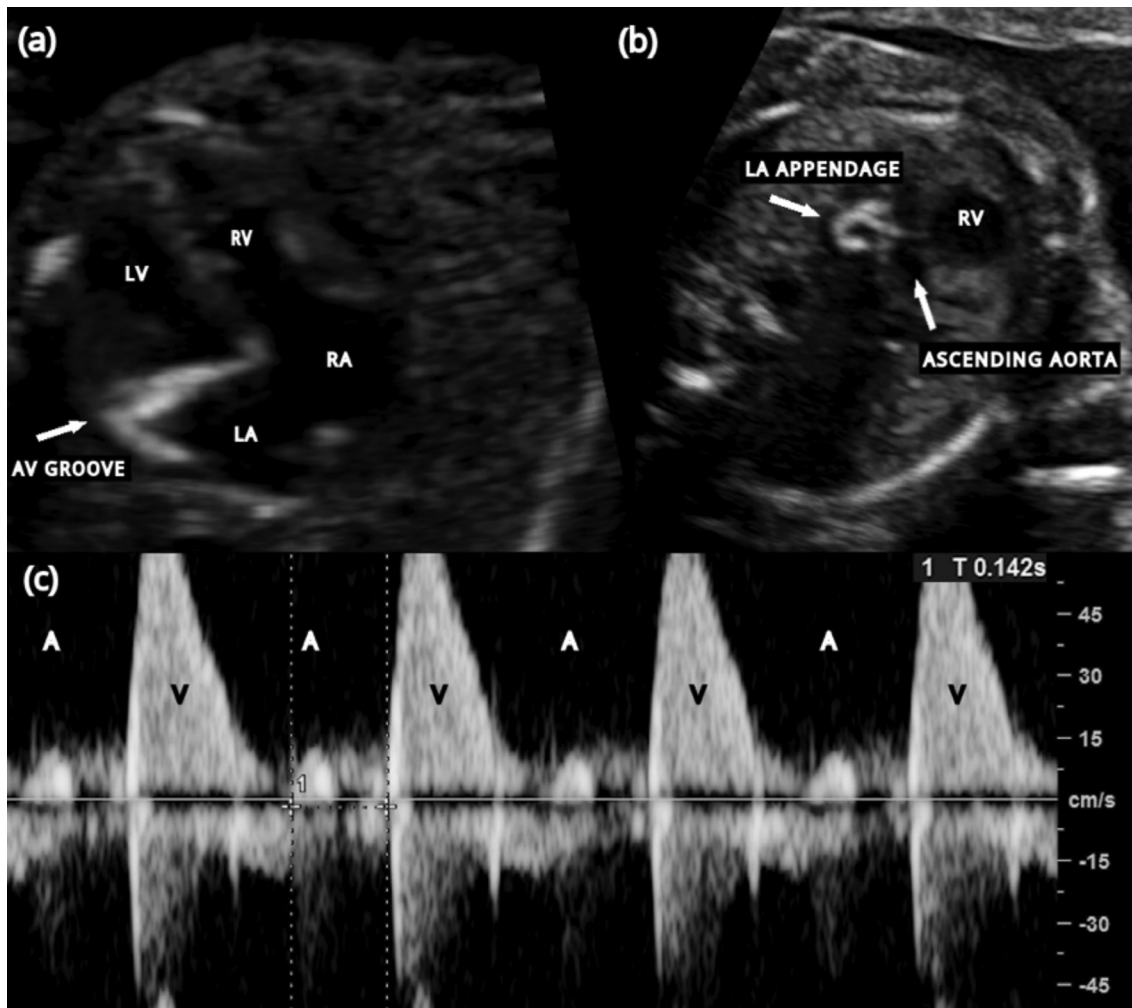
Figure 3: (a) Echogenic left atrioventricular groove onto the lateral wall of the left atrium. (b) Echogenic left atrial appendage adjacent to the ascending aorta. (c) SVC/Aortic Doppler demonstrating normal 1:1 atrioventricular (AV) conduction and measurement of mechanical AV interval. LA = Left atrium, LV = Left ventricle, RA = Right atrium, RV = Right ventricle, A = A wave of SVC Doppler flow, V = aortic Doppler flow.

Wenckebach 2nd degree AV block (Mobitz Type I) or the higher grade Mobitz type II is not possible. Average heart rate was below 100 beats/minute varying from approximately 75 beats/minute in 2:1 block to 150 beats/minute when in what appeared to be sinus rhythm. There was mild cardiomegaly (cardiac area 36%, circumference 60% of thoracic measurement).

Maternal admission was arranged for frequent fetal monitoring. A female was delivered in good condition 48 hours later by caesarean section at 35/40 weeks gestation due to poor biophysical profile.

Immediately post-delivery there was a period of sinus rhythm with 1:1 AV conduction. By 12-18 hours of life Wenckebach conduction had consistently returned as the predominant rhythm with an average heart rate of 105/minute over the next 24 hours. See Figure 2c. The heart was structurally normal on echocardiography with normal right sided pressures for a newborn infant. There was no evidence of endocardial fibroelastosis. Left ventricular end-diastolic dimension was within normal limits (-0.7 z scores) with LV and septal wall thickness at the upper limit of normal (+2.0 and +1.8 z scores respectively). There were no other significant problems of prematurity.

With close postnatal follow-up, CHB with accelerated junctional rhythm was noted on ECG at 7 weeks of age and confirmed on Holter monitoring. Left ventricular function remained normal on echocardiography with left ventricular

end diastolic dimension mildly increased (+2.5 z scores) with normal wall thickness (LV +1.3, septal wall -0.6 z scores) and no echocardiographic features to suggest pulmonary hypertension.

She remains well at 7 months of age growing and developing normally in CHB with an accelerated junctional rhythm with normal left ventricular dimensions and function.

Case 3

A G2P1 mother presented for routine morphology ultrasound scanning at 20/40 gestation where her fetus was suspected to have an abnormality of the mitral valve which was intensely echogenic. The fetus was otherwise normal with no mitral regurgitation noted. A fetal echocardiogram was arranged. The echocardiogram confirmed a densely echogenic left AV groove around the mitral valve annulus extending into the left atrium, left atrial appendage and around the aortic root. See Figure 3. AV conduction was normal with a mechanical AV interval towards the upper limit of normal for gestation. The only previous similar appearing heart encountered by the author was in the setting of CHB in a mother with anti-Ro Ab's. The presumed cause of the densely echogenic myocardium in the CHB fetus was endocardial fibroelastosis (myocardial scarring and fibrosis) which is associated with dilated cardiomyopathy and death. Maternal bloods were sent which identified strongly positive anti-Ro antibodies.

The fetus was followed closely throughout the pregnancy with the mechanical AV interval remaining within normal limits, and normal appearing ventricular functional parameters throughout the pregnancy. Following delivery an ECG confirmed normal AV conduction with a PR interval within normal limits for age and heart rate. The echogenic myocardium persisted, however, over the first 3 months of life became less echogenic relative to the remainder of the heart. Left and right ventricular function and AV conduction remained normal throughout follow up in the first year of life.

Discussion

Whilst CHB is the most widely studied and recognised aspect of fetal exposure to anti-Ro antibodies, there are numerous reports of complications beyond those illustrated in this report. These include sinus bradycardia[6], first degree AV block[1,3], second degree AV block[2], atrial flutter[2], tricuspid valve chordal rupture with severe tricuspid regurgitation[5] and dilated cardiomyopathy.[4,7]

Maternal anti-Ro and La antibodies are present in the multisystem autoinflammatory disorder systemic lupus erythmatosis (SLE), Sjogren's syndrome and other autoimmune disorders. These autoantibodies are also naturally occurring in otherwise well women without clinical features of autoimmune disease in 7.6% (anti-Ro) and 5.0% (anti-La) of pregnancies, with 1.2% of women having moderate to high anti-Ro titres putting their fetuses at risk of developing CHB in a recently published study of 15198 women.[8] With the incidence of CHB of 1:10000-15000 pregnancies, less than 1% of women with moderate to high titres of anti-Ro antibodies will have a fetus with CHB. However, women with SLE and moderate to high titres of anti-Ro antibodies had a 6.9% chance of a fetus with CHB in the same study (approximately 10x the risk of the women with no features of autoimmune disease).

The autoantibodies are able to cross the placenta and are associated with inflammation throughout the fetal myocardium with a predilection for the conduction tissue of the atrioventricular node.[7,12,13] Experimental models have demonstrated prolongation of AV conduction in fetal mice exposed to high concentrations of anti-Ro antibodies,[14] whilst exposure in susceptible individuals hypothetically related to HLA haplotype can result in endocardial fibroelastosis (EFE) reflecting permanent injury.[15] The importance of identifying EFE is that whilst it only occurs in only approximately 5% of cases of CHB, it is present in 33% of deaths.[16] Case 3 was particularly concerning given the possible EFE with high titre positive anti-Ro antibodies and therefore risk of development of AV block and or cardiomyopathy related to myocardial injury.

Treatment for established CHB does not reverse the damage to the AV conduction system. Debate still exists as to the benefits of corticosteroid therapy if given to all fetuses with CHB.[17] One of the most important reasons for identification of an affected child is the potential for protection of the subsequent fetus, with a recent historical cohort reporting a potential protective effect of maternal hydroxychloroquine against development of CHB.[9] The incidence of recurrence of CHB in subsequent pregnancies exposed to hydroxychloroquine was 7.5% vs untreated 21.7%. This remains an area of ongoing research to develop strategies for prevention. The risk of CHB in a pregnancy subsequent to one of the less serious manifestations described above is unknown.

The cases noted in this report demonstrate several of the complications of maternal anti-Ro and La antibodies which are often not identified due to lack of recognition of the varying presentations in the fetus. The first case in particular highlights a theoretical missed opportunity for prevention of CHB in the subsequent pregnancy had maternal anti-Ro and La antibodies been considered as the cause tricuspid valve chordal rupture.

Finally, as demonstrated in the figures, accurate assessment of fetal arrhythmias requires careful Doppler and M-mode examination. At any gestation, abnormal fetal rhythm which is not clearly due to atrial ectopy (the commonest non-sinus rhythm in the fetus) warrants further expert evaluation.

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