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REVIEW ARTICLE

Echogenic Fetal Heart Without Conduction Defect in Maternal Autoimmune Disease: A Lesser Known Association

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Abstract Positive anti-Ro/SSA and anti-La/SSB antibodies in pregnant mothers are strongly associated with fetal congenital heart block (CHB). Increased echogenicity of fetal endo-myocardium is one of the lesser known manifestations of maternal autoimmune disease. In this retrospective analysis of data from the last ten years (2010–2019) at our fetal medicine unit, we identified nine fetuses presenting in the second trimester with isolated increased echogenicity of the endo-myocardium without CHB. In three cases, mothers had a pre-existing autoimmune disease. The others were diagnosed with positive autoimmune antibodies following evaluation for the echogenic fetal heart. One fetus developed a first-degree heart block at 33 weeks and another had a second-degree heart block three weeks after presentation. There was no fetal mortality. All were live-born. One fetus with tachycardia and ventricular dysfunction died within a few days of birth. Both babies with heart block are stable and on medical follow-up, while others remain asymptomatic with a normal rhythm. There seems a spectrum of fetal disease caused by maternal auto-antibodies affecting the endo-myocardium but sparing the conduction system. In fetuses with echogenic hearts, evaluation of maternal autoimmune status should be part of the protocol for optimal fetal and maternal care.

Keywords Fetal echocardiography · Echogenic heart · Anti Ro/SSA · Anti La/SSB · Congenital heart block · Endocardial fibroelastosis · Fetal lupus

Introduction

Autoimmune congenital heart block (CHB) is a passive, immune-mediated, acquired medical condition that is seen in the fetus/infant of a mother who has an autoimmune medical condition and/or is positive for relevant autoantibodies [1]. These antibodies are known to cross the transplacental barrier in-utero, deposit in the myocardium, and result in inflammation, fibrosis, and ultimately irreversible myocardial damage. These may damage the conduction tissues during fetal development leading to blocking of signal conduction at the atrioventricular (AV) node in an otherwise structurally normal heart [2]. The severity of this autoimmune CHB is well illustrated by a global mortality rate of 20% and a pacemaker rate of 64% [3]. Apart from CHB, other cardiac manifestations include transient fetal first-degree heart block, sinus bradycardia, late-onset dilated cardiomyopathy (DCM), endocardial fibroelastosis (EFE), echogenic endo-myocardium and cardiac malformations [4]. Also, valvular insufficiency resulting from dysfunction of the tensor apparatus is considered to be a severe complication of autoimmune congenital heart block and has been demonstrated in 1.6 percent of cases [1].

Fetal growth restriction, increased rates of preterm delivery and pre-eclampsia are some of the commonest extracardiac complications of maternal autoantibodies

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affecting the pregnancy and its overall outcome [5]. Endocardial fibroelastosis (EFE) is known as a form of myocardial fibrosis seen on echocardiography as patchy echogenicity on the endocardial surfaces of the fetal heart. Endocardial fibroelastosis has been reported in about 7% of infants affected by congenital heart block [1].

As isolated endo-myocardial involvement seems a lesser-known entity, we describe a cohort of fetuses who had 'echogenic heart' but no heart block at presentation, in mothers positive for anti-Ro and/or anti-La antibodies.

Methods

Retrospective data retrieval was carried out on fetuses reported as having 'echogenic heart' in antenatal ultrasound from Jan 2010 to Dec 2019 in our unit. Obstetric history, ultrasound and fetal echocardiography (FE) findings were analysed. Among these, fetuses of mothers with either known autoimmune disease or detected to be anti-Ro, anti-La antibody-positive following abnormal FE status were selected for antenatal and postnatal analysis. Fetuses with associated structural heart disease or with heart block at the time of presentation were excluded from the study.

A total of nine cases were identified from the available medical records. Apart from a detailed anatomical survey on ultrasound, these fetuses had been evaluated for growth, amniotic fluid, and associated aneuploidy soft markers like nuchal fold, ventriculomegaly, pelviectasis, echogenic small bowel, humerus length, nasal bone and aberrant right subclavian artery (ARSA). Fetal diagnosis of 'echogenic heart' was made by fetal echocardiography either following suspicion in routine ultrasound or when referred for FE. Fetal endo-myocardium showing increased echogenicity at the ventricular wall, valvular surface, crux of heart, septae or walls of outflows were described as 'echogenic heart'. Echogenicity was usually compared with the echo density of bone to exclude over-diagnosis caused by suboptimal machine settings. Fetal echocardiography included functional assessment of heart and mechanical PR interval measurement once echogenicity was detected. Mechanical PR interval was measured using pulsed Doppler technique, plotted against gestational age and fetal heart rate and considered abnormal if it was beyond an upper limit published by Wojakowski et al. [6] As per our policy, these mothers were advised testing for anti-Ro, anti-La antibodies and TORCH screening as part of the initial workup. Prenatal genetic testing was advised whenever idiopathic arterial calcification was suspected. Maternal age, underlying diagnosis of autoimmune diseases, parity, history of miscarriages, cardiac illness or congenital heart block in the family and usage of maternal medications especially corticosteroids were noted. Ultrasound findings at the time of the diagnosis and in-utero follow up details of these fetuses were retrieved. Post-natal clinical findings and echocardiography details were obtained from available medical records provided by parents with informed consent.

Results

A total of nine fetuses of mothers with positive autoimmune antibodies were diagnosed with an 'echogenic heart' without atrioventricular (AV) block or bradycardia at the time of detection. (Figs. 1, 2) Maternal characteristics are shown in Table 1. The median gestational age at the time of diagnosis was 21 weeks 2 days and the median maternal age was 25 years. One case was a twin pregnancy in which the other twin had demised in-utero. Three mothers (cases 1, 2, 3) were known cases of Sjogren syndrome and were already on treatment. Positive anti-Ro/anti-La antibody status in the rest (67%) was discovered only after the evaluation of the echogenic fetal heart. Cases 4, 7 and 8 received maternal dexamethasone as fetal therapy. Case 4 and 8 had significant ventricular dysfunction wherein the team decided to try dexamethasone to improve in-utero survival; Case 7 developed 2nd degree heart block at 23 weeks of gestation when dexamethasone was indicated by our center's policy. (Fig. 3) TORCH screening was done by four patients and none of these showed evidence of recent infection.

Three mothers (cases 5, 8, 9) did not come for an in-utero follow-up to our center, but we included them in the study group as we could collect information on the post-natal outcome in all. In-utero FE and follow-up review findings are shown in Table 2. All but one had a normal rate and rhythm at presentation. Case 8 had tachycardia with 1:1 AV conduction (refer to Fig. 4 and Online Resource 1) which had persisted till delivery, which was presumed to be due to myocarditis caused by inflammation. Case 7 developed a second-degree heart block three weeks after the presentation and case 4 showed a first-degree block at 33 weeks on follow-up. The rest had normal AV conduction and rate throughout. Among the sites which showed echogenicity, the aorta was most commonly affected followed by atrioventricular junction/ AV valves. Pericardial effusion was significant only in the cases which showed ventricular dysfunction. Cases 4 and 8 showed ventricular dysfunction at presentation; this was considered to be caused by myocardial inflammation in the former who had moderate effusion too and in case 8 it was probably tachycardia-induced or myocarditis. One fetus developed growth restriction during late gestation when all others showed normal growth patterns throughout the

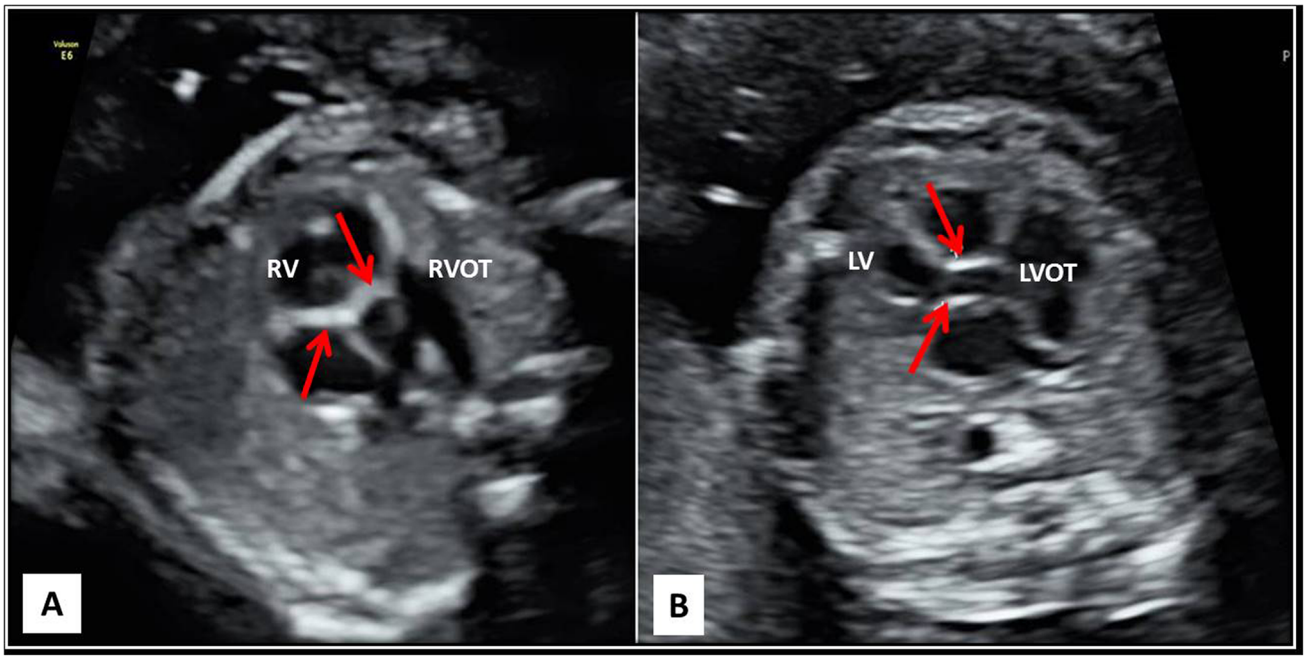

Fig. 1 Representative image showing echogenic sites (red arrows) in the fetal heart (A) Right ventricular outflow (RVOT) view shows increased echogenicity of the aorta, tricuspid annulus and infundibulum. (B) Left ventricular outflow tract (LVOT) view shows an echogenic wall of the aorta

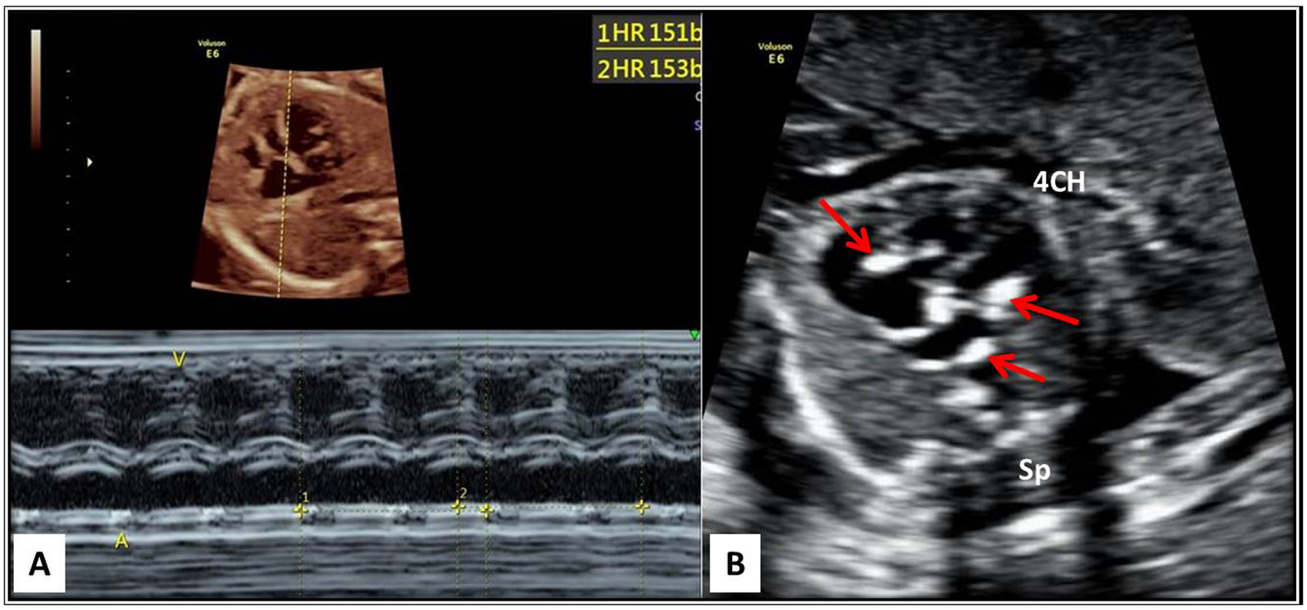

Fig. 2 (A) M mode rhythm assessment of the echogenic fetal heart shows normal 1:1 atrio-ventricular conduction with normal rate. A-atrium, V-ventricle (B) Representative image of apical four-chamber view (4CH) with red arrows showing increased echogenicity of Crux, Atrioventricular valves, atrial wall and atrial septum

pregnancy. Among the three who had soft aneuploidy markers, only one had invasive genetic testing showing normal karyotype.

All were live-born non-dysmorphic babies with seven delivered at full term. Preterm birth was seen in the cases which developed heart block on follow-up (Cases 4 and 7). The baby with persistent tachycardia demised soon after birth. All others survived and were asymptomatic with only two on medical follow-up for heart block. Postnatal data with follow-up details are shown in Table 3.

Table 1 Depicts antenatal maternal characteristics

S. No	Maternal age (years)	Gravida	Known autoimmune disease	CHB or LUPUS in offsprings	Indication for Referral	Gestational age at diagnosis	Antenatal treatment for autoimmune disease
1	29	Third	YES	Yes; fetal CHB, terminated	Maternal autoimmune disease, Previous CHB	20 weeks	Corticosteroids†, IVIG
2	24	Primi	YES	NO	Second opinion as atrio-ventricular valve thickening	23 weeks + 2 days	Corticosteroids†
3	27	Primi	YES	NO	Maternal autoimmune disease	21 weeks + 5 days	Corticosteroids† and HCQ
4	30	Primi (Twin Gestation-twin B)	NO	NO	Second opinion for TWIN A IUFD, TWIN B as ?hydrops fetalis	21 weeks	Corticosteroids*
5	22	Primi	NO	NO	Second opinion for Echogenic Outflow Tracts	22 weeks + 4 days	Corticosteroids† and HCQ
6	25	Primi	NO	NO	Second opinion For Echogenic Aorta	21 weeks + 2 days	Corticosteroids†
7	24	Primi	NO	NO	Routine anomaly scan and FE	20 weeks	Corticosteroids*
8	25	Second	NO	Yes; fetal CHB, terminated	Second opinion as suspected cardiac abnormality	20 Weeks + 3 days	Corticosteroids*
9	33	Second	NO	NO	II opinion for suspected cardiac disease	24 weeks + 1 day	No treatment taken

CHB complete heart block; *HCQ* Hydroxychloroquine; *IUFD* intrauterine fetal demise; *dexamethasone; †prednisolone

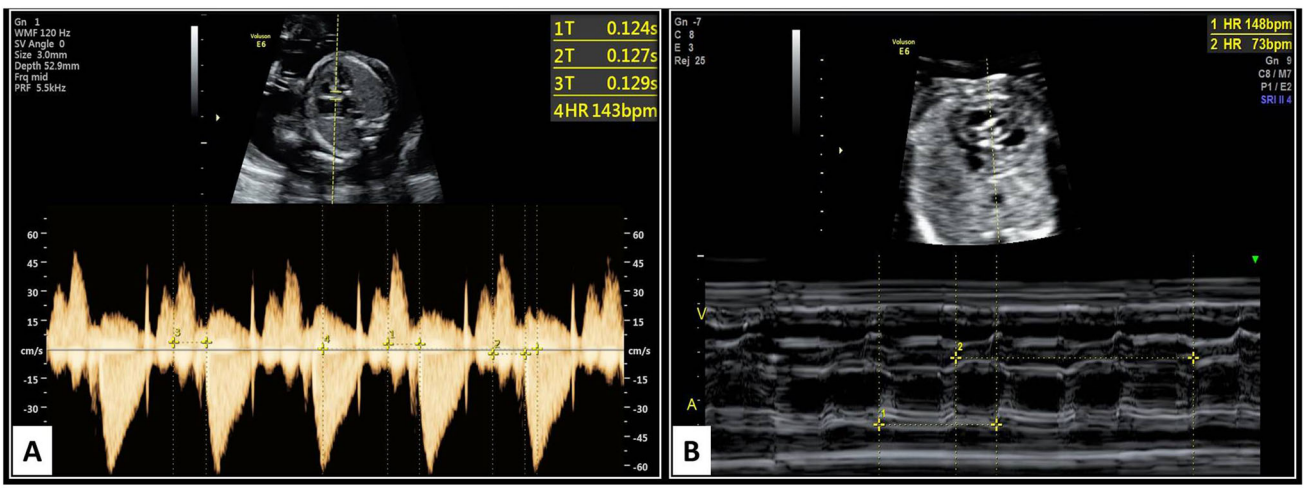

Fig.3 Spectral Doppler image for case no. 7 showing **a** Normal PR interval and normal FHR at 20 weeks gestation. **b** At 23 weeks gestation, fetus developed A-V block with a ventricular heart rate of 64–76 bpm

Discussion

Based on observations made in this case series, we want to highlight the type of 'fetal lupus' where only 'echogenic heart' can be the presenting feature. To the best of our knowledge, this study seems to be the largest series of isolated 'fetal echogenic heart' in maternal autoimmune disease reported so far in the literature. This is probably because of our unit's policy on evaluating maternal anti-body status in all echogenic fetal hearts, which evolved due

Table 2 Shows fetal echocardiographic findings.

Sr. No	Areas showing echogenicity	Heart size	Rhythm	FHR	PR interval (ms)	Pericardial Effusion	Ventricular function	Growth	Liquor	Aneuploidy soft markers	In-utero review
1	Aortic and mitral valve annuli	N	N	145	N (126)	No	N	N	N	None	Normal rhythm; oligohydramnios at 32 weeks
2	Ventricular septum, aortic and pulmonary valves	N	N	152	N (122)	No	N	N	N	Unossified Nasal Bone	Normal rhythm
3	Tricuspid and mitral valve	N	N	134	N (102)	No	N	N	N	None	Normal rhythm
4	Crux, subaortic area and aortic valve	Increased	N	158	N (136)	Moderate	Biventricular Dysfunction	N	N	None	1st degree heart block at 33 weeks (PR interval 170 ms)— persistent till term
5	Crux and aorta	N	N	152	N (128)	No	N	N	N	None	Normal rhythm*
6	aorta and crux, multiple echogenic foci In both ventricles	N	N	151	(130)	Mild	N	N	N	None	Mild biventricular hypertrophy at 32 weeks; Normal rhythm
7	Crux and outflow tracts	N	N	143	N (127)	No	N	N	N	None	Fetal bradycardia at 23 weeks with varying AV block (2^{nd} and 3^{rd} degree) ventricular heart rate 64–76/min. With mild pericardial effusion, TR and MR, cardiomegaly. Remained same till 35 weeks with growth in lower centiles as GA advanced
8	Outflow tracts	Increased	Tachycardia with 1:1 conduction	234	Abnormal	Mild	Biventricular Dysfunction	N	N	DV a wave reversal, Echogenic small bowel	Details not known*
9	Endocardium Of Right ventricle	N	N	150	N (124)	Mild	N	N	N	Unossified Nasal Bone	Normal rhythm*

Case serial number order as shown in Table 1

Crux atrioventricular junction; *DV* ductus venosus; *N* Normal

*In these cases in-utero review was carried out elsewhere

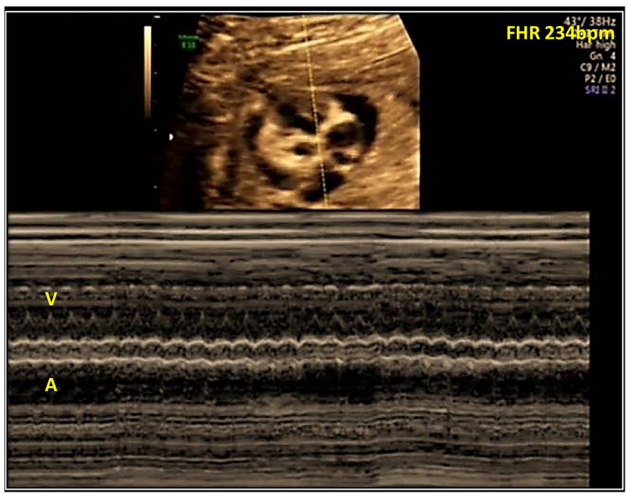

Fig. 4 Spectral Doppler image for case no. 8 showing echogenic endo-myocardium, mild pericardial effusion and tachycardia (FHR 234 bpm) with 1:1 AV conduction

to the observation of echogenic hearts in antibody-induced fetal heart blocks. The fact that in 6 mothers the antibody-positive status was detected only after fetal evaluation for echogenic heart explains the need for awareness of this entity amongst fetal care physicians, which is the main aim of this study. In our observation, the association with maternal autoimmune status is less commonly/rarely considered when a fetus presents with signs of endo-myocardial inflammation unless heart block is the presenting feature, and commonly carried out investigations are for infective or genetic etiology.

The association of endocardial fibroelastosis with echogenic endo-myocardium and autoantibody-associated congenital heart block was first reported by Hogg in 1957 [7]; whereas the positive correlation of maternal autoantibodies and congenital AV block was originally suggested from a single case report published in 1966 [8]. Most of the studies reported after that have established this association but none of these had cases with isolated fetal cardiac echogenicity [1, 3, 4]. In 2002, Nield et al. [2] reported three cases of severe endocardial fibroelastosis, mainly ventricular in children without CHB born to mothers with anti-Ro/SSA antibodies. For the first time, using immune-histochemical studies, they successfully demonstrated that the fetal immune system played a role in the evolution of myocardial damage seen in these patients. Two other publications by authors Raboisson et al.[9] and Pises et al.[10] had mentioned similar observations.

Unless maternal autoimmune antibody testing is made part of the protocol, the actual incidence of fetal cardiac involvement may remain under-reported. Evaluation for autoimmune status is beneficial not only for the fetus but has important implications for the mother too, as many mothers may develop clinical signs and symptoms later in life [11]. Besides, the presence of maternal autoantibodies places subsequent offspring at risk of fetal or neonatal lupus and heart block.

Another condition that can mimic ‘echogenic heart’ is ‘Idiopathic arterial calcification’, but endo-myocardial involvement is extremely rare in it and maternal auto-antibodies will be negative [12]. In 5 cases TORCH infection could not be ruled out by testing, as all of these mothers had positive auto-antibody titers, they were considered unlikely to have a primary infective cause.

With only one postnatal mortality in this series, the in-utero survival and short term postnatal outcome in the survivors seems reasonable, as including the 2 babies who have the likelihood of getting a permanent pacemaker in the future, all others remain asymptomatic. Due to the small number of cases with different maternal therapy methods, it is not possible to comment on the association between maternal variables and postnatal outcomes. However, as steroids have been shown to improve in-utero survival in fetal heart blocks [13], we wonder if it had a role in our cases too. In the case of postnatal mortality, we could only presume the cause of death to be due to the detrimental effect of tachycardia, myocarditis or both as the demise happened immediately after birth and detailed evaluation was not performed. In two cases where heart block evolved after the first presentation, the progression to heart block was rapid in one case and slow in the other. The latter case progressing further to second-degree block one year after birth, implicates either an ongoing inflammation or sequelae of fibrosis.

Despite the information provided by prenatal evaluation, the required attention was not seen to be given during postnatal assessment in many. Information on functional parameters or the nature of endo-myocardium was not mentioned in the postnatal reports. Only in two cases, the autoimmune status of babies was mentioned in the records. And a cardiac follow-up plan was not mentioned except in those with heart blocks. There is a necessity for regular cardiac workup in these children to rule out persistent myocardial damage and only then we may be able to understand the long term prognosis as well as their future risk for cardiovascular disease.

Conclusion

Isolated echogenic endo-myocardium without heart block can be the presenting feature in fetuses of mothers with positive autoimmune antibodies. The in-utero course seems variable with some progressing to heart block. Fetal survival and short term postnatal outcome seem better than that reported for fetuses who present initially with heart

Table 3 Postnatal demography of all cases; case serial number order as shown in Table 1

S. No	Gender F/M	Birth Wt (kg)	Term/ Preterm	Mode of delivery	Immediate status after birth	Evaluated for Lupus	Echo after birth	Postnatal rhythm	Neonatal outcome	Latest follow-up
1	F	2.25	Term	LSCS	Asymptomatic, malar rash	Yes. Positive	Normal	Normal	asymptomatic	4.5 years, Alive and Healthy
2	F	2.9	Term	LSCS	Asymptomatic	No	Normal	Normal	asymptomatic	14 months old; Alive and healthy
3	F	2.9	Term	LSCS	Asymptomatic	Yes. Normal	Normal	Normal	asymptomatic	Not known
4	M	2.8	Preterm	LSCS	asymptomatic; readmitted at 60 days of life; treated for sepsis and seizures	No	Echogenic aorta and pulmonary artery wall	Normal	Persistent 1st degree heart block - asymptomatic	1 year 6 months old, Developed 2:1 heart block at 1 year; Echo-normal; on medical follow-up*
5	M	2.7	Term	LSCS	Observed for Meconium stained liquor, asymptomatic	No	Small subaortic VSD, Small secundum ASD, Mild TR, Moderate PAH, Dilated RA,RV	Normal	asymptomatic	18 months old; asymptomatic; on medical follow-up
6	M	2.5	Term	NVD	Asymptomatic	No	Normal	Normal	asymptomatic	1 year old; Alive and healthy
7	F	2.08	Preterm	LSCS	Asymptomatic	No	Normal ventricular function, Mild TR, Trivial MR	Complete heart block, rate 66/min	asymptomatic	2 months old, asymptomatic, On follow-up
8	F	3	Term	NVD	Tachycardia intrapartum and after birth	No	Not done	tachycardia	Succumbed	–
9	F	2.25	Term	LSCS	Asymptomatic	No	Normal	Normal	asymptomatic	8 months old- Alive and healthy

*only case in which follow-up echo could be done in our center. *LSCS* caesarean section, *NVD* normal vaginal delivery, *VSD* ventricular septal defect, *TR* tricuspid regurgitation, *MR* mitral regurgitation, *ASD* atrial septal defect, *PAH* pulmonary artery hypertension, *Echo* echocardiography

block. Increased awareness about this entity is essential among the fetal and postnatal care-providers to know the actual incidence, intra-uterine course and postnatal long term sequelae of this fetal cardiac finding.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Consent for Publication Written informed consent taken from the patients.

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