Spectrum of fetal echocardiographic findings in fetuses of women with clinical or serologic evidence of systemic lupus erythematosus

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Abstract

Objective. To assess the prevalence of cardiac abnormalities in fetuses of women with clinical or serologic evidence of systemic lupus erythematosus (SLE).

Methods. A retrospective review of fetal echocardiograms performed secondary to maternal SLE or connective tissue antibodies with or without fetal complete heart block (CHB) was performed to evaluate the prevalence of fetal structural heart disease, valve regurgitation, abnormal ventricular function, pericardial effusion, endocardial fibroelastosis and rhythm abnormalities.

Results. Forty-one fetuses were studied. One fetal demise occurred. Three fetuses had structural abnormalities, including d-transposition of the great arteries ($n = 1$) and pulmonic stenosis ($n = 2$). Seventeen fetuses had valve regurgitation. The prevalence of valve regurgitation was: tricuspid ($n = 15$), mitral ($n = 6$), pulmonic ($n = 4$) and aortic ($n = 2$). Two fetuses with pulmonic insufficiency had pulmonic stenosis. Four fetuses had CHB, one of which developed atrial flutter. Prolongation of the mechanical AV interval occurred in five fetuses; none developed CHB.

Conclusions. In addition to CHB and myocardial dysfunction, structural heart defects occur in fetuses of women with serologic or clinical evidence of SLE. In our series, this occurred more frequently than reported for the general population. Valve regurgitation was present in all fetuses with CHB and many in sinus rhythm and may represent cardiac inflammation. Pulmonic insufficiency *in utero* may be a marker for a structural valve abnormality.

Keywords: *Lupus erythematosus, systemic, congenital heart defect, heart block, fetal echocardiography*

Introduction

Neonatal heart block and myocardial dysfunction are the most commonly known sequelae of exposure to maternal systemic lupus erythematosus (SLE) antibodies. Recently, prolongation of the QTc interval, first and second degree heart block and sinus bradycardia have also been reported in this population [1].

Although congenital heart disease has been reported to occur at higher frequency in fetuses with complete heart block (CHB) [2–4], the prevalence of structural heart disease in fetuses with exposure to maternal connective tissue disease antibodies has not been well described. The pathogenesis of structural heart disease is still incompletely understood and likely multifactorial. Evidence suggests that certain *in-utero* maternal factors that affect the fetal environment may be associated with congenital cardiovascular defects [5].

Valvular heart disease is a clinically important form of structural heart disease in adult patients with SLE. Acquired valve thickening and/or regurgitation in adults is a significant cause of morbidity and mortality in this group [6].

We sought to determine the frequency of cardiac abnormalities identified by fetal echocardiography in fetuses referred for evaluation because of maternal SLE or anti-SSA or anti-SSB antibodies documented either in the presence or absence of associated fetal cardiac conduction abnormalities.

Methods

A retrospective review of fetal echocardiograms and medical records was performed in women referred to

the Fetal Heart Program of Children's National Medical Center between 2001 and 2006 because of either: 1) clinical evidence of maternal SLE or presence of maternal anti-SSA or anti-SSB antibodies associated with SLE or other connective tissue diseases such as Sjogren syndrome or 2) diagnosis of maternal lupus or documentation of positive antibodies after referral for fetal CHB was made. This study was approved by the Children's National Medical Center IRB. Records were reviewed for: 1) clinical evidence of maternal SLE or presence of maternal anti-SSA or anti-SSB antibodies (determined either prior to echocardiogram or subsequent to diagnosis of fetal CHB); 2) age of mother; 3) other maternal medical conditions; 4) medication exposure. Fetal echocardiograms were reviewed for: 1) abnormalities in intracardiac structure; 2) cardiac rhythm; 3) mechanical atrioventricular (AV) interval; 4) valve regurgitation; 5) cardiac ventricular function and 6) presence of a pericardial effusion. The mechanical AV interval, which is representative of the postnatal electrical PR interval, was defined as the measured time interval in milliseconds between the onset of the mitral A wave (beginning of atrial systole) and the onset of aortic outflow on a Doppler tracing in the 5-chamber echocardiographic view [7] (Figure 1). If abnormalities were identified on the fetal scan, a postnatal echocardiogram was reviewed if available. Gestational age of the fetus at first echocardiogram, and number of studies done at our institution were also recorded.

All fetal echocardiograms were performed on a Phillips 7500 or IE 33 machine with a curvilinear c3540 probe or 3–8 mHz phased array transducer.
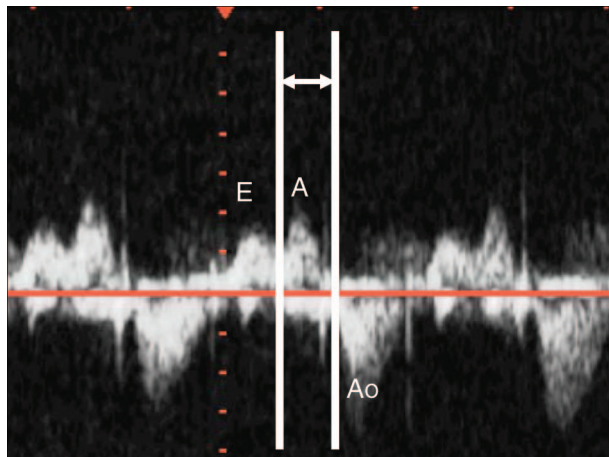

Figure 1. Mechanical atrioventricular interval on a fetal M-mode tracing. The mechanical atrioventricular interval (AV) is the measured time interval in milliseconds between the onset of the mitral A wave to onset of aortic outflow on a Doppler tracing in the 5-chamber echocardiographic view. A, a wave of active mitral filling; Ao, ventricular output; E, passive mitral filling. Arrows denote the AV interval.

Women were advised to follow-up at 1–2 week intervals.

Valve insufficiency was defined as visualisation of a color Doppler signal after valve closure. Fetal echocardiograms were interpreted by a single reader specialising in fetal imaging.

Results

Of a total of 3312 fetal echocardiograms performed during the study period, 136 were done secondary to diagnosis of maternal SLE or positive SLE antibodies. A total of 41 fetuses in 35 women with clinical or serologic evidence of SLE were evaluated. Of these, there was a single fetal demise identified during imaging. The etiology of this demise is unknown. Demographics of mothers evaluated are documented in Table I. Antibody profiles are documented in Table II. Echocardiographic findings are shown in Figure 2.

Congenital complete heart block

CHB occurred in four of 40 (10%) surviving fetuses. Figure 3 shows Doppler evidence of AV dissociation with a normal atrial rate and low ventricular escape rate. There were no deaths secondary to CHB. Two patients with CHB had pericardial effusions. Three of four patients (75%) received a pacemaker in the

Table I. Demographics of study population.

Number of women	35
Number of fetuses	41
Maternal age (mean, range)	30 (17–42) years
Gestational age at presentation (mean, range)	23 weeks (12–36)
Echocardiograms per fetus (mean, range)	3.6 (1–12)
Coexisting risk factors	Advanced maternal age (8)
	Asthma (1)
	Maternal diabetes (1)
	Family history of heart disease (1)
	None (18)
	Maternal renal disease (1)
	Paternal Marfan (1)
	Maternal methyltetrahydrofolate reductase deficiency (1)
	Maternal rheumatoid arthritis (1)
	Unknown (2)

Table II. Antibody profile of women referred to our center for an indication of maternal SLE or SLE antibodies.

Anti SSA only	6
Anti-SSA and anti-SSB	6
Clinical SLE, antibody profile not specified	14
Lupus antibody positive, specific type unspecified	7
Anticardiolipin	2

first 2 weeks of life. One patient was followed without a pacemaker and had a ventricular rate of >70 beats/min. One patient with CHB went on to develop a cardiomyopathy thought to be pacing induced, which improved after changing to a biventricular pacemaker system. One patient with CHB had endocardial fibroelastosis of the right and left ventricles diagnosed *in utero* (Figure 4), and devel-

oped atrial flutter at 30 3/7 weeks gestation (Figure 5), prompting delivery by emergent Caesarean section.

Structural heart disease

Structural heart defects occurred in 7.5% of fetuses in the study population. One fetus in sinus rhythm had d-transposition of the great arteries and two fetuses with CHB had a thickened and stenotic pulmonary valve. Figure 6(a,b) shows the postnatal cross-sectional and longitudinal images of the pulmonary valve in a fetus diagnosed with pulmonic stenosis. Pulmonic stenosis was defined by abnormal valve morphology with leaflet thickening, post-stenotic dilatation of the main pulmonary artery
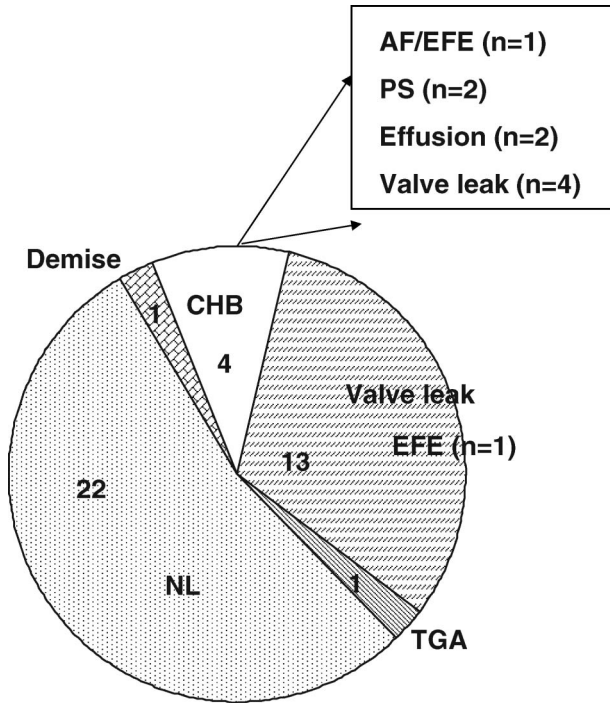

Figure 2. Summary of echocardiographic findings in fetuses of women with SLE or SLE antibodies. AF, atrial flutter; CHB, complete heart block; EFE, endocardial fibroelastosis; NL, normal; PS, pulmonic stenosis; TGA, transposition of the great arteries.
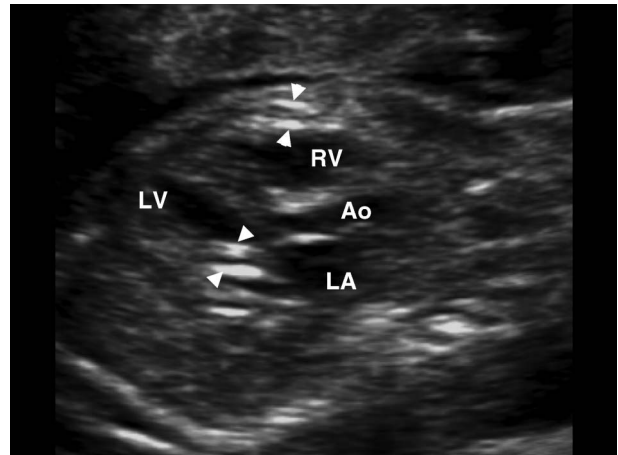

Figure 4. Endocardial fibroelastosis in the right and left ventricles of a fetus with congenital complete heart block. Arrows show areas of brightness suggestive of endocardial fibroelastosis. Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.
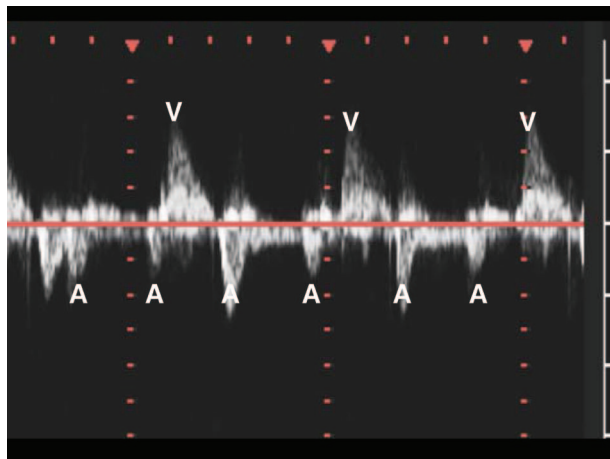

Figure 3. Congenital complete heart block in a fetus exposed to maternal SLE antibodies. Doppler tracing showing atrioventricular dissociation in a fetus with congenital complete heart block. A, atrial contraction; V, ventricular contraction.
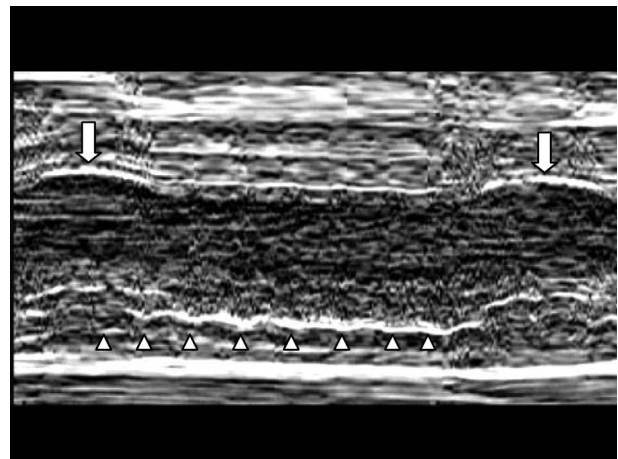

Figure 5. M-mode of fetus with complete heart block showing atrial flutter. Triangles indicate atrial contractions and arrows indicate ventricular contractions. The atrial rate was 460 and ventricular rate was 60.
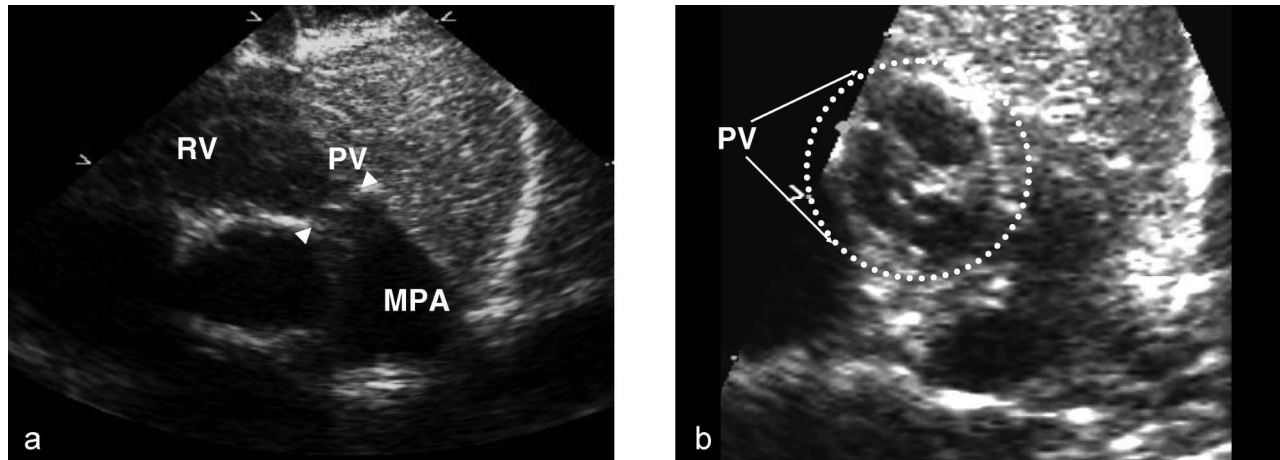
Figure 6. Valvar pulmonic stenosis in a neonate with complete heart block. (a) Parasternal short axis view showing the pulmonic valve in a fetus with pulmonic stenosis and complete heart block. Note the thickened valve leaflets and post-stenotic dilatation of the main pulmonary artery. MPA, main pulmonary artery; PV, pulmonary valve; RV, right ventricle. Triangles point to the thickened valve. (b) Pulmonic valve en face in a neonate with pulmonic stenosis. Note the circle outlining the valve. PV, pulmonary valve.

and turbulence by color Doppler at the level of the valve. Both fetuses with valvar pulmonic stenosis developed pulmonic insufficiency *in utero*. Peak gradients by Doppler were 19 and 31 mmHg, and postnatal intervention was not performed.

Valve regurgitation

Valve regurgitation occurred in 17 of 40 fetuses (42.5%). Regurgitation of all valves was seen. Fifteen fetuses had tricuspid regurgitation, six fetuses had mitral regurgitation, four fetuses had pulmonic regurgitation and two fetuses had aortic regurgitation. In the majority of cases, this was a transient phenomenon and resolved prior to delivery.

The four patients with CHB had regurgitation of multiple valves. This included the mitral and tricuspid valve in all four cases, and the pulmonic valve in three cases. Two of the fetuses with pulmonary insufficiency developed pulmonic stenosis. In addition, two fetuses in sinus rhythm had transient insufficiency of multiple valves. One of these fetuses was born to a mother with a previous child with CHB. The fetal echocardiograms were otherwise normal, with no ventricular dysfunction or rhythm disturbances. In one fetus with tricuspid regurgitation and pulmonary insufficiency, the pulmonic insufficiency resolved prior to birth. In the second fetus, aortic, mitral and tricuspid insufficiency resolved prior to birth.

Isolated valve regurgitation of only the tricuspid, mitral or aortic valve was observed in 11 fetuses in sinus rhythm. Nine patients had isolated tricuspid regurgitation. It was graded as trivial in eight and mild in one; trivial is defined as the presence of a color jet of insufficiency that occurred during systole after valve closure, but that is not holosystolic.

Of these, seven had *in-utero* resolution, one had postnatal resolution and one with tricuspid regurgitation from 23–27 weeks had no postnatal echocardiogram. None of these fetuses had arrhythmias or structural heart disease *in utero*. One fetus had trivial mitral insufficiency *in utero*, but postnatal follow-up was not available. One patient had trivial aortic insufficiency at 21 weeks and mechanical AV interval prolongation from 0.09 to 0.13–0.14 s during the time the insufficiency was documented. The aortic insufficiency resolved prior to delivery. This fetus was noted to have increased echogenicity in both ventricles suggestive of echogenic foci versus myocardial scarring of the right and left ventricular papillary muscles (Figure 7). After delivery, the baby had normal ventricular function and the echobright foci, though present, were not thought to be clinically significant.

Lupus antibody status

Eleven of 15 fetuses with tricuspid regurgitation had mothers with known positive antibody status; four of 11 were the fetuses with CHB. All three fetuses with pulmonic insufficiency had mothers with known positive antibody status (two with CHB). The mother of the fetus with TGA was referred for SLE; however, specific antibody status is unknown. Of six fetuses with mitral regurgitation, five had positive antibody status (four with CHB). Of two fetuses with aortic insufficiency, one had positive antibody status and one had unknown antibody status.

Heart function

Heart function could be measured by M-mode shortening fraction in 20 studies. Fractional
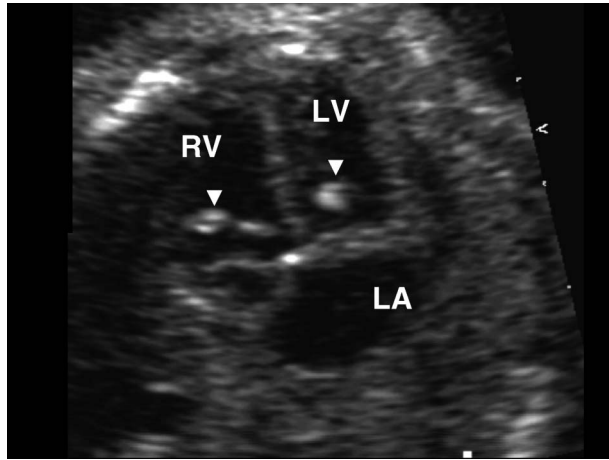
Figure 7. Biventricular endocardial fibroelastosis in a fetus. Areas of echogenic foci in both ventricles on fetal echocardiogram of a fetus with trivial aortic insufficiency and prolongation of the mechanical AV interval. These areas were thought to represent endocardial fibroelastosis. Arrows indicate the echogenic foci. LA, left atrium; LV, left ventricle; RV, right ventricle.

shortening ranged from 28% to 53%, which is considered normal by calculated z-scores in our laboratory.

Mechanical AV interval

The mechanical AV interval could be assessed in 103 of 136 studies. The mechanical AV interval was found to be prolonged by greater than 2 standard deviations above normal to 0.14 s in five fetuses in sinus rhythm. Four fetuses were referred after a diagnosis of CHB, and mechanical AV interval data prior to developing heart block were not available. None of the five fetuses with a prolonged AV interval went on to develop CHB. Two of these five fetuses had tricuspid regurgitation, and 1 had aortic insufficiency. Of note is that no fetuses had an AV interval > 3 SD above normal, the criteria utilised for initiation of *in-utero* therapy in a recent large prospective trial evaluating the utility of mechanical AV interval monitoring in fetus born to mothers with connective tissue antibodies [8].

Maternal medications

No medications were initiated for signs or symptoms relating to the fetal heart. In some cases mothers were treated with steroids as part of standard care for SLE, or with dexamethasone by their maternal-fetal medicine specialist. Overall the following numbers of women were treated with medications during pregnancy: terbutaline (1), dalteparin (1), prednisone or unspecified type of steroids (11), low molecular weight heparin (1), hydroxychloroquine (7), aspirin (6), labetalol (1), calcitriol (1), dexamethasone (2)

and azathioprine (1). No correlation was noted between initiation of medications and any fetal echocardiographic parameter study.

Discussion

In this study of fetuses of women with clinical or serologic evidence of SLE, structural heart defects occurred in 7.5% of fetuses, which is more common than reported for the general population [9]. Valve regurgitation was also common, occurring in 42.5% of fetuses in this population.

An increased prevalence of congenital heart disease has been reported in fetuses with CHB, but has not been well described in fetuses of women with SLE or related antibodies. In a series of 165 pregnancies with connective tissue disease and anti-SSA antibodies, the prevalence of anatomic cardiac abnormalities was found to be 2.8%, also higher than the general population [10]. Abnormalities included d-transposition of the great arteries with pulmonary hypoplasia and ventricular septal defect, univentricular malformation, pulmonary hypoplasia and isolated ventricular septal defect. Interestingly, the lesions identified in our study were similar, with one fetus having transposition of the great arteries and two fetuses having pulmonary valve disease. The linkage between transposition of the great arteries and SLE is unknown, and this finding could be sporadic. The mother of the fetus in our study was of advanced maternal age at 35 years, and had active lupus, but did not have any other known maternal risk factors found to be associated with fetal cardiac conal truncal abnormalities. Given the retrospective nature of this study, her specific antibody status is unknown. Given that major cardiac morphogenesis is completed by 8 weeks gestation, the increased prevalence of this structural defect is unclear. A larger population based analysis should be undertaken to identify potential causes of the increased prevalence of structural heart disease in fetuses with SSA antibodies and/or CHB. The possible association between pulmonic stenosis and SLE is more obvious, since in our series this finding was limited to fetuses with CHB, and accompanied by pulmonary insufficiency. Pulmonary valve disease may represent the result of an antibody-mediated valvulitis. Both fetuses in our study had thickened valve leaflets with decreased mobility. Nodules along the pulmonic and tricuspid valve cusps have been described on a pathologic examination of an expired fetus with CHB [11], and pulmonic stenosis and pulmonary and tricuspid valve abnormalities have been described in infants with CHB in a national neonatal lupus registry. [2] Pulmonic stenosis in these cases may represent a form of congenital heart defect that was acquired

during fetal life secondary to intrauterine exposure to maternal antibodies.

Valve regurgitation of single and multiple valves was common in our study population. Interestingly, for the majority of fetuses, valve insufficiency was identified during the period between 19 and 31 weeks, which parallels the course of antibody mediated CHB which typically occurs between 18 and 24 weeks gestation [2]. One fetus did develop mild tricuspid regurgitation at 37 weeks, simultaneous with an abnormal Doppler pattern suggestive of restriction in the patent ductus arteriosus. In the two patients with pulmonary valve abnormalities, pulmonary insufficiency was noted on the fetal scan. In all cases of trivial mitral, aortic and tricuspid regurgitation, the valve regurgitation did not prove to be clinically significant. In adults, valvulitis of the mitral and aortic valves can occur in patients with SLE [6,12]. We speculate that a transient antibody mediated valvulitis or inflammation of the papillary muscles resulting in regurgitation may take place in fetuses of women with SLE or asymptomatic women with SLE-related antibodies. Fetuses with CHB and valvar pulmonic stenosis may represent the more severe and non-transient spectrum of the disease process.

The significance of trivial or mild tricuspid regurgitation on fetal echocardiogram is controversial. The prevalence of fetal tricuspid regurgitation in structurally normal hearts has been reported to be as high as 6.8%. Huhta and colleagues [13] report that when valve regurgitation is present, a causative agent can be found in most cases and the valve insufficiency likely represents abnormal physiologic conditions. Abnormal conditions in his study included pericardial effusion, abnormal rhythm, atrial septal aneurysm, congestive heart failure, myocardial hypertrophy or extracardiac malformation [13]. In our high risk population, isolated tricuspid insufficiency was a transient phenomenon in almost all cases and was not associated with fetal morbidity. Further research is needed to determine whether the tricuspid regurgitation was due to transient abnormalities in cardiovascular physiology, valvulitis induced by lupus antibodies or a normal finding.

In-utero pulmonic insufficiency in our series was associated with postnatal structural pulmonary valve disease. Although the valve disease was not significant enough to merit intervention, both babies born with pulmonic stenosis will undergo serial follow-up to assess for progression of valve disease. Valve pathology was not noted in fetuses with aortic and mitral valve insufficiency, though the numbers of fetuses in these groups was small.

A future area of investigation will be a more detailed analysis of the maternal serology in fetuses with valve regurgitation to determine whether valve regurgitation is associated with anti-SSA and anti-SSB antibodies, similar to CHB, or whether antiphospholipid antibodies, which have a controversial role in adult SLE valve pathology, play a role.

Limitations of this study include the small sample size and limitations inherent in retrospective studies. In addition, because this was a retrospective review, a significant limitation is that maternal antibody status and steroid treatment regimens for all patients were not available through the medical records at our institution. However, 19/35 patients had documentation of being 'lupus antibody' positive, with 12/19 (%) explicitly listing anti-SSA and/or anti-SSB antibodies. Fourteen women had clinical findings of SLE with unavailable antibody status. These women were referred from maternal-fetal medicine specialists, whose practice it is to refer mothers for fetal cardiac evaluation only when anti-SSA or anti-SSB are positive. Our database query terms did yield two women with anticardiolipin antibodies, neither of whom had findings and whose exclusion would not change the findings of our study.

Our results suggest that fetuses born to mothers with clinical or serologic evidence of SLE, with or without conduction abnormalities, exhibit a spectrum of cardiac abnormalities that extend beyond CHB and myocardial dysfunction. These fetuses may be at increased risk for structural heart defects, particularly those involving the valves and how they function. We believe that these valve abnormalities represent a form of congenitally acquired structural heart disease. Larger prospective studies on fetuses born to mothers with SLE, both with and without conduction abnormalities, are needed to assess not only heart rate and rhythm, but also cardiac function, structure and valve morphology.

Acknowledgements

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