Ultrasound Obstet Gynecol 2001; **18**: 131–134

Cardiac function in fetuses with intracardiac echogenic foci

S. DEGANI, Z. LEIBOVITZ, I. SHAPIRO, R. GONEN and G. OHEL

Department of Obstetrics and Gynecology, Bnai Zion Medical Center and Faculty of Medicine, Technion — Israel Institute of Technology, Haifa, Israel

KEYWORDS: Cardiac function, Doppler ultrasound, Fetal echocardiography, Intracardiac echogenic focus/foci

ABSTRACT

Objective *To evaluate cardiac dimensions and function in euploid fetuses with intracardiac echogenic foci.*

Study design *Forty-eight fetuses with a single cardiac echogenic focus situated in the left ventricle had echocardiography performed at 22–24 weeks of gestation. Fifty normal fetuses at 22–24 weeks' gestation served as controls. Two-dimensional and M-mode directed fetal echocardiography were used to exclude cardiac anomalies and measure right and left ventricular free walls and interventricular septal thickness and ventricular systolic and diastolic dimensions. Cardiac size was expressed as a ratio of ventricular wall thickness/biparietal diameter, and cardiac function was expressed as ventricular shortening fraction. Doppler fetal echocardiography measurements included pulmonary and aortic maximum systolic velocities and time to peak velocities as indices of ventricular systolic function, and the ratio between early ventricular filling (E-wave) and active atrial filling (A-wave) peak velocities at the level of the atrioventricular valves as an index of ventricular diastolic function.*

Results *Early ventricular filling/active atrial filling peak velocity ratios were significantly lower in fetuses with intracardiac echogenic foci than in control fetuses. In the mitral valve the ratio was 0.37 ± 0.14 (0.039) (mean ± SD (95% confidence interval for difference between the means)) vs. 0.59 ± 0.19 (0.052) and in the tricuspid valve it was 0.42 ± 0.16 (0.045) vs. 0.62 ± 0.21 (0.058). No significant differences were found in cardiac dimensions, ventricular shortening fraction and Doppler systolic indices.*

Conclusion *Euploid fetuses with intracardiac echogenic foci show low E/A ratio values in midtrimester echocardiography. This finding might indicate cardiac diastolic dysfunction.*

INTRODUCTION

Intracardiac echogenic foci (ICEF) in the chromosomally normal fetus are not associated with an increased risk of cardiac anomaly[1–10]. These small, discrete structures that probably represent microcalcifications of the papillary muscles[11–13] move in synchrony with atrioventricular valves during the cardiac cycle. The foci tend to persist over gestation; however, reports regarding postnatal resolution are varied. Most series in which neonatal echocardiography was obtained demonstrated persistence of the ICEF[1,2,6], while others reported resolution of the foci in 20–90% of cases[7–9]. Although cardiac dysfunction has not been reported in recent literature on ICEF in euoploid fetuses, the significance of ICEF to cardiac function has not been explored.

The purpose of our study was to evaluate cardiac dimensions and function in euploid fetuses with ICEF and compare them to structurally and chromosomally normal controls.

MATERIAL AND METHODS

The study group consisted of 48 fetuses at 22–24 weeks of gestation following a previously diagnosed single echogenic focus in the left ventricle. The foci were detected on routine transvaginal examination at 14–17 weeks of gestation. These fetuses were then compared with 50 similarly aged normal fetuses undergoing routine sonographic examination. Cases with either multiple foci or right ventricular foci that have been reported as poor prognostic signs[14] were not included. Fetuses with abnormal prenatal follow up or postnatal outcome were excluded from the study.

Fetal surveillance included dating and a targeted sonographic examination at an appropriate gestational age. Studies were performed with one of two scanners (Ultramark 9, HDI, Advanced Technology Laboratories Inc., Bothell, WA, USA and Diasonics Synergy, GE, Haifa, Israel) with 3.5- or 4–7-MHz convex probes.

Fetal measurements included biparietal diameter, abdominal circumference, femur length, estimation of fetal weight and cardiac/thoracic area.

Two-dimensional fetal echocardiography was used to exclude a structural cardiac anomaly.

M-mode directed fetal echocardiography included measurements of left and right ventricular free wall and interventricular septal thickness and ventricular systolic and diastolic

Correspondence: Dr S. Degani, Department of Obstetrics and Gynecology, Ultrasound Unit, Bnai Zion Medical Center, POB 4940, Haifa 31048, Israel (e-mail: sdegani@tx.technion.ac.il)

Received 18-8-00, Revised 18-2-01, Accepted 23-3-01

dimensions. The M-mode cursor was placed perpendicular to the interventricular septum just below the atrioventricular valves at the level of the four-chamber view and tracings were recorded at 50 mm/s. A biventricular activity tracing was used to measure ventricular wall and interventricular septal thickness with electronic calipers.

Cardiac size was expressed as ratio of wall thickness/biparietal diameter and cardiac function was expressed as ventricular shortening fraction ((ventricular diastolic dimension – ventricular systolic dimension)/ventricular diastolic dimension).

Doppler fetal echocardiography measurements included: (1) pulmonary arterial and aortic maximum systolic velocities (2) time to peak velocity which was calculated as the time difference from the onset of the waveform to its peak velocity[15] and (3) the ratio between E-wave (early ventricular filling) and A-wave (active atrial filling) peak velocities (the E/A ratio)[16] at the level of both atrioventricular valves as an index of ventricular diastolic function. Doppler measurements were repeated three times in each case by the same operator (S.D.).

Statistical significance was determined by a two-tailed Student's *t*-test to compare group mean values; when the criteria for conducting the *t*-test were not met, the non-parametric Wilcoxon Rank-Sum Test was applied to the data.

RESULTS

Successful measurements and Doppler recording were obtained in all cases. Resolution of the echogenic foci occurred by 22–24 weeks of gestation in 8 of 48 (17%) cases. At birth, none of the infants had clinical signs of cardiac failure. Neonatal echocardiography was performed in 39 infants of the study group; persistent ICEF at the level of the chordae and papillary muscles was demonstrated in 38 infants.

Maternal–fetal characteristics

Clinical characteristics of the study and control groups were similar; there was no significant difference between maternal age, parity, gestational age at examination, and sonographic estimated fetal weight between the two groups.

Table 1 Fetal cardiac two-dimensional measurements

Measurement	*Study group* (n = *48*) *(mean ± SD)*	*Control group* (n = *50*) *(mean ± SD)*
GA (weeks)	23 ± 1.5	23 ± 1.4
CA/TA	0.29 ± 0.15	0.28 ± 0.06
IVST (mm)	3.13 ± 0.57	2.92 ± 0.47
RVWT (mm)	2.94 ± 0.72	2.43 ± 0.55
LVWT (mm)	2.92 ± 0.64	2.29 ± 0.54
IVST/BPD	0.05 ± 0.01	0.06 ± 0.02
RVWT/BPD	0.05 ± 0.01	0.05 ± 0.01
LVWT/BPD	0.06 ± 0.02	0.05 ± 0.01

There were no significant differences between study and control groups. GA, gestational age; CA/TA, cardiac/chest area; IVST, interventricular septum thickness; RVWT, right ventricular wall thickness; LVWT, left ventricular wall thickness; BPD, biparietal diameter.

Fetal cardiac two-dimensional echocardiographic measurements

Cardiac/thoracic area ratio and ventricular walls' thickness are depicted in Table 1. The mean thickness of the right and left ventricular walls and of the interventricular septum in the study group were higher than those of the control group, although the differences were not statistically significant.

Fetal cardiac function

No significant difference was found in ventricular shortening fraction (Table 2) of both cardiac ventricles as compared to controls.

Doppler fetal echocardiography

The intraobserver coefficient of variation for the Doppler measurements was 8.9%. The atrioventricular waveforms obtained showed a characteristic biphasic pattern. The E/A ratios were significantly lower in fetuses with ICEF than in control fetuses (Table 3, Figure 1). The mean fetal heart rate (± SD) was 144 ± 15 bpm; no influence was found on E/A values in this range. No significant differences were found in either aortic or pulmonary artery peak velocities or in time to peak velocities.

DISCUSSION

Intracardiac echogenic foci have been sonographically detected in 0.5–20% of fetuses[2,17] with an overall frequency of 5.6%[7]. These structures typically measure 1–4 mm in diameter but can be as large as 18 mm[4,5]. Descriptions such as 'peas', 'bright reflectors' or 'golf balls'[3,18,19] reflect the bone-like echogenicity of the foci in their intracardiac location. Multiple echogenic foci or diffuse echogenicity in the fetal heart, especially when the right ventricle is also involved, have been described in association with other pathologies and may signal poor prognosis[14].

The origin of ICEF is not clear; it has been suggested to be the embryologic result of incomplete fenestration of the

Table 2 Fetal ventricular contractility function

Measurement	*Study group* (n = *48*) *(mean ± SD)*	*Control group* (n = *50*) *(mean ± SD)*
GA (weeks)	23 ± 1.5	23 ± 1.4
RVDD (mm)	7.84 ± 2.30	7.89 ± 2.43
LVDD (mm)	7.79 ± 2.41	7.80 ± 2.29
RVDD/LVDD	1.04 ± 0.06	1.05 ± 0.03
RVSD (mm)	4.62 ± 1.91	4.99 ± 1.78
LVSD (mm)	4.36 ± 2.11	4.78 ± 2.21
RVSF (%)	0.41 ± 0.05	0.36 ± 0.04
LVSF (%)	0.44 ± 0.09	0.39 ± 0.04
RVSF/LVSF	0.93 ± 0.06	0.92 ± 0.05

There were no significant differences between study and control groups. GA, gestational age; RVDD, right ventricular diastolic dimension; LVDD, left ventricular diastolic dimension; RVSD, right ventricular systolic dimension; LVSD, left ventricular systolic dimension; RVSF, right ventricular shortening fraction; LVSF, left ventricular shortening fraction.

chordae tendinae or excessive thickening of the papillary muscles[1,17]. Abnormal development of the microvasculature may lead to early ischemic changes in the papillary muscle[12]. Studies have shown that microcalcifications of the papillary muscles correspond to the sonographically localized echogenic foci[11–13].

Fetal cardiac assessment using B-mode real time scan with the assistance of M-mode and Doppler ultrasound enables definition of cardiac developmental morphology and function. However, the role of fetal echocardiography in an otherwise normal fetus with ICEF is controversial[2,6,20]. In studies that examined fetuses or neonates, the presence of ICEF and a normal karyotype or phenotype did not confer an increased risk of congenital heart malformations[6–8].

No data have been reported on the persistence of ICEF into childhood and its significance at this age. Most series in which postnatal echocardiograms were obtained demonstrated persistence of ICEF in the majority of cases; the overall frequency of observed neonatal resolution is 44%[1,2,6–9].

Whether these foci are normal variants of the development of the atrioventricular apparatus or not, our study is the first to observe associated changes in cardiac function. Our first impression of cardiac hypertrophy with thickened ventricular septal and free walls was not substantiated by statistical analysis. Systolic function as expressed by the ventricular shortening fraction was also without significant difference as compared to controls.

Although the study group was restricted to fetuses with echogenic foci in the left ventricle only, it was surprising to find low E/A ratios in both ventricles. This unexpected finding may indicate that it is not only the papillary muscles that are involved in the ischemic changes of the microvasculature. It may be speculated that there is damage to the myocardium and that the focal calcium deposits are markers of this damage.

The lower E/A ratios at the level of both atrioventricular valves found in these fetuses might indicate impaired ventricular diastolic function. No significant modifications of systolic indices such as aortic and pulmonary peak velocities or time to peak velocity were observed in the fetuses examined. The early phase (E peak) in the biphasic pattern of Doppler flow at the atrioventricular valves represents the passive filling of the ventricles, whereas the late phase represents the active ventricular filling during atrial contraction. During intrauterine life there is dominance of the atrial phase[16,21]. This may be explained by the less compliant fetal heart compared with the postnatal myocardium[22]. The variation in E/A ratio throughout pregnancy could be influenced by cardiac preload, represented by venous return flow, and

Table 3 Fetal Doppler echocardiographic measurements

Measurement	*Study group (n = 48) (mean ± SD)*	*Control group (n = 50) (mean ± SD)*	*Significance*
GA (weeks)	23 ± 1.5	23 ± 1.4	NS
Mitral E/A ratio	0.37 ± 0.14	0.59 ± 0.19	$P < 0.005$
Tricuspid E/A ratio	0.42 ± 0.16	0.62 ± 0.21	$P < 0.005$
PV, aorta (cm/s)	63 ± 22	67 ± 24	NS
TPV, aorta (ms)	42 ± 19	39 ± 17	NS
PV, pulmonary artery (cm/s)	59 ± 25	55 ± 27	NS
TPV, pulmonary artery (ms)	38 ± 16	40 ± 19	NS

GA, gestational age; E/A, early ventricular filling/active atrial filling peak velocities; PV, peak velocity; TPV, time to peak velocity; NS, not significant.

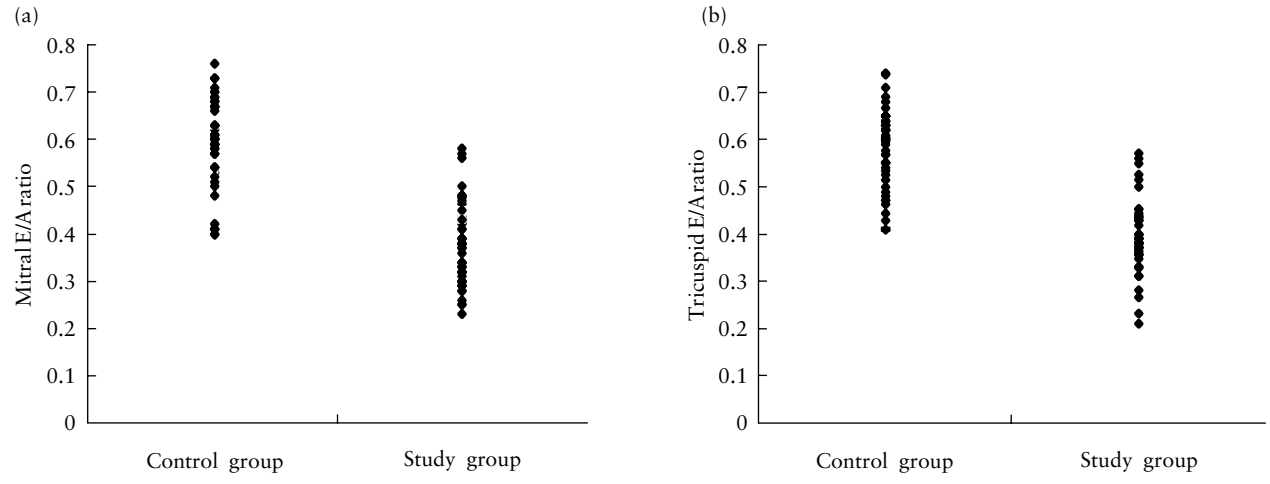

Figure 1 Individual early ventricular filling/active atrial filling (E/A) peak velocities of study group compared to control group for mitral valve (a) and tricuspid valve (b). Mitral valve 95% confidence interval between the means was 0.039 for the study group and 0.052 for the control group ($P < 0.005$); tricuspid valve 95% confidence interval between the means was 0.045 for the study group and 0.058 for the control group ($P < 0.005$).

afterload, represented by peripheral vascular resistance and the progressive decrease in placental impedance[23]. The low values of the E/A ratio may suggest decrease in preload, reduced ability of active fetal myocardial relaxation or valvular dysfunction. It has been suggested that such diastolic changes might precede systolic dysfunction[17]. A further postnatal echocardiographic study is now being undertaken to determine whether these are only transitory prenatal changes or changes that persist into infancy and childhood.

In conclusion, euploid fetuses with ICEF showed low E/A ratios on midtrimester echocardiography. This finding might indicate cardiac diastolic dysfunction, but deserves further study to clarify the significance, persistence and outcome.

REFERENCES

1 Schechter AG, Fakhry J, Shapiro LR, Gewitz MH. In utero thickening of the chordae tendinae: a cause of intracardiac echogenic foci. *J Ultrasound Med* 1987; 6: 691–5

2 How HY, Villafane J, Parihus RR, Spinnato JA II. Small hyperechoic foci of the fetal cardiac ventricle: a benign sonographic finding? *Ultrasound Obstet Gynecol* 1994; 4: 205–7

3 Simpson JM, Cook A, Sharland G. The significance of echogenic foci in the fetal heart: a prospective study of 228 cases. *Ultrasound Obstet Gynecol* 1996; 8: 225–8

4 Achiron R, Lipitz S, Gabbay U, Yagel S. Prenatal ultrasonographic diagnosis of fetal heart echogenic foci: No correlation with Down syndrome. *Obstet Gynecol* 1997; 89: 945–8

5 Manning JE, Ragavendra N, Sayre J, Laifer-Narin SL, Melany ML, Grant EC, Crandall BF. Significance of fetal intracardiac echogenic foci in relation to trisomy 21: a prospective sonographic study of high-risk pregnant women. *AJR Am J Roentgenol* 1998; 170: 1083–4

6 Petrikovsky BM, Challenger M, Wyse LJ. Natural history of echogenic foci within ventricles of the fetal heart. *Ultrasound Obstet Gynecol* 1995; 5: 92–4

7 Wax JR, Mather J, Steinfeld JD, Ingardia CJ. Fetal intracardiac echogenic foci: Current understanding and clinical significance. *Obstet Gynecol Surv* 2000; 5: 303–11

8 Dildy GA, Judd VE, Clark SL. Prospective evaluation of the antenatal incidence and postnatal significance of the fetal echogenic cardiac focus: a case control study. *Am J Obstet Gynecol* 1996; 175: 1008–12

9 Merati R, Lovotti M, Norchi S, Teatini A, Tenore AC, Belloni C. Prevalence of fetal left ventricular hyperechogenic foci in a low risk population. *Br J Obstet Gynaecol* 1996; 103: 1102–4

10 Bromley B, Lieberman E, Laboda L, Benacerraf BR. Echogenic intracardiac focus: a sonographic sign for fetal Down syndrome. *Obstet Gynecol* 1995; 86: 998–1001

11 Brown DL, Roberts DJ, Miller WA. Left ventricular echogenic focus in the fetal heart: Pathologic correlation. *J Ultrasound Med* 1994; 13: 613–6

12 Roberts DJ, Genest D. Cardiac histopathology characteristics of trisomies 13 and 21. *Hum Pathol* 1992; 23: 1130–40

13 Lehman CD, Nyberg DA, Winter TC, Kapur RP, Resta RG, Luthy DA. Trisomy 13 syndrome: Prenatal US findings in a review of 33 cases. *Radiology* 1995; 194: 217–22

14 Bronshtein M, Jakobi P, Ofir C. Multiple fetal intracardiac echogenic foci: not always a benign sonographic finding. *Prenat Diagn* 1996; 18: 131–5

15 Rizzo G, Arduini D, Romanini C, Mancuso S. Doppler echocardiographic evaluation of time to peak velocity in the aorta and pulmonary artery of small for gestational age fetuses. *Br J Obstet Gynaecol* 1990; 97: 603–7

16 Rizzo G, Arduini D, Romanini C, Mancuso S. Doppler echocardiographic assessment of atrioventricular velocity waveforms in normal and small for gestational age fetuses. *Br J Obstet Gynaecol* 1988; 95: 65–9

17 Levy DW, Mintz MC. The left ventricular echogenic focus: a normal finding. *AJR Am J Roentgenol* 1988; 150: 85

18 Vibhakar NI, Budorick NE, Scioscia AL, Harby LD, Mullen ML, Sklansky MS. Prevalence of aneuploidy with a cardiac intraventricular echogenic focus in an at risk population. *J Ultrasound Med* 1999; 18: 265–8

19 Sepulveda W, Cullen S, Nicolaidis P, Hollingsworth J, Fisk NM. Echogenic foci in the fetal heart: a marker of chromosomal abnormality. *Br J Obstet Gynaecol* 1995; 102: 490–2

20 Sepulveda W, Romero D. Significance of echogenic foci in the fetal heart. *Ultrasound Obstet Gynecol* 1998; 12: 445–9

21 Meijboom EJ, De Smedt MCH, Visser GHA, Jager W, Bossina KK, Huisijes HJ. Cross-sectional Doppler echocardiographic evaluation of the fetal cardiac output during the second and third trimester of pregnancy: a longitudinal study. In Jones CT, Nathanielsz PW, eds. *The physiological development of the fetus and newborn*. London: Academic Press, 1985: 749–52

22 Romero T, Covell J, Friedman WF. A comparison of pressure-volume relations of the fetal, newborn and adult heart. *Am J Physiol* 1972; 222: 1285–90

23 Rudolph A. Distribution and regulation of blood flow in the fetal and neonatal lamb. *Circ Res* 1985; 57: 811–21