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The association between isolated fetal echogenic cardiac foci on second-trimester ultrasound scan and trisomy 21 in low-risk unselected women

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KEYWORDS: aneuploidy screening; echogenic cardiac foci; trisomy 21; ultrasound marker

ABSTRACT

Objectives *To determine the prevalence of and the association between trisomy 21 and isolated fetal echogenic cardiac foci (FECF) identified in the second trimester in an unselected low-risk population.*

Methods *All cases with isolated FECF were collected by reviewing the antenatal ultrasound database for 3 consecutive years. In order to include all trisomy 21 cases for the same period, the regional cytogenetics database and pediatric databases were examined. A 2 × 2-table analysis was performed to establish the sensitivity, specificity and positive and negative predictive values of isolated FECF as a screening test for trisomy 21 in a low-risk unselected population.*

Results *In the 3-year period of the study the total number of deliveries was 11 105, of which 10 769 (97%) had a routine detailed anomaly scan between 16 and 24 weeks' gestation. There were 311 cases (2.9%) of isolated FECF. Among these there was only one case (0.3%) of trisomy 21. In the same period, the total number of trisomy 21 cases was 14. Accordingly, the sensitivity of isolated FECF for detecting trisomy 21 was 7.1% and the specificity was 97.1%. Positive and negative predictive values of FECF were 0.3% and 99.9%, respectively.*

Conclusion *In an otherwise healthy pregnancy, the finding of isolated FECF on a routine second-trimester anomaly scan is normal and should not be considered as a risk factor for trisomy 21 in an unselected low-risk population.*

INTRODUCTION

Microcalcifications in the human fetal papillary heart muscle, fetal echogenic cardiac foci (FECF), sometimes termed 'golfballs', may be a feature of autosomal trisomies[1,2], in particular trisomy 21[3–6] and trisomy 13[1,3,5,7]. When identified as part of a routine fetal anomaly ultrasound examination at around 20 weeks' gestation, this may lead to clinical uncertainty about the possible risk of trisomy 21[8], particularly in women at no increased risk of aneuploidy[9]. As a result, the presence of this sonographic marker may lead to unnecessary invasive investigations and additional stress for the parents. We investigated the prevalence of isolated FECF in association with trisomy 21 in a low-risk unselected pregnant population and question whether karyotyping is indicated when FECF is found at the routine second-trimester anomaly scan.

METHODS

The antenatal ultrasound database including obstetric ultrasound reports and videos of routine second-trimester anomaly scans performed between 18 and 24 weeks' gestation was reviewed for the 3 years of 1997, 1998 and 1999. All pregnancies with isolated FECF (i.e. without other associated sonographic markers or anomalies) were examined. FECF was defined as having been identified when intracardiac echogenic structures, comparable to bone and measuring more than 1 mm in diameter, were observed in the four-chamber view in the anteroposterior and transverse planes. The location and number of the foci were noted. The ultrasound machines which were used during the study period were: Toshiba Ecocee (Toshiba Medical Systems, Crawley, West Sussex, UK), UM9 ATL and ATL 3000 (Philips, Reigate, Surrey, UK) and all examinations were carried out by trained and experienced sonographers. The occurrence of trisomy 21 was established by reviewing regional cytogenetics and pediatric databases. This enabled us to identify all cases of a fetus with trisomy 21 which had had an anomaly scan in the second trimester

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and had been born in our hospital during the study period. The anomaly scan videos of those trisomy 21 cases which did not have FECF were also retrospectively reviewed to ensure that no cases with an echogenic focus had been missed. A 2 × 2-table analysis was performed to establish the sensitivity, specificity and positive predictive value (PPV) and negative predictive value (NPV) of FECF as a screening test for trisomy 21. Software Epi Info 6® was used for the statistical calculations.

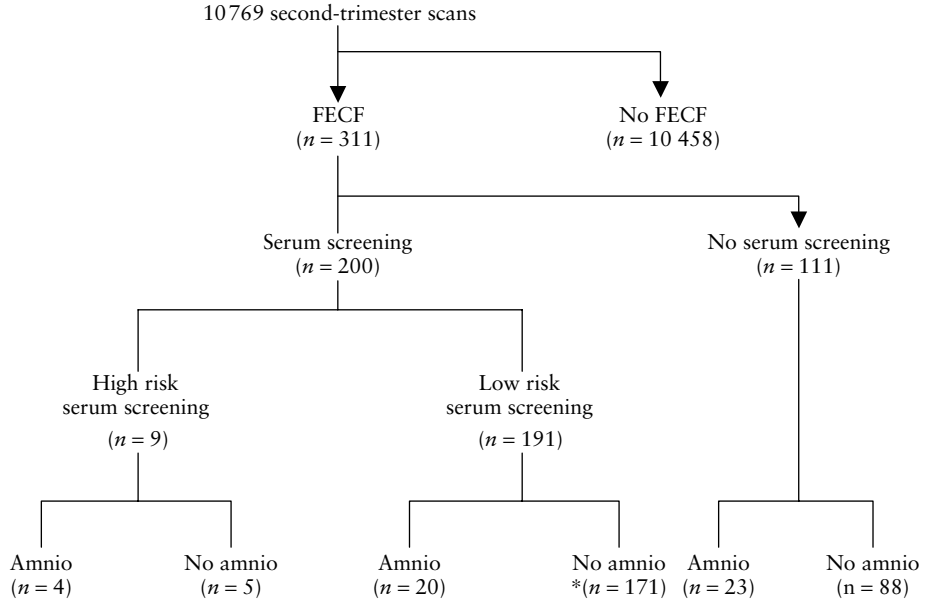
RESULTS

There were 311 cases (2.9%) of isolated FECF among 10 769 fetuses which had a detailed second-trimester (16–24 weeks) ultrasound examination during the study period. The mean ± SD age of those women with isolated FECF was 29.6 ± 5.2 (range, 16–45) years. Within the age groups: 25–29 years, 30–34 years, 35–39 years and ≥ 40 years, our study comprised 34%, 32%, 16% and 2% of women; this is similar to the age ranges of the UK's pregnant population of 34%, 28%, 10% and 2%, respectively, in the same period. The total number of women delivering a baby in this period with trisomy 21 was 14, giving a birth incidence of 0.1% ($n = 14/10\,769$) for our unselected obstetric population. Only one of these trisomy 21 babies ($n = 1/14$ (7.1%)) had an isolated FECF (Fisher's exact test, $P = 0.33$). When the ultrasound examination videos of the other 13 trisomy 21 cases were examined retrospectively, there were no cases of missed FECF among them. The rate of trisomy 21 occurring among the babies with FECF was 0.3% ($n = 1/311$). The remainder of the 310 cases of isolated FECF had no chromosomal abnormality either on fetal karyotyping or on clinical examination of the neonate before discharge. In 95% of the cases ($n = 297$) there was a single FECF. This was situated in the left ventricle of the heart in 261 cases (84%) and in the right ventricle in 36 cases (11.5%). In 20 of 311 cases (6.4%) there was more than one FECF, but the left ventricle was involved in all the cases. In 14 cases (4.5%) the FECF occurred in more than one heart chamber. Of these, 13 occurred bilaterally in the ventricles ($n = 13/311$ (4.1%)). There was one case (0.3%) in which the FECF occurred in both left atrium and left ventricle. The single case of trisomy 21 with FECF had a single focus in the left ventricle. In this case the maternal age was 37 years and her risk of trisomy 21 as a result of serum screening was estimated to be 1/365. The diagnosis was established postnatally after the woman declined karyotyping following discussion of the risks. Of the 311 cases of FECF, 200 women (64%) underwent serum screening. In 191 women (95.5%) the result was described as low risk (< 1/250). In the remaining nine cases (4.5%) the risk was described as being high (> 1/250). A total of 47 women opted for prenatal karyotyping by amniocentesis. Four of these had high-risk serum screening results and 20 had low-risk serum screening results. Twenty-three women chose to have karyotyping without serum screening. The karyotype result in all these cases was normal. A flow chart of the scheme of management is shown in Figure 1.

By analyzing 2 × 2 tables the sensitivity, specificity, PPV and NPV of FECF as an indicator for trisomy 21 were assessed. The results were 7.1%, 97.1%, 0.3% and 99.9%, respectively (Table 1).

DISCUSSION

Many studies have found no association between FECF and aneuploidy[10–15]. Previous studies which suggested



*The single case of trisomy 21 with a FECF was in this group.

Figure 1 Flow diagram showing the management of cases with fetal echogenic cardiac foci (FECF) on routine ultrasound examination.

Table 1 2 × 2-table analysis of cases of fetal echogenic cardiac foci (FECF) and trisomy 21

	Number of cases				
	Trisomy 21 (−)	*Trisomy 21 (+)*	*Total*	*Likelihood ratio*	*CI*
FECF (+)	310	1	311	2.48	0.37 to 16.43
FECF (−)	10 445	13	10 458	0.96	0.83 to 1.11
Total	10 755	14	10 769		
Sensitivity	7%				−6 to 21
Specificity	97%				97 to 97
PPV	0.3%				0 to 0
NPV	99.9%				100 to 100

Fisher's exact test, $P = 0.33$.

a link between FECF and aneuploidy, particularly trisomy 21, have been carried out in high-risk obstetric populations[2,4–6,9,16] or in a selected population at a tertiary referral center[17,18]. Those studies involving low-risk women which found no association usually involved overseas obstetric populations[12–14] and were mostly conducted in selected subpopulations[13,14], with the exception of the study by Thilaganathan *et al.*[15]. These researchers found that in an unselected obstetric population with prior, effective, routine Down's syndrome screening, the association between isolated FECF and Down's syndrome was no longer significant. As a result, a variation in obstetric practice still exists and the debate continues.

The prevalence of isolated FECF in the second trimester was 2.9% in our unselected population. There was only one case of trisomy 21 (0.3%) among the 311 cases of isolated FECF. In that case the maternal age was 37 years, but the serum screening result, which incorporates maternal age, reported a low risk of trisomy 21. The prevalence of FECF has been quoted to be as low as 0.46%[19] and as high as 22%[10] in the second and third trimesters of pregnancy. The prevalence of FECF may be affected by the timing of the ultrasound examination during pregnancy, as some FECF resolve or develop late[12,14], and also by whether the FECF was detected in pregnancies at high risk (Table 2) or low risk (Table 3) of aneuploidy. In high-risk cases, Schechter *et al.*[20] found the prevalence of isolated FECF in the second trimester to be 3.5% (26/738). When prospective studies in low-risk women are considered, the prevalence lies mainly between 0.4% and 7.4%[12–15,17,19]. However, only two of these studies[13,15] examined the prevalence of isolated FECF in the second trimester, finding it to be 0.9%[15] and 4.9%[13]. Our prevalence of 2.9% is consistent with their findings, lying within this range. Although our study was retrospective, we report the highest number of cases of isolated FECF published in the literature. We found an increasing number of FECF cases in consecutive years such that the number of cases of FECF in 1999 was more than was the number of cases in 1997 and 1998 combined. This is likely to be due to the use of higher resolution ultrasound equipment in the year 1999 which might have increased the detection rate. Increased experience of our sonographers in detecting these markers might also have played a role. As a result, the prevalence of FECF is likely to be higher than 2.9%, and if the number of cases in 1999 is considered to be more representative of the sample, the prevalence would be above 4%, similar to the prevalence quoted by Dildy *et al.*[13]. Some authors considered only left ventricular FECF[12] yet right ventricular FECF can account for up to 25% of cases[14] and this may explain the variation in reported prevalence. The overall prevalence of isolated FECF with known outcome in low-risk case studies (Table 3) was 1.8% (804/45 225). This result excludes the study by Jaffe *et al.*[18] which did not mention the sample size. In calculating the corrected prevalence of FECF in studies with high-risk cases (Table 2), the studies of Bronshtein *et al.*[21] (who only listed multiple FECF) and Bromley *et al.*[9] (who did not specify the sample size) were excluded. This resulted in a prevalence of 4% (535/13 637). The difference in prevalence between high-risk case studies and low-risk studies was highly statistically significant (Yates corrected χ^2 test = 217.78, $P < 0.001$).

Table 2 Isolated fetal echogenic cardiac foci (FECF) in case studies of populations at high risk of aneuploidy

Reference	n	*FECF* (n *(%)*)	*Aneuploidy (isolated FECF)* (n)	*Trisomy 21 (isolated FECF)* (n)
Schechter *et al.*, 1987[20]	738	26 (3.5)	1 (1)	1 (1)*
Levy and Mintz, 1988[10]	118	24 (20)	0	0
Bromley *et al.*, 1995[4]	1334	66 (4.9)	Not studied	4 (2)†
Petrikovsky *et al.*, 1995[11]	1139	41 (3.6)	0	0
Bronshtein *et al.*, 1996[21]	25 725	44 (0.17)	1 (0)	0
Bromley *et al.*, 1998[9]	Not stated	290 (−)	14 (1)	11 (1)‡
Manning *et al.*, 1998[6]	901	24 (2.7)	3 (2)	3 (2)*
Bettelheim *et al.*, 1999[27]	6995	150 (2.1)	5 (1)	3 (0)
Vibhakar *et al.*, 1999[16]	2412	204 (8.5)	18 (9)	11 (7)*
Total	39 362	869 (2.2)§	42 (14)	33 (13)

*Maternal age and serum screening status unknown. †Of the four cases, in three maternal age was advanced, and in the other the maternal serum alpha-fetoprotein level was low. ‡In the single isolated trisomy 21 case, the maternal age was 41 years. §The corrected prevalence was 4% (535/13 637) having excluded Bronshtein *et al.*[21] (only quoted multiple FECF) and Bromley *et al.*[9] (sample size not quoted).

Table 3 Isolated fetal echogenic cardiac foci (FECF) in case studies of populations at low risk of aneuploidy

Reference	*Gestation (weeks)*	n	*FECF (n (%))*	*Aneuploidy (n (%))*	*Trisomy 21 (n (%))*
How *et al.*, 1994[19]	2nd and 3rd trimesters	5395	21‡ (0.4) (unselected)	0	0
Dildy *et al.*, 1996[13]	16–24.9	506	25 (4.9) (selected)	0	0
Simpson *et al.*, 1996[17]*	14–32	3290	205 (6.2) (selected)	1 (1)	1 (0.5)
Merati *et al.*, 1996[12]	17–31	1148	33§ (3.2) (unselected)	0	0
Achiron *et al.*, 1997[14]	13–16 and 20–22	7200	163 (2.3) (selected)	0	0
Jaffe *et al.*, 1999[18]	16 (mean)	Unknown	110 (selected)	5 (4.5)	2 (1.8)
Thilaganathan *et al.*, 1999[15]	18–23	16 917	144 (0.9) (unselected)	0	0
Present study	16–24	10 769	311 (2.9) (unselected)	1 (0.3)	1 (0.3)
Total		45 225†	914	7 (0.8)	4 (0.4)

*There was another case with unbalanced translocation which was diagnosed as having diaphragmatic hernia and dysmorphic features postnatally. Also, 205 of 228 cases with known outcome were considered. †The total sample includes all the above studies except the study of Jaffe *et al.*[18]. ‡Twenty-one of 25 cases, and §33 of 37 were isolated FECF excluding other ultrasound findings.

FECF as a screening test

With only one of 311 cases of isolated FECF having trisomy 21, we calculate the sensitivity of FECF as 7.1%, specificity 97.1%, PPV 0.3% and NPV 99.9% (Table 1). When we compared the case of trisomy 21 involving an isolated FECF with the cases of trisomy 21 without FECF, the difference was not statistically significant (Fisher's exact test, $P = 0.33$; Table 1). In view of the lower prevalence of trisomy 21 (0.1%) in our obstetric population, we found a lower sensitivity (7.1%) and PPV (0.3%) for isolated FECF than did those studies of high-risk cases which examined FECF with associated sonographic anomalies. Manning *et al.*[6] found the sensitivity and PPV to be 18% and 13% in a high-risk population (trisomy 21 prevalence, 1.9%; FECF prevalence, 3%), respectively. The same figures in the study of Bromley *et al.*[4] were 18% and 6%, respectively (trisomy 21 prevalence, 1.6%; FECF prevalence, 4.9%). Bromley *et al.*[4] also extrapolated the PPV to a population of lower risk. They calculated that in women with an age-based risk of 1/1000 (equivalent to around 30 years of age) the PPV would be 0.39%, which is compatible with our findings since the median age in our series was 30 years. In a later study Bromley *et al.*[9] evaluated the risk of isolated FECF in women with ages below 35 years and 35 years and above. The risk of aneuploidy was 0% and 0.8%, respectively, which is also consistent with our findings. For younger women at lower risk of aneuploidy, this is unlikely to be an acceptable level at which women should opt for invasive prenatal karyotyping, considering the associated risk of pregnancy loss of 1%[22].

FECF and aneuploidy in high-risk cases

In case studies of women at high risk, an association has been found between FECF and aneuploidy[2,5], mainly trisomy 13[1,7] and trisomy 21[1,4,6]. Roberts and Genest[1] reviewed the pathology slides of 415 cases with aneuploidy and/or other anomalies. Seven of 18 cases (39%) of trisomy 13, and 14 of 85 cases (16%) of trisomy 21, had FECF histologically. Only six cases of the control (non-trisomy 13 and 21) cases (2%) had FECF ($P < 0.001$). Of these 27 cases of aneuploidy, 19 had FECF as part of multiple congenital anomalies. In the study by Schechter *et al.*[20], in which 738 second-trimester fetuses were studied, there was one case of trisomy 21 among 26 cases (3.8%) with isolated FECF. However, the study involved high-risk cases, and so is not comparable with our study.

Isolated FECF and aneuploidy in low-risk cases

It would be appropriate to compare our study with those that investigated the finding of isolated FECF in a low-risk population (Table 3). Two such studies[12,19] included cases with FECF which were associated with other abnormal sonographic findings. In our study, we included only cases of isolated FECF (Table 3).

Most of the studies came from tertiary referral centers[13,14,17–19] which normally deal with a different and inherently higher risk population than do hospitals dealing with a low-risk unselected population like ours. In four of the studies the population consisted of selected cases[13,14,17,18], with those with maternal and fetal risk factors for fetal abnormality being excluded. Despite this our study involving unselected women had the highest number of FECF cases reported in the literature.

Other studies in low-risk populations do not support the association between FECF and aneuploidy[12–15,19]. Like ours, all of these studies used the second-trimester ultrasound examination, but three studies[12,17,19] also included scans done in the early third trimester. Combining these eight studies, there were 914 cases of isolated FECF with known outcome. Aneuploidy was found in seven cases (0.8%), of which four were trisomy 21 (0.4%), which is in agreement with our study (0.3%). When those cases of aneuploidy with isolated FECF were compared, those in the high-risk group had a 2.33 relative risk (RR) over those with low risk ($0.95 < RR < 5.75$; Yates corrected $\chi^2 = 2.81$, $P = 0.09$). However, when cases of trisomy 21 were considered, there was a 3.79-fold increased risk in high-risk women compared with low-risk women ($1.24 < RR < 11.57$; Yates corrected $\chi^2 = 5.17$,

$P = 0.02$). Accordingly, we agree with Wax and Philput[23], that the frequency of trisomy 21 is increased when the patient belongs to a high-risk patient population even in the cases with isolated FECF. In contrast, in low-risk unselected cases, we support the view of Thilaganathan *et al.*[15] that the association between isolated FECF and trisomy 21 is not strong enough to warrant prenatal karyotyping in an otherwise healthy fetus that is not at risk of chromosomal abnormality.

FECF and its location

In our study the majority of cases of FECF were single (93.6%), consistent with other studies[12,16]. We also found 6.4% of the cases to have multiple FECF in one or more chambers of the heart and this supports the findings of Vibhakar *et al.*[16]. While Merati *et al.*[12] found four of 37 cases (10.8%) to have interventricular septal FECF, our series had no such cases.

The most commonly cited chamber of the heart for the detection of FECF in euploid fetuses and those with trisomy 21 is the left ventricle[4,5,9]. This is attributed to the larger size of the left papillary muscle[10]. This finding ranges between 60%[17] and 100%[6,20] in euploid fetuses, in keeping with our findings; in 84% of cases in our study FECF occurred in the left ventricle. The only case of trisomy 21 that we found involved a left ventricular FECF.

The second most common site for the detection of FECF in our study was the right ventricle (11.5%), with reported rates of between 0%[6] and 25%[14]. The lowest and highest quoted biventricular FEFC rates are 0%[6,13] and 17%[17], respectively; we found this rate to be 4.1%. Wax and Philput[23] in a review of nine studies found a statistically significant association between aneuploidy and biventricular FECF but not left or right ventricular FECF.

We also report here a case of atrial FECF in which a left atrial FECF was associated with a left ventricular FECF. The atrium is a rare site for FECF[8] and to our knowledge it has not been studied histologically. Since the atria do not contain papillary heart muscle, it would be interesting to know the histological nature of such an echogenic focus.

Recently three studies have provided conflicting results yet an additional contribution to the debate. In a general pregnant population, Prefumo *et al.*[24] found that an isolated FECF detected at the time of the 20-week scan did not significantly change the risk of trisomy 21, but they took into account previous nuchal translucency measurements as well as background risk[24]. In contrast, Huggon *et al.*[25] suggested FECF to be associated with an increased risk of trisomy 21 by a factor of 3.0, but the study was based on fetal echocardiograms at a fetal cardiology referral center.

Nyberg *et al.*[26] examined 186 fetuses with trisomy 21 and compared the sonographic findings with a control group, looking at six different soft markers. They highlighted the fact that known karyotype usually constitutes an overestimate of risk. Four of the markers (including FECF), even as isolated findings were statistically associated with an increased risk of trisomy 21. When presented as an age-adjusted sonographic risk assessment, isolated FECF nearly doubled the risk of trisomy 21.

We conclude that the sensitivity and PPV of an isolated FECF in a low-risk population is too low to influence the decision for prenatal karyotyping for the detection of trisomy 21. The risk of the procedure-related pregnancy loss would be much higher than the detection rate of this chromosomal abnormality. In an otherwise unselected healthy pregnancy with a fetus at low risk of aneuploidy, the discovery of an isolated FECF on routine detailed anomaly scanning in the second trimester is normal and should not be considered as a risk factor for trisomy 21. It should therefore not in itself initiate prenatal karyotyping.

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REFERENCES

1. Roberts DJ, Genest D. Cardiac histologic pathology characteristics of trisomies 13 and 21. *Hum Pathol* 1992; **23**: 1130–1140.
2. Whitlow BJ, Lazanakis ML, Kadir RA, Chatzipapas I, Economides DL. The significance of choroid plexus cysts, echogenic heart foci and renal pyelectasis in the first trimester. *Ultrasound Obstet Gynecol* 1998; **12**: 385–390.
3. Brown DL, Roberts DJ, Miller WA. Left ventricular echogenic focus in the fetal heart: pathologic correlation. *J Ultrasound Med* 1994; **13**: 613–616.
4. Bromley B, Lieberman E, Laboda L, Benacerraf BR. Echogenic intracardiac focus: a sonographic sign for fetal Down syndrome. *Obstet Gynecol* 1995; **86**: 998–1001.
5. 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**: 490–492.
6. Manning JE, Ragavendra N, Sayre J, Laifer-Narin SL, Mellany ML, Grant EG, 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**: 1083–1084.
7. 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**: 217–222.
8. Wax JR, Mather J, Steinfeld JD, Ingardia CJ. Fetal intracardiac echogenic foci: current understanding and clinical significance. *Obstet Gynecol Surv* 2000; **55**: 303–311.
9. Bromley B, Lieberman E, Shipp TD, Richardson M, Benacerraf BR. Significance of an echogenic intracardiac focus in fetuses at high and low risk for aneuploidy. *J Ultrasound Med* 1998; **17**: 127–131.
10. Levy DW, Mintz MC. The left ventricular echogenic focus: a normal finding. *AJR Am J Roentgenol* 1988; **150**: 85–86.
11. Petrikovsky BM, Challenger M, Wyse LJ. Natural history of echogenic foci within ventricles of the fetal heart. *Ultrasound Obstet Gynecol* 1995; **5**: 92–94.
12. 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**: 1102–1104.
13. 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**: 1008–1012.
14. 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**: 945–948.
15. Thilaganathan B, Olawaiye A, Sairam S, Harrington K. Isolated fetal echogenic intracardiac foci or golf balls: is karyotyping indicated? *Br J Obstet Gynaecol* 1999; **106**: 1294–1297.
16. 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 patient population. *J Ultrasound Med* 1999; **18**: 265–268.
17. 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**: 225–228.
18. Jaffe R, Cherot E, Allen T, Glantz JC. Significance of echogenic foci in the left ventricle of the fetal heart in a low-risk population. *Fetal Diagn Ther* 1999; **14**: 345–347.
19. How HY, Villafane J, Parihus RR, Spinnato JA. Small hyperechoic foci of the fetal cardiac ventricle: a benign sonographic finding? *Ultrasound Obstet Gynecol* 1994; **4**: 205–207.
20. Schechter AG, Fakhry J, Shapiro LR, Gewitz MH. In utero thickening of the chordae tendinae. *J Ultrasound Med* 1987; **6**: 691–695.
21. Bronshtein M, Jakobi P, Ofir C. Multiple fetal intracardiac echogenic foci: not always a benign sonographic finding. *Prenat Diagn* 1996; **16**: 131–136.
22. Tabor A, Philip J, Madsen M, Bang J, Obel EB, Norgaard-Pedersen B. Randomised controlled trial of genetic amniocentesis in 4606 low-risk women. *Lancet* 1986; **1**: 1287–1293.
23. Wax JR, Philput C. Fetal intracardiac echogenic foci: does it matter which ventricle? *J Ultrasound Med* 1998; **17**: 141–144.
24. Prefumo F, Presti F, Mavrides E, Sanusi AF, Bland JM, Campbell S, Carvalho JS. Isolated echogenic foci in the fetal heart: do they increase the risk of trisomy 21 in a population previously screened by nuchal translucency? *Ultrasound Obstet Gynecol* 2001; **18**: 126–130.
25. Huggon IC, Cook AC, Simpson JM, Smeeton NC, Sharland GK. Isolated echogenic foci in the fetal heart as a marker of chromosomal abnormality. *Ultrasound Obstet Gynecol* 2001; **17**: 11–16.
26. Nyberg DA, Souter VL, El-Bastawissi A, Young S, Luthhardt F, Lutl DA. Isolated sonographic markers for detection of fetal Down syndrome in the second trimester of pregnancy. *Ultrasound Med* 2001; **20**: 1053–1063.
27. Bettelheim D, Deutinger J, Bernaschek G. The value of echogenic foci ('golfballs') in the fetal heart as a marker of chromosomal abnormalities. *Ultrasound Obstet Gynecol* 1999; **14**: 98–100.

