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CLINICAL ARTICLE

Chromosomal and cardiac anomalies in fetuses with intracardiac echogenic foci

T.R.M. Gonçalves [a,b,*], M.M. Zamith [a,b], C.G.V. Murta [b], L.C. Bussamra [a,b], M.R. Torloni [a,b], A.F. Moron [a,b]

[a] *Fetal Medicine Unit of Hospital e Maternidade Santa Joana, São Paulo, SP, Brazil*
[b] *Fetal Medicine Unit, São Paulo Federal University, São Paulo, SP, Brazil*

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Abstract

Objective: To evaluate the prevalence of intracardiac echogenic foci (ICEF) and the association between ICEF and chromosomal and cardiac anomalies in Brazilian women. *Methods:* In a cross-sectional observational study, 373 of the 23,360 genetic sonograms performed at a private maternal—fetal medicine clinic over 5 years showed intracardiac echogenic foci (ICEF). These 373 sonograms were reviewed for chromosomal and cardiac anomalies and associations were analyzed using the χ^2 test or the Fisher exact test. $P<0.05$ was considered significant. *Results:* The prevalence of ICEF was 1.7%. Cardiac anomalies were detected in 10 sonograms (2.7%) and chromosomal anomalies in 14 (3.7%). There were cardiac defects in 6 (1.7%) of the 359 euploid fetuses with isolated ICEF. Of the 373 women who had fetuses with ICEF, 295 were younger than 35 years and 78 were 35 years or older. There were 6 fetuses (2.1%) with aneuploidy in the younger group and 8 (10.3%) in the older group. *Conclusion:* The prevalence of ICEF was 1.7%, and there was an association between cardiac and chromosomal anomalies. Women carrying fetuses with ICEF should be offered fetal echocardiography and karyotyping.

1. Introduction

Intracardiac echogenic foci (ICEF) are small areas of increased echogenicity located in the vicinity of the papillary muscles or chordae tendinae inside the fetal ventricles and moving synchronously with

* Corresponding author. Rua Maceió 162, Vila Barcelona, São Caetano do Sul, SP CEP 09551-030, Brazil. Tel.: +55 11 4224 6698; fax: +55 11 5572 4449.
E-mail address: telmarmg@uol.com.br (T.R.M. Gonçalves).

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the cardiac valves [1]. First described by Schechter et al. [2] in 1987, they are also known as "golf balls," "pearls," or "bright reflectors" [3].

The prevalence of ICEF varies between 0.17% [4] and 20% [5] according to the population studied, gestational age, fetal position, and equipment quality. The highest prevalence is found among Asian, Middle-Eastern, and African-American populations [6]. Little information exists regarding the incidence and significance of these foci in Hispanic populations [6—8].

Schechter et al. [2] suggested that the bulbous thickening of the chordae tendinae, perhaps secondary to incomplete fenestration, might give rise to ICEF. According to Levy and Mintz [5], ICEF occur during the formation of the papillary muscles and may be a normal variant of the process of myocardial excavation. Histologic studies have demonstrated that ICEF correspond to the mineralization of the papillary muscles [9].

Initially described as a benign finding [2,5], the clinical significance and association of ICEF with chromosomal and cardiac anomalies remain controversial. Most authors agree that echogenic foci cause no hemodynamic modification despite their intracardiac location, and do not seem to be associated with functional or structural cardiac anomalies in euploid fetuses [2,3].

Some have suggested a possible association between ICEF and fetal aneuploidy [10—12], while others consider ICEF a benign and transient finding [2,5,9].

Chromosomal and cardiac anomalies have a profound impact on perinatal management and gravely affect parents. The objectives of this study were to determine the prevalence of ICEF and the possible association of ICEF with congenital heart disease and aneuploidy in a Brazilian population, and, consequently, improve prenatal counseling based on national data.

2. Patients and methods

This cross-sectional observational study reviewed the records of all the women who underwent genetic sonograms between August 1998 and July 2003 at the Fetal Medicine Unit of the Hospital e Maternidade Santa Joana in São Paulo, Brazil. The sonograms were performed later than the 16th week of pregnancy, but not because of abnormal serum results since this screening laboratory evaluation is not routinely available in Brazil. Although there were both low- and high-risk pregnancies in the study population, 82% of the referring indications were routine anatomical survey. The records of women with live singleton fetuses who had ICEF were selected and reviewed to collect maternal age and gestational age at the time of the ultrasonographic scan as well as data on the presence of chromosomal anomalies and cardiac defects. The results of all echocardiograms and the karyotypes of fetuses with ICEF were reviewed, and birth records were also reviewed for neonatal karyotype, description of dysmorphic features, neonatal echocardiogram, and signs of cardiac anomalies. Cases without data on perinatal outcome were excluded.

All genetic sonograms were performed by one of eight experienced maternal—fetal medicine specialists who had been trained and were supervised by the unit coordinator (AFM). Echogenic intracardiac focus was defined as an echogenicity in the region of the papillary muscles that was comparable to that of bone. All examinations were performed with high-resolution ultrasonographic equipment (Logic Pro 500 or Voluson 730; General Electric, USA) using transabdominal 3.5-MHz transducers. Each study was documented by hard-copy images. There were no changes in equipment or the method of evaluating ultrasonographic results that could have affected findings during the 5-year study.

According to department protocol, once an ICEF was detected, the woman was informed about the finding and the fetus was checked on another occasion—for possible associated structural or functional cardiac anomalies. This echocardiographic procedure was performed using a bidimensional color Doppler and M-mode by a single examiner (MMZ), a pediatric cardiologist with ample experience in fetal examination. Additionally, the woman was informed about the possible association of ICEF with aneuploidy and offered genetic counseling and fetal karyotype, if desired.

The following outcomes were analyzed: overall prevalence of ICEF; prevalence, according to maternal age, of cardiac and chromosomal anomalies in fetuses with ICEF; specific types of cardiac anomalies detected; and whether these anomalies were isolated or associated with aneuploidy.

Qualitative variables were expressed as absolute and relative frequencies. Possible associations between variables were investigated using the χ^2 test or the Fisher exact test, when appropriate. $P<0.05$ was considered statistically significant. The positive predictive value of ICEF in the detection of aneuploidy was calculated.

The study was approved by the ethics committee of the Hospital e Maternidade Santa Joana.

3. Results

During the study period 23,360 women underwent genetic sonograms between the 16th and the 34th

Table 1 Age of 373 singleton fetuses with intracardiac echogenic focus and maternal age at the time of ultrasonographic examination

Age	Number (%)
Gestational age (weeks)	
<21	116 (31.1)
21–25	191 (51.2)
26–30	53 (14.2)
31–34	13 (3.5)
Maternal age (years)	
<20	12 (3.2)
20–24	49 (13.1)
25–29	119 (31.9)
30–34	115 (30.8)
≥35	78 (20.9)

week of their pregnancies. Of the 23,756 fetuses observed 411 had ICEF, for an overall prevalence of 1.7%. However, 38 of these fetuses were excluded from the study, 9 because they were not singleton and 29 because information on perinatal outcome was not available. Thus, 373 fetuses with ICEF were included in the study, for a prevalence of 1.6%.

Maternal age in the ICEF group ranged between 16 and 43 years (median, 30 years; mean ± S.D., 29.7 ± 5.4 years). Seventy-eight women (20.9%) were 35 years or older. The median gestational age of the 373 study fetuses at the time of ultrasonographic screening was 22 weeks and their mean gestational age was 22 ± 3.4 weeks (Table 1).

Almost 95% of the fetuses (n = 54) had a single focus, 8% (n = 18) had 2 foci, and 0.2% (n = 1) had 3 foci. The vast majority (96.8%) of the foci were located in the left ventricle.

All 373 fetuses with ICEF underwent fetal echocardiography, and cardiac anomalies were detected in eight—all confirmed by neonatal echocardiography. Two additional cardiac anomalies (small ventricular septal defects) were detected on postnatal examinations, for a total of 10 fetuses (2.7%) with both ICEF and congenital heart defects (Table 2). Maternal age, specific cardiac anomalies, and chromosomal defects are presented in Table 3.

Excluding the four fetuses with cardiac anomalies as well as aneuploidy, the prevalence of cardiac anomalies in euploid fetuses with ICEF was 1.6% (6 of 369).

A total of 74 women (19.8%) underwent invasive procedures for fetal karyotyping during the antenatal period for various motives (maternal age, anxiety, ICEF, other fetal anomalies). Thirty-five women (9.4%), all younger than 35 years, underwent invasive procedures only because of the finding of an isolated ICEF. There were no fetal losses attributed to fetal karyotyping.

Fourteen (3.7%) of the 373 fetuses with ICEF had abnormal karyotypes, all confirmed by cytogenetic studies. Of these 14 fetuses, 12 were diagnosed antenatally and 2 (both with trisomy 21) from neonatal blood sampling. There were 9 cases of trisomy 21, 2 cases each of trisomy 13 and trisomy 18, and 1 case of triploidy. The triploid fetus and all fetuses with trisomy 13 and 18 had various structural anomalies in association with ICEF. In five (55.6%) of the nine fetuses with trisomy 21, the only anomaly detected sonographically was an intracardiac echogenic focus, and two of these five fetuses were carried by women younger than 35 years. Table 4 presents the association between chromosomal and cardiac anomalies.

Among the 259 fetuses with isolated ICEF that were carried by women younger than 35 years and, therefore, were considered to be at low risk for aneuploidy, 2 (0.8%) had trisomy 21. In this subgroup, the positive predictive value of an isolated ICEF in the detection of trisomy 21 was 0.8%.

4. Discussion

The overall prevalence of ICEF in this study, which involved fetuses at high and low risk, was 1.7%, which is similar to the 0.17% to 3.2% reported in studies involving low-risk populations [4,13]. Achiron et al. [14] reported a higher prevalence

Table 2 Maternal age and fetal anomalies in 373 singleton fetuses with intracardiac echogenic focus

Fetal anomaly	Maternal age, (years) number (%)		
	<35 n = 295	≥35 n = 78	Total
None	258 (87.5)	59 (75.6)	317
Anomalies present	38 (12.5)	22 (24.4)	60
Cardiac, isolated	4 (10.5)	1 (4.6)	5
Chromosomal, isolated	2 (5.3)	3 (13.6)	5
Structural, isolated	28 (73.6)	12 (54.5)	40
Cardiac + structural	0	1 (4.6)	1
Chromosomal + structural	2 (5.3)	3 (13.6)	5
Cardiac + chromosomal + structural	2 (5.3)	2 (9.1)	4

Table 3 Cardiac defects in 10 fetuses with intracardiac echogenic focus

Fetus number	Cardiac defect	Maternal age (years	Gestational age at detection (weeks)	Karyotype	Other anomalies
1	VS	29	21	Nl	No
2	VS	29	21	Nl	No
3	VS	35	25	Nl	No
4	VS + Aortic hypoplasia	33	24	Nl	No
5	Left ventricular fibroelastosis	20	32	Nl	No
6	Dextrocardia	36	29	Nl	Pleural effusion, ascites
7	VS	29	22	Triploid	Single UA + IUGR + oligohydramnios
8	VS	37	23	Trisomy 13	Cranium, thoracic hypoplasia, clubfeet, pyeloectasis
9	VS	39	22	Trisomy 18	Clubfeet, micrognathia, hydrocephalus, camptodactyly
10	AS	33	24	Trisomy 21	Increased NT

Abbreviations: AV, atrial and ventricular septal; IUGR, intrauterine growth retardation; NT, nuchal translucency; UA, umbilical artery; VS, ventricular septal.

of ICEF in their low-risk population (7.4%), which could be explained by a lower gestational age at the time of the ultrasonographic examination (it ranged from 13 to 16 weeks). In fact, ICEF tend to disappear over time, as demonstrated by various longitudinal studies [13—16]. In the present study, the mean gestational age of the fetuses when they were detected as having ICEF, 22 weeks, is similar to that in most other studies and corresponds to the period where most genetic sonograms are performed.

De la Vega and Verdiales [7] identified ICEF in 1.6% of 485 Hispanic fetuses. In the only other Brazilian study published, ICEF were detected in 1.4% of 3980 low-risk fetuses undergoing routine echocardiography to detect cardiac malformations [8]. A study comparing the prevalence of ICEF among different ethnic groups reported its presence in 3.4% of 1490 Hispanics, a proportion that did not differ significantly from the 3.3% observed for 4090 fetuses carried by white women [6]. The present study, involving 373 fetuses with ICEF in a population of more than 23,000 pregnant women, is probably the largest on ICEF in a Latin-American population. Based on its findings and the available literature, it seems that the prevalence of fetuses with ICEF is similar in Hispanic women and white women at low risk.

Table 4 Chromosomal and cardiac anomalies in 373 fetuses with intracardiac echogenic focus[a]

Chromosomal anomalies	Cardiac anomalies		
	Yes number (%)	No number (%)	Total
Yes	4 (28.6)	10 (71.4)	14
No	6 (1.7)	353 (98.3)	359
Total	10 (2.7)	363 (97.3)	373

[a] $P = 0.002$.

The overall prevalence of cardiac anomalies in fetuses with ICEF was 2.7%, which is higher than the prevalence reported in most studies but similar to the 3.2% observed by Wax and Philput [17]. Unlike in other publications [2,3,12—14], even after excluding cases with chromosomal anomalies, the 1.6% rate of cardiac defects found in euploid fetuses was twice that expected in the general newborn population, which is 0.8% [18]. The rate of cardiac defects in the entire cohort was not available, but may be presumed to be similar to the rate expected in the general population since the more than 20,000 pregnant women whose records were reviewed were unselected. The higher diagnostic rate of cardiac defects in this study may be explained in part by the fact that all fetuses with ICEF underwent a detailed echocardiographic assessment performed by a specialist. Had not this thorough cardiac evaluation been performed in all cases, it is possible that most of the smaller septal defects would have been undetected and the rate of cardiac anomalies would have been lower. Even with antenatal echocardiography, two cases of cardiac anomalies (small septal defects) were not diagnosed antenatally. Ventricular septal defects are the most common type of congenital heart malformation to be overlooked, even after a detailed fetal examination. Detection is very dependent on image quality, the size and site of the defect, and ultrasonographic equipment. Since the findings of this study, the cardiologist who performs all fetal echocardiographic evaluations has been devoting greater attention to fetuses with ICEF. Sometimes a second examination is performed at a later gestational age to better explore the fetal heart, especially when image quality is suboptimal. The exact mechanism involved in the appearance of echogenic foci in

fetuses with cardiac anomalies is unclear. Recently, Perfumo et al. [19] raised the possibility of an association between increased nuchal translucency in the first trimester and ICEF in the second trimester, suggesting that cardiac dysfunction may be involved in the etiology of both these findings.

Intracardiac echogenic foci have been reported in fetuses with trisomy 13, 18, and 21, with triploidy, and with 45,X [2,10–12,20]. The 3.7% incidence of aneuploidy in this study was lower than that reported for high-risk populations, which ranges from 4.8% [20] to 33% [9], and similar to the 0% to 4.5% range reported by various studies evaluating fetuses at low risk [12,14,21,22]. As in other studies, trisomy 21 was the main chromosomal anomaly identified in fetuses with ICEF. The 2.4% prevalence of trisomy 21 in fetuses with ICEF observed in this study was within the 0.44–13% range reported by others [12,21,23].

The positive predictive value of ICEF for trisomy 21 in the low-risk subgroup (maternal age <35 years and no additional ultrasonographic findings) was 0.8%, which was lower than the 5% to 13% reported in studies involving high-risk populations [10,21,23]. After excluding women older than 35 years and fetuses with associated structural anomalies, Winter et al. [24] reported a 2% positive predictive value of isolated ICEF for aneuploidy.

The prevalence of trisomy 21 for all fetuses at low risk (maternal age <35 years and no fetal anomaly on ultrasonographic examination) could not be obtained. However, outcome for the 259 low-risk fetuses with isolated ICEF was available and among these fetuses there were 2 cases of trisomy 21. Although this single observation may be statistically misleading, the prevalence of trisomy 21 plus isolated ICEF among the fetuses of women younger than 35 years was 0.8%, which was higher than the 0.5% prevalence of trisomy 21 expected among the fetuses of women aged 35 years or older. Specifically, the 0.8% prevalence of trisomy 21 observed in this study in low-risk fetuses with isolated ICEF corresponds approximately to the risk of trisomy 21 expected in the fetuses of 38-year-old women, which is 1:129. Therefore, based on this risk, the authors believe that young women carrying a fetus with isolated ICEF should be offered genetic counseling, and consideration should be given to fetal karyotype testing. If other risk factors are present, including maternal age greater than 35 years, these considerations should be emphasized. Owing to the small number of women younger than 35 years who had fetuses with both isolated ICEF and trisomy 21, it was impossible to perform more sophisticated statistical calculations. However, a recent systematic review indicated that the finding of isolated ICEF increases the risk of trisomy 21 by five to seven times with increasing maternal age [25].

There are several potential limitations to this study. Its cross-sectional nature reduces its methodological power compared with other study designs. Ideally, the perinatal results of all the fetuses that were evaluated sonographically and found to be without ICEF during the study period should have been obtained to compare the prevalence of aneuploidy and the prevalence of cardiac defects among that group. Unfortunately, this was impossible because of time constraints and the small number of investigators. Nevertheless, this report provides valuable data concerning the prevalence and significance of ICEF in a large Latin-American population.

The topic of ICEF as a marker for chromosomal anomalies is still controversial. Large multicentric prospective studies, similar to those conducted for nuchal translucency, are needed to definitively establish the value of ICEF and other soft markers in the detection of fetal aneuploidy. Efforts should be made to find a multiplying factor that could be applied to the basic risk of the fetus, in order to eliminate the existing doubts that plague ultrasonographers, obstetricians, and pregnant women about the real significance of this and other soft ultrasonographic markers.

5. Conclusion

The prevalence of ICEF in this Brazilian population was 1.7%. Contrary to findings from other studies, euploid fetuses with ICEF had twice the risk of cardiac anomalies of the general newborn population. The prevalence of trisomy 21 in fetuses with isolated ICEF carried by women younger than 35 years was 0.8%, which corresponds to the prevalence of trisomy 21 expected for 38-year-old women. These findings suggest that Brazilian women carrying fetuses with ICEF should be offered fetal echocardiography and genetic counseling.

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