

Perinatal outcome of fetuses with echogenic intracardiac focus

M. Özürmeli^{1,*}, M. Sucu², E. Arslan², S. Büyükkurt²¹Derince Research and Education Hospital, Department of Obstetrics and Gynecology, Kocaeli (Turkey)²University of Çukurova, School of Medicine, Department of Obstetrics and Gynecology, Perinatology Unit, Adana (Turkey)

Summary

Objective: Echogenic intracardiac focus (EIF), a microcalcification of the papillary muscles in either or both ventricles of the fetal heart, is one of the more common ultrasonographic soft markers of trisomy 21. This study aimed to determine the relationship of EIF with trisomies in the presence of various ultrasonographic findings. **Materials and Methods:** A retrospective study of second-trimester obstetric sonograms (18–24 weeks) was conducted at a tertiary care center over a two-year period. The patients were divided into three groups: isolated EIF (group 1), EIF with at least one soft marker (group 2), and EIF with structural anomalies (group 3). All the groups were divided into subgroups on the basis of a screening test (maternal age \geq 35, positive combined-triple-quadruple tests). The incidence of chromosome anomalies was evaluated. **Results:** The authors examined 8,300 patients during the study period and found 170 fetuses with isolated EIF (group 1), 26 fetuses with EIF and soft markers (group 2), and 37 fetuses with EIF and structural anomalies (group 3). Thirteen (8%) patients underwent fetal karyotyping in group 1, 10 (38%) in group 2, and 22 (60%) in group 3. The rate of the invasive test was higher in fetuses exhibiting EIF accompanied by at least one of the soft markers. No trisomy was detected in group 1 or 2. **Conclusion:** The risk of aneuploidy did not increase in either isolated EIF or in cases with other soft markers but only in cases with structural anomalies.

Key words: Diagnosis; Prenatal ultrasonography; Trisomies; Abnormality; Congenital.

Introduction

Second trimester ultrasonography is used to detect fetal anomalies and the markers commonly associated with trisomies, which have been used to determine the risk of Down syndrome [1, 2]. Echogenic intracardiac focus (EIF) is one of the so-called soft markers. EIF, a microcalcification of the papillary muscle in either or both ventricles of the fetal heart, does not typically present an acoustic shadow and moves synchronically to the atrioventricular valves [3]. It is of no clinical significance except in increasing the risk of Down syndrome [4].

The incidence of EIF reported in the literature is about 5% [5]. A positive likelihood ratio has been reported of between 1.8 and 5.4 for isolated EIF, which represents between a twofold and five-fold increased risk for trisomy 21 [6]. The type of population studied may influence these differences in likelihood ratios, with the values of the likelihood ratio usually lower in low-risk populations than in high-risk populations [7]. Management has not been clearly identified when EIF is accompanied by other soft markers.

In this study, the authors investigated the relationship of EIF when it is isolated and when accompanied by other soft markers and structural anomalies.

Materials and Methods

This retrospective study was conducted at Çukurova University Hospital's prenatal ultrasound unit between November 1, 2014 and October 31, 2016. During this time, 8,300 patients underwent a routine second trimester

anatomical survey (18–24 post-menstrual weeks). Patients that exhibited EIF in the fetal ultrasound examination were analyzed. The data were collected from the digital patient recording system.

The authors diagnosed EIF in the fetal ultrasound examination after a comparison with the echogenicity of the adjacent bone. All the sonographic evaluations were performed by one of the four authors using a convex volumetric transducer (RAB 6-D 2-7 MHz and RAB2 5L) probe. In all cases, the patient underwent a detailed fetal ultrasound examination according to ISUOG (International Society of Ultrasound in Obstetrics and Gynecology) guidelines [8, 9]. The ultrasonographic soft markers of trisomy 21 (increased nuchal fold, nasal bone hypoplasia, echogenic bowels, short femur and humerus, and pelviectasis) were also evaluated.

The patients were divided into three groups: patients with isolated EIF, those with EIF and at least one soft marker, and those with EIF and structural anomalies, designated as groups 1, 2, and 3, respectively. All the groups were divided into subgroups according to trisomy screening tests (maternal age \geq 35, positive combined-triple-quadruple tests). If an EIF was identified, the mothers were counseled regarding the risk of aneuploidy based on the other risk factors, including trisomy screening test results, other ultrasonographic markers, and major anomalies. Fetal karyotyping was offered to all women in groups 2 and 3 and to women in group 1 with a positive biochemical trisomy screening test. The cases with isolated EIF and a normal trisomy screening test were offered amniocentesis if they strongly desired it.

Table 1. — Demographic features and location of EIF

	Group 1 (n = 170)	Group 2 (n = 26)	Group 3 (n = 37)
Mean maternal age	31.4 ± 5.9 (19-44)	31.6 ± 6 (19-41)	29.2 ± 7 (18-42)
Mean gestational age	21.8 ± 2.5 (15-31)	21.7 ± 2.7 (16-28)	21.7 ± 5.1 (15-33)
EIF location (ventricle, n)			
Left / Right / both	153 / 7 / 10	2021/3/2	36 / 1 / 0
Outcomes			
Term	157	23	6
Preterm	13	3	4
Termination of pregnancy			27

Data presented as N (%) or mean ± standard deviation.

Table 2. — Outcomes of fetuses with EIF

	Group 1 (n = 170)	Group 2 (n = 26)	Group 3 (n = 37)	P value
High risk in screening tests /Karyotype	17/5	4/1	3/3	
Low risk in screening tests /Karyotype	153/8	22/9	34/19	
Total n/ Karyotype	170/13	44/130	37/22	
Total n / Chromosome anomalies (%)	170/0 (0%)	26/0 (0%)	37/7 (18,9%)	0.0001
In total Karyotype n / Chromosome anomalies (%)	13/0 (0%)	10/0 (0%)	22/7 (31,8%)	0.013

Table 3. — Fetuses with structural anomalies

Structural anomalies	N
Intracranial anomalies	15
Heart anomalies	8
Gastrointestinal tract anomalies	4
Urinary tract anomalies	1
Spinal anomalies	5
Skeletal anomalies	2
Face and neck anomalies	5
Fetal hydrops	1

The neonatal outcomes were obtained from electronic medical reports, or the family was interviewed by telephone. All the pregnant women were informed and provided written consent to participate in the study. The study was approved by the ethics committee of Çukurova University.

For each continuous variable, normality was checked by the Kolmogorov-Smirnov and Shapiro-Wilk tests and by histograms. Comparisons between the groups were applied using Student's *t*-test or the ANOVA test for normally distributed data. The categorical variables between the groups were analyzed using the chi-squared test. A *p* value of less than 0.5 was considered to be significant. The results are presented as mean ± SD (min-max) and n (%). All the reported *p*-values are two tailed.

Results

An analysis of the 233 (2.8%) patients with EIF found 170 (73%) fetuses with isolated EIF, 26 (11%) with EIF and soft markers, and 37 (16%) with EIF and structural anomalies

(groups 1, 2, and 3, respectively). The majority of the patients were detected as having isolated EIF. The mean maternal age was 29.7 years, and the mean gestational age at the time of the study was 22 weeks. The demographic features of the patients and the location of the EIF are shown in Table 1. In the screening test, 17, 4, and 3 patients were at high risk in groups 1, 2, and 3, respectively. Thirteen (8%) patients underwent fetal karyotyping in group 1, 10 (38%) in group 2, and 22 (60%) in group 3. The outcomes are summarized in Table 2. The rate of the invasive test was higher in fetuses with EIF accompanied by at least one soft marker. No trisomy was detected in groups 1 and 2. Chromosome anomalies were detected only in group 3. The structural anomalies in group 3 are described in Table 3.

Discussion

Soft markers were identified through improvement in high-definition ultrasound machines, and they are accepted as anatomic variants. Because they were initially employed in first-trimester screening tests, the use of soft markers in trisomy screening caused confusion. Many studies evaluated the importance of soft markers in the population of patients who had not had first-trimester screening or were at high risk in the combined test. However, fewer studies searched for soft markers in the population of patients at low risk in the combined test [10, 11]. In the current study, the number of low-risk patients in the screening tests was higher in all groups. The authors recommended karyotype analysis of all the patients in groups 2 and 3 even if the risk in the screening tests was low. No chromosomal abnormality was found in either the isolated EIF cases or the EIF cases accompanied by other soft markers.

Most studies decide against performing an invasive pro-

cedure in cases in a low-risk population or in isolated EIF [11-15]. The invasive test rate increases even in the low-risk group [4]. This is consistent with the findings in the literature that soft markers are weakly related with chromosomal abnormalities while structural abnormalities had a stronger association with chromosomal abnormalities.

Some studies suggest that EIF in the right ventricle or in both ventricles increases trisomy risk above that of EIF in only the left ventricle [16]. The present findings do not support this, and the authors found no chromosomal abnormalities in either group.

The higher rate of invasive procedures in group 2 than in group 1 may be related to maternal anxiety. The ultrasound findings of soft markers could be wrongly evaluated as structural malformations by the mothers, which could increase the rate of invasive procedures [4, 17]. Even though the mothers were informed that soft markers are seen at higher rates in fetuses with no structural abnormalities and that they are weakly related with the risk of chromosomal abnormalities, some understood this as a higher risk situation.

The frequency of EIF in the present study does not reflect that described in the literature. EIF has been found in 5% of patients in the literature [5, 18], but the rate in the present study was lower. This may be explained by the high sensitivity in the present study, which was conducted at a reference center. To prevent false positives, the gain of the ultrasound machine had to be decreased, and the echogenic focus in the fetal heart had to be compared with bone echogenicity [18]. This approach decreases false positive diagnoses and thus decreases maternal anxiety and hence the rate of invasive procedures.

Reporting isolated EIF cases, especially in low-risk patients, may be detrimental rather than beneficial [4]; the probability of the presence of Down syndrome in these fetuses is lower than the rate of miscarriage due to amniocentesis [5]. The presences of EIF is an independent risk factor for an increased rate of invasive procedures. For these reasons, the option of not reporting the isolated EIF in low-risk patients may merit discussion [4].

This study showed that the risk of aneuploidy did not increase in either isolated EIF cases or in EIF cases with other soft markers. EIF and other soft markers should be evaluated as anatomical variants. Mothers may feel confined due to the weak relation of soft markers with aneuploidy. Especially in women at low risk in screening tests, the presence of EIF and other markers is insignificant. Chromosome anomalies are related only to structural anomalies. One limitation of the present study is its retrospective character. Furthermore, the impact of the referring clinicians' advice on the referred patients could not be excluded in this study.

Conclusion

When EIF is diagnosed during an ultrasonographic scan without any major structural abnormalities, there is no as-

sociation with chromosomal abnormalities even if accompanied by other markers. In such cases, karyotyping should be performed only at the insistence of the mother.

Ethics Approval and Consent to Participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Çukurova University Ethics Committee (approval number: 2016/15).

Conflict of Interest

The authors declare no competing interests.

Submitted: December 12, 2018

Accepted: March 04, 2019

Published: June 15, 2020

References

- [1] Nyberg D.A., Souter V.L., El-Bastawissi A., Young S., Luthardt F., Luthy D.A.: "Isolated sonographic markers for detection of fetal Down syndrome in the second trimester of pregnancy". *J. Ultrasound Med.*, 2001, 20, 1053.
- [2] Bromley B., Lieberman E., Shipp T.D., Benacerraf B.R.: "The genetic sonogram: a method of risk assessment for Down syndrome in the second trimester". *J. Ultrasound Med.*, 2002, 21, 1087.
- [3] Facio M.C., Hervías-Vivancos B., Broullón J.R., Avila J., Fajardo-Expósito M.A., Bartha J.L.: "Cardiac biometry and function in euploid fetuses with intracardiac echogenic foci". *Prenat. Diagn.*, 2012, 32, 113.
- [4] Chasen S.T., Razavi A.S.: "Echogenic intracardiac foci: disclosure and the rate of amniocentesis in low-risk patients". *Am. J. Obstet. Gynecol.*, 2013, 209, 377.
- [5] Bromley B., Lieberman E., Laboda L.A., Benacerraf B.R.: "Echogenic intracardiac focus, a sonographic sign for Down Syndrome?" *Obstet. Gynecol.*, 1995, 86, 998.
- [6] Doubilet P.M., Copel J.A., Benson C.B., Bahado-Singh R.O., Platt L.D.: "Choroid plexus cyst and echogenic intracardiac focus in women at low risk for chromosomal anomalies: the obligation to inform the mother". *J. Ultrasound Med.*, 2004, 23, 883.
- [7] Rodriguez R., Herrero B., Bartha J.L.: "The continuing enigma of the fetal echogenic intracardiac focus in prenatal ultrasound". *Curr. Opin. Obstet. Gynecol.*, 2013, 25, 145.
- [8] Salomon L.J., Alfirevic Z., Berghella V., Bilardo C., Hernandez-Andrade E., Johnsen S.L., et al.: "ISUOG Clinical Standards Committee. Practice guidelines for performance of the routine mid-trimester fetal ultrasound scan". *Ultrasound Obstet. Gynecol.*, 2011, 37, 116.
- [9] Carvalho J.S., Allan L.D., Chaoui R., Copel J.A., De Vore G.R., Hecher K., et al.: "ISUOG Practice Guidelines (updated): sonographic screening examination of the fetal heart". *Ultrasound Obstet. Gynecol.*, 2013, 41, 348.
- [10] Wax J.R., Pinette M.G., Cartin A., Blackstone J.: "Second-trimester genetic sonography after first-trimester combined screening for trisomy 21". *J. Ultrasound Med.*, 2009, 28, 321.
- [11] Sood M., Rochelson B., Krantz D., Ravens R., Tam Tam H., Vohra N., et al.: "Are second-trimester minor sonographic markers for Down syndrome useful in patients who have undergone first-trimester combined screening?" *Am. J. Obstet. Gynecol.*, 2010, 203, 408.
- [12] Ouzounian J.G., Ludington C., Chan S.: "Isolated choroid plexus cyst or echogenic cardiac focus on prenatal ultrasound: is genetic amniocentesis indicated?" *Am. J. Obstet. Gynecol.*, 2007, 196, 595.
- [13] Huang S.Y., Shaw S.W., Cheuh H.Y., Cheng P.J.: "Intracardiac echogenic focus and trisomy 21 in a population previously evaluated by first-trimester combined screening". *Acta Obstet. Gynecol. Scand.*, 2010, 89, 1017.
- [14] Shanks A.L., Odibo A.O., Gray D.L.: "Echogenic intracardiac foci:

- associated with increased risk for fetal trisomy 21 or not?" *J. Ultrasound Med.*, 2009, 28, 1639.
- [15] Sotiriadis A., Makrydimas G., Ioannidis J.P.: "Diagnostic performance of intracardiac echogenic foci for Down syndrome: a meta-analysis". *Obstet. Gynecol.*, 2003, 101, 1009.
- [16] Bromley B., Lieberman E., Shipp T.D., Richardson M., Benacerraf B.R.: "Significance of an echogenic intracardiac focus in fetuses at high and low risk for aneuploidy". *J. Ultrasound Med.*, 1998, 17, 127.
- [17] Lorente A.M., Moreno-Cid M., Rodríguez M.J., Bueno G., Tenías J.M., Román C., *et al.*: "Meta-analysis of validity of echogenic intracardiac foci for calculating the risk of Down syndrome in the second trimester of pregnancy". *Taiwan J. Obstet. Gynecol.*, 2017, 56, 16.
- [18] Wax J.R., Mather J., Steinfeld J.D., Ingardia C.J.: "Fetal intracardiac echogenic foci: current understanding and clinical significance". *Obstet. Gynecol. Surv.*, 2000, 55, 303.

Corresponding Author:

MEHMET ÖZSÜRMELE, M.D.

Derince Research and Education Hospital

Department of Obstetrics and Gynecology

Kocaeli (Turkey)

e-mail: ozsurmeli@gmail.com