Case-controlled Study

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Correlation between fetal ventricular echogenic foci in pregnancy and fetus chromosomal anomaly: a case-control study in Bandar Abbas city

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Background: Ventricular echogenic foci are small structures within the hearts of some fetuses. These small areas result from increased echogenicity in the ventricles of fetuses located near the papillary muscles. An association between these foci and chromosomal abnormalities in fetuses has been reported. Considering that chromosomal abnormalities are a major cause of prenatal death, this study aimed to determine the value of fetal echogenic foci as markers for chromosomal abnormalities.

Materials and methods: Fetal echocardiography was performed by an experienced cardiologist on 149 pregnant women in the second trimester. Of these, 75 were reported to have positive echogenic foci, and 74 were reported to have no echogenic foci. Subsequently, the three chromosomal anomalies including trisomies 21, 18, and 13 were examined. The information of the individuals, including gestational age and echogenic foci, was recorded.

Results: Based on the findings of the present study, seven infants (4.7%) had trisomy 21, four infants (2.7%) had trisomy 13, and six infants (4.1%) had trisomy 18. The mean gestational age of pregnant women with positive and negative echogenic foci was 21.07 ± 3.23 and 21.03 ± 3.09, respectively. No significant relationship was found between ventricular echogenic foci and trisomy 21, 18, or 13.

Conclusion: The present study suggests no significant relation between the presence of echogenic foci and chromosomal trisomies. This finding indicates that additional tests are required to confirm chromosomal abnormalities when echogenic intracardiac foci are present, especially in high-risk fetuses. Moreover, the absence of echogenic focus does not rule out chromosomal disorders.

Keywords: aneuploidy, case-control, chromosomal anomaly, down syndrome, echogenic foci, trisomy 13, trisomy 18, trisomy 21

Introduction

Congenital heart diseases are a leading cause of mortality among newborns[1,2]. Aneuploidy, characterized by an abnormal chromosome count resulting from the inheritance of one or more additional chromosomes (trisomy) or the absence of one chromosome (monosomy), represents a significant category of genetic disorders. These chromosomal abnormalities occur in ~0.4% of births, exerting profound effects on both prenatal and postnatal development[3]. Among the notable types of aneuploidies, trisomy 21, commonly known as Down syndrome, stands out as the most prevalent one[4]. Trisomy 18, also referred to as Edward syndrome, follows closely in frequency, albeit with a more severe phenotype and higher rates of stillbirth and fetal loss, underscoring its clinical importance[5–7]. Similarly, trisomy 13, known as Patau syndrome, represents another significant aneuploidy, though less common than trisomy 21 and 18, yet associated with substantial risks of maternal and fetal mortality, as well as a cause of congenital anomalies and intellectual disabilities[8,9].

Given the profound implications of aneuploidies and other congenital heart disease on both affected individuals and their families, prenatal screening for these chromosomal abnormalities has become an integral component of routine obstetric care[10]. Based on the guidelines provided by the American College of

HIGHLIGHTS

- Echogenic foci in fetal hearts not linked to chromosomal trisomies.
- Study finds no significant association between echogenic foci and trisomies.
- Additional tests are advised to confirm chromosomal abnormalities.
- Absence of echogenic focus doesn't exclude chromosomal disorders.

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Obstetricians and Gynecologists (ACOG), second-trimester screening is typically conducted through ultrasonography, typically performed between the 18th and 22nd weeks of pregnancy. During these screenings, various markers are evaluated to assess the risk of aneuploidy, including nuchal translucency measurement, maternal serum biomarkers, and structural anomalies detected via ultrasound examination[11–13].

One such marker that has garnered attention in prenatal screening is the presence of an echogenic intracardiac focus (EIF) observed during routine fetal echocardiography. An EIF appears as a small, bright focus within the fetal heart, typically visualized in the standard four-chamber view[14,15]. While the presence of an EIF has been associated with an increased risk of aneuploidy, particularly trisomy 21, its significance as a standalone marker remains a topic of debate. Studies investigating the relationship between EIFs and aneuploidy have produced conflicting results, with some suggesting a strong association while others report no significant correlation[16,17]. Anderson and colleagues conducted a population-based study evaluating isolated fetal intracardiac echogenic focus and its association with trisomy 21. They concluded that there was no significant association between them. However, Manning and colleagues, in their study involving 901 women, found a significant association[18,19].

The objective of this study is to provide further insights into the value of identifying EIFs as a marker for aneuploidy. By evaluating a population of pregnant women undergoing fetal echocardiography, we aimed to assess the correlation between EIFs and chromosomal abnormalities, including trisomy 21, 18, and 13. Additionally, we aimed to determine whether EIFs can serve as reliable predictors of aneuploidy in low populations, thereby informing clinical decision-making regarding the need for additional diagnostic testing and counseling.

Material and methods

Study design and setting

The current study employed a case-control design to investigate the relationship between fetal ventricular echogenic foci and chromosomal anomalies in pregnant women. The study has been reported in line with the STROCSS criteria[20].

Ethical considerations

The study protocol was registered and adhered to the ethical guidelines outlined in the Helsinki declaration. Written consent was obtained from all participants, and they were informed of their right to withdraw from the study at any stage.

Study population

All pregnant women in their second trimester who presented to Hospital during the study period were eligible for inclusion. Exclusion criteria included patients who declined to participate or encountered technical issues with fetal heart echo.

Data collection

Echocardiography

Echocardiograms were performed by an experienced cardiologist using a VIVID S5 machine from Norway, equipped with 3 and 7 MHz probes.

Questionnaire

A trained individual collected patient information using a structured questionnaire. Data collected included gestational age and fetal echocardiography findings, such as ventricular echogenic foci and heart abnormalities.

Follow-up procedures

After delivery, all newborns underwent comprehensive examinations to detect heart issues and chromosomal disorders. Additional diagnostic tests were conducted if deemed necessary.

Statistical analysis

Data analysis was performed using SPSS version 23 statistical software. The $\chi 2$ test and Student's *t*-test were used for categorical variables to investigate differences between the two groups (women who gave birth to children with chromosomal anomalies and those with normal deliveries). The Kolmogorov–Smirnov test was employed to assess the distribution of quantitative data. Parametric tests such as the independent *t*-test and Pearson's correlation coefficient were applied for normally distributed data, while non-parametric tests including the Mann–Whitney test and Spearman's correlation coefficient were used for non-normally distributed data. The significance level was set at P less than 0.05. The sample size in each group was estimated at 73 individuals, with 80 pregnant women ultimately enrolled in each group to account for a 10% dropout rate.

$$\frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2[S_1^2 + S_2^2]}{(\mu_1 - \mu_2)^2} \cong 73$$

$\alpha =$ 0.05 effective size:0.5
$\beta =$ 0.1

Results

Participant selection and baseline characteristics

A total of 11 pregnant women were excluded from the study due to technical difficulties or lack of consent, resulting in a final analysis cohort of 149 participants. This cohort consisted of 74 pregnant mothers in the negative echogenic focus group and 75 pregnant mothers in the positive echogenic focus group. Table 1 displays the chromosomal abnormality data for the study fetuses, indicating that 7 (4.7%) embryos exhibited trisomy 21, 4 (2.7%) embryos exhibited trisomy 13, and 6 (4.1%) embryos exhibited trisomy 18. The mean gestational age of the embryos was 21.04 ± 3.14 weeks.

Correlation between echogenic foci and chromosomal abnormalities

Based on the analysis results presented in Table 2, there was no statistically significant difference observed in gestational age between pregnant women with positive and negative echogenic foci (21.07 ± 3.23 vs. 21.03 ± 3.09, $P = 0.948$). Additionally, our investigation revealed no significant relationship between the presence of echogenic foci and the occurrence of Trisomy 21, Trisomy 13, and Trisomy 18 among the participants, as

Table 1

Frequency of chromosomal abnormalities in study fetuses

Variant	Frequency (percentage), *n* (%)
Trisomy 21	
No	142 (95.3)
Yes	7 (4.7)
Trisomy 13	
No	145 (97.3)
Yes	4 (2.7)
Trisomy 18	
No	143 (95.9)
Yes	6 (4.1)

demonstrated in Table 3 ($P = 0.685$, $P = 0.989$, and $P = 0.395$, respectively) (Table 3).

Discussion

The ACOG and the National Institute of Child Health and Human Development recommend genetic screening for all pregnant women. These screening protocols encompass a range of diagnostic modalities, including maternal serum testing for various biomarkers during the first and second trimesters, as well as ultrasound examinations performed in both the early and mid-trimester stages. Ultrasound, in particular, is useful in detecting alterations in fetal anatomy, encompassing a spectrum from overt structural anomalies to subtle deviations that may indicate specific medical conditions[14,21].

Echogenic intracardiac foci have been observed in a range spanning from 0.5 to 20% of normal fetuses[22]. These foci arise due to the presence of calcifications in the papillary muscles. Importantly, echogenic intracardiac foci serve not only as an ultrasonographic observation but have also been documented at a higher frequency in autopsy examinations of fetuses with trisomy 21 and trisomy 13 compared to those with chromosomally normal karyotypes[23]. Prior research has demonstrated that the presence of isolated echogenic intracardiac foci within the left or right ventricles is linked to an increased incidence of fetal cardiac abnormalities[24,25].

The findings from prior investigations examining the relationship between ventricular echogenic foci and Down syndrome have yielded conflicting results. Achiron *et al.*[26] reported no statistically significant correlation between ventricular echogenic foci and the occurrence of trisomy 21, aligning with our own observations. However, the study conducted by Huggon and colleagues reported a significant association between ventricular echogenic foci and trisomy 21. Nonetheless, the reliability of their conclusion is questioned, primarily due to the number of trisomy 21 cases exceeding the anticipated frequency[27].

Table 2

Correlation analysis of gestational age and presence of echogenic focus

Echogenic focus	Gestational age (mean ± standard deviation)	*P*
No	21.03 ± 3.09	0.948
Yes	21.07 ± 3.23	

Table 3

Correlation analysis of echogenic intracardiac foci with trisomy 21, 13, and 18

Trisomy type	Negative echogenic foci (percentage), *n* (%)	Positive echogenic foci, *n* (%)	*P*
Trisomy 21			
No	70 (46.9)	72 (48.3)	0.685
Yes	4 (2.6)	3 (2.0)	
Trisomy 13			
No	72 (48.3)	73 (48.9)	0.989
Yes	2 (1.3)	2 (1.3)	
Trisomy 18			
No	70 (46.9)	73 (48.9)	0.395
Yes	4 (2.6)	2 (1.3)	

In our study, we conducted an assessment of the potential relationship between ventricular echogenic foci and trisomy 18, ultimately revealing no statistically significant correlation between them (Fig. 1). Conversely, Gonçalves and colleagues reported a substantial association between chromosomal abnormalities and echogenic intracardiac foci. They emphasized that pregnant women carrying a fetus with ventricular echogenic foci should be recommended for karyotype testing[28].

Additionally, our investigation revealed no statistically significant correlation between ventricular echogenic foci and trisomy 13. These findings are consistent with the findings of Chen *et al.*[29], who also reported no significant association between ventricular echogenic foci and trisomy 13. However, in a study with a higher prevalence of trisomy 13 cases compared to our own, Béné *et al.*[30] identified a significant correlation between echogenic intracardiac foci and trisomy 13. Furthermore, How and colleagues and Petrikovsky and colleagues observed 25 out of 5395 and 41 out of 139 cases with echogenic intracardiac foci, respectively, revealing no discernible links between these findings and the presence of any chromosomal abnormalities[31,32].

Most of the studies conducted have examined populations consisting of fetuses with a heightened risk of chromosomal abnormalities and mothers exhibiting risk factors such as advanced maternal age or abnormal serum screening results[33]. Conversely, studies carried out in low-risk populations have indicated that echogenic cardiac foci are likely an alternative manifestation of a normal variant when considered as an isolated finding[22,34]. In clinical practice, when a fetus presents with isolated echogenic intracardiac foci and lacks other risk factors for aneuploidy, healthcare professionals should, primarily consider the general risk of chromosomal aneuploidy. Consequently, for such cases, screening methods such as cell-free DNA screening or first or second-trimester screening are recommended to assess the risk of whole chromosome aneuploidy. However, it is not typically advised to opt for interventional prenatal diagnostic procedures as the initial approach[35].

We also conducted an investigation into the relationship between gestational age and ventricular echogenic foci, yielding results consistent with those reported by Dildy and colleagues. In line with our findings, they found no statistically significant correlation between these two variables[36].

In the context of high-risk pregnancies, several studies have reported that echogenic intracardiac foci do not pose an increased risk of trisomy 21 in fetuses lacking other high-risk factors[37–40].

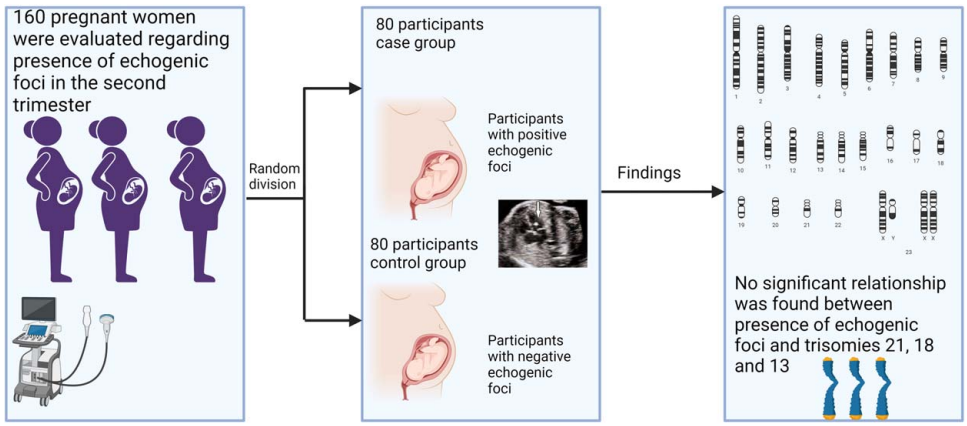

Figure 1. Study process and the findings.

Moreover, Lorente *et al.*[16] have also concluded that echogenic intracardiac foci should be used for identifying fetuses at high risk for trisomy 21.

One important consideration is the psychological impact of children with anomalies on their parents[41,42]. Parents often face a complex array of emotions, including anxiety, fear, and uncertainty about the future[43,44]. Clinical psychologists play a pivotal role in providing emotional support and guidance. They are equipped to help parents process their feelings, cope with the stress of the diagnosis, and prepare for the challenges ahead[45,46]. Psychologists can offer therapeutic interventions tailored to the parents' specific needs, helping them to build resilience and develop coping strategies. Equally important is the role of peer support. Parents often find relief and understanding in communities of individuals who have undergone similar experiences. Peer support groups offer a platform for sharing experiences, exchanging information, and providing emotional support. These groups can be a valuable resource, helping parents to feel less isolated and more empowered to handle their situations[47–49]. The collaboration between psychologists and peer support groups creates a comprehensive support system. Psychologists provide professional, evidence-based guidance, while peer support groups offer practical advice and emotional comfort. Together, they form a holistic approach to caring for parents facing the diagnosis of trisomy in their unborn child[50,51].

Study limitations

However, certain limitations should be acknowledged to contextualize the study's findings. The relatively small sample size of 149 pregnant women may have restricted the generalizability of the results to a broader population. Additionally, the study's retrospective nature and reliance on a single experienced cardiologist for echocardiography raised potential biases. To enhance the robustness of future investigations, consideration should be given to a larger and more diverse sample, prospective study designs, and the involvement of multiple observers. Moreover, the study's focus on specific chromosomal anomalies (trisomies 21, 18, and 13) may have limited its applicability to a broader spectrum of chromosomal disorders.

Conclusion

Based on the outcomes of this study, it has been determined that there is no statistically significant correlation between the presence of echogenic intracardiac foci and trisomies 13, 18, and 21. These findings underscore the critical importance of further diagnostic evaluations to confirm chromosomal abnormalities in cases where echogenic intracardiac foci are identified, particularly within high-risk patient cohorts. It is essential to emphasize that the absence of echogenic foci does not definitively rule out the presence of chromosomal disorders. Therefore, relying solely on echogenic intracardiac foci as a primary marker for prenatal screening is not advisable. Instead, integrating the assessment of echogenic intracardiac foci with other sonographic and laboratory findings can significantly enhance the accuracy and efficacy of prenatal screening protocols.

Ethical approval

The present study was approved by Hormozgan University of Medical Sciences ethical committee. The registry number is IR.HUMS.REC.1400.197.

Consent

Informed consent was obtained from participants involved in the study. All methods were conducted in accordance with relevant guidelines and regulations.

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Author contribution

M.R. and S.R. designed the study. E.A.-S., M.S.A. and M.-H.K. drafted the paper. S.M.H. and N.Y.A. contributed to the study design. A.E.B. and A.G. are responsible for data analysis. S.N., M.R., and S.R. are responsible for data acquisition. All authors are responsible for the interpretation of data, critical revision of intellectual content, and approval of this paper.

Conflicts of interest disclosure

The authors declare that they have no competing interests.

Research registration unique identifying number (UIN)

Our study is an original study and not a systematic review. We have our own ethical verification code supported by Hormozgan University of Medical Sciences IR.HUMS.REC.1400.197).

Guarantor

Shahrokh Rajaei.

Data availability statement

Data from the study can be provided from the corresponding author on reasonable request.

Provenance and peer review

None.

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