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Echogenic intracardiac foci: Associated with increased risk for fetal trisomy 21 or not?

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Echogenic Intracardiac Foci

Associated With Increased Risk for Fetal Trisomy 21 or Not?

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Objective. The purpose of this study was to evaluate the impact of an echogenic intracardiac focus (EIF) on the risk for fetal trisomy 21 (T21) in populations with differing prevalence of T21. ***Methods.*** A retrospective cohort study of pregnancies presenting to our prenatal ultrasound units over 16 years (1990–2006) was conducted. Contingency table analysis of the presence of an EIF and diagnosis of fetal T21 was performed. The groups analyzed included the following: (1) all fetuses with EIF plus other sonographic markers, (2) EIF as an isolated sonographic marker, (3) those younger than 35 years with an isolated finding of EIF, and (4) a group with an isolated finding of EIF excluding those at increased risk for T21 on serum screening. ***Results.*** Echogenic intracardiac foci were found in 2223 of 62,111 pregnancies (3.6%), and T21 was diagnosed in 218 pregnancies (0.4%). The presence of an EIF along with other markers was associated with a statistically significant risk for T21 (positive likelihood ratio [LR], 4.4; 95% confidence interval [CI], 3.2–6.0; $P < .05$). An isolated EIF was not associated with a statistically significant increased risk for T21 in patients younger than 35 years (positive LR, 1.7; 95%, CI 0.7–4.1) and those without abnormal serum screening results for aneuploidy (positive LR, 1.6; 95% CI, 0.8–3.1). ***Conclusions.*** The finding of an isolated EIF on prenatal sonography does not significantly increase the risk for fetal T21 in populations not otherwise at an increased risk for the disorder. An isolated EIF should be considered an incidental finding in patients younger than 35 years and in those without abnormal serum aneuploidy screening results. ***Key words:*** Down syndrome; echogenic intracardiac focus; fetal trisomy 21; prenatal diagnosis; sonography.

Abbreviations
CI, confidence interval; EIF, echogenic intracardiac focus; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; T21, trisomy 21

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An echogenic intracardiac focus (EIF) is defined as an echogenic area appearing within the heart that has sonographic brightness equivalent to that of bone. It is a finding commonly detected during routine anatomic surveys. Echogenic intracardiac foci represent microcalcification and fibrosis of the papillary muscle or chordae but are not by themselves associated with myocardial dysfunction or cardiac structural anomalies.[1,2]

Echogenic intracardiac foci were initially considered normal variants. However, pathologic literature in the early 1990s began to suggest a potential association with trisomy 21 (T21). A case report of 3 fetuses with papillary mineralization noted that 1 of the 3 subsequently was discovered to have T21.[3] Another study noted that 16% of fetuses with T21 had microcalcification of the papillary muscles.[4] This was in contrast to only 2% of fetuses with normal chromosome constitutions with this finding. Many studies linking the presence of an EIF to an increased risk

for T21 soon followed. A meta-analysis in 2003 reported that 15% to 30% of fetuses with T21 had an EIF, whereas this finding was present in only 4% to 7% of unaffected fetuses.[5] The conclusion was that the presence of an EIF increased the risk of Down syndrome.

More recent studies have attempted to clarify the impact of EIF detection during sonographic evaluation of the fetus. Recent evidence has suggested that the finding of an isolated EIF does not confer an increased risk for T21.[6–8] Additionally, the initial studies used patients referred for invasive genetic testing, which represented a high-risk patient population. It is unclear whether the results of these studies could be applied to low-risk patients (eg, patients <35 years and patients with normal serum aneuploidy screening results).

The current body of literature describes trends but does not provide tangible adjusted risk estimates to aid in counseling. Most of these studies were limited by the low prevalence of T21 in low-risk groups. The objective of the study was to evaluate the impact of an EIF on the risk of fetal T21 in populations with differing a priori risk and to determine the screening efficiency and likelihood ratios (LRs) for T21 in fetuses found to have EIFs on sonography. This information would be useful for adjusting a patient's risk before invasive diagnostic testing.

Materials and Methods

This was a retrospective cohort study of pregnancies presenting to our prenatal ultrasound units over 16 years (1990–2006). Approval from the Institutional Review Board at our center was obtained. All fetal anomalies were coded since the beginning of the study time frame in our prenatal database. A computerized database search was performed to identify patients with EIFs and stratified on the basis of a priori risk factors. Gestational ages were confirmed by either first- or second-trimester sonography.

An EIF was defined as a fetal intracardiac lesion that appeared as bright as bone and was detected in at least 2 of 4 standard views during a cardiac examination. The standard views include the apical (4-chamber), lateral (septal), left ventricular outflow tract, and cardiac short axis. In cases in which a karyotype was obtained, the diagnosis of an EIF was made sonographically before knowledge of the karyotype. Fetal karyotypes were confirmed either by prenatal chromosomal analysis or postnatal examination. When postnatal examination findings were suspicious for a chromosomal abnormality, the karyotype was confirmed by a formal postnatal study. Dedicated outcome coordinators routinely obtain outcome information on patients seen in our center.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the presence of an EIF and T21. Positive and negative LRs were then determined, and the 95% confidence intervals (CIs) around these estimates were calculated. Contingency table analysis of the presence of an EIF and diagnosis of fetal T21 for screening efficiency parameters was performed. The groups analyzed included the following: (1) all fetuses with EIF plus other sonographic markers, (2) a group the same as group 1 except that the EIF was an isolated sonographic marker, (3) those younger than 35 years with an isolated finding of an EIF independent of serum screening; and (4) a group with an isolated finding of an EIF excluding those at increased risk for T21 on serum screening. The statistical significance for the association of an EIF and T21 was determined by calculating the P values. $P < .05$ was considered statistically significant. All statistical analyses were performed with Stata version 9.0 software (StataCorp, College Station, TX).

Results

In the cohort of 62,111 pregnancies referred for sonography and genetic evaluation, EIFs were diagnosed in 2223 fetuses (3.6%). Trisomy 21 was diagnosed in 218 of the overall cohort (0.4%). Characteristics of the study cohort and indications for sonography are shown in Table 1. Thirty-four of the 218 T21 cases had an EIF, and it was an isolated finding in 14 cases. A list of associated sonographic findings in the nonisolated EIFs is presented in Table 2.

Analyzing women younger than 35 years allowed evaluation of 42,964 pregnancies. In this cohort, there were 80 cases of T21 (0.1%). Five of the 80 cases (6.3%) had an isolated EIF. There

were 1536 pregnancies with an isolated EIF in the 42,884 pregnancies without T21 (3.6%).

In the cohort of patients without evidence of an increased risk for aneuploidy on serum screening, there were 57,373 pregnancies available for analysis. In this group, there were 155 cases of T21 (0.3%), and 8 of 155 (5.2%) had an EIF, compared with the 1848 fetuses with an isolated EIF in the 57,218 pregnancies without T21 (3.2%).

Efficiency parameters of an EIF in patients with differing a priori risk for the diagnosis of T21 were obtained. The sensitivity, specificity, PPV, NPV, and positive and negative LRs were calculated and are displayed in Table 3. For patients with an EIF (including any other sonographically detected anomalies), the positive LR was 4.4 (95% CI, 3.2–6.0). When an EIF was an isolated finding, the positive LR was 2.0 (95% CI, 1.2–3.3). For patients younger than 35 years with an isolated EIF, the positive LR was 1.7 (95% CI, 0.7–4.1). For patients with low-risk serum screening for aneuploidy, the positive LR was 1.60 (95% CI, 0.8–3.1).

For the entire cohort, there were 2368 patients with major anomalies, constituting 3.81% of the study population. These major anomalies included central nervous system defects, congenital heart disease, a diaphragmatic hernia, omphalocele, gastroschisis, a cleft lip, a clubfoot, and renal disorders. Among the patients older than 35 years, 493 had a major anomaly (2.6%). In the patients with abnormal serum screening results, there were 148 patients with a major anomaly (3.1%).

Table 1. Characteristics of the Study Group

Characteristic	n	%
Mean maternal age ± SD, y	30 ± 6.5	
Mean gestational age at time of sonography ± SD, wk	19.4 ± 1.9	
Maternal race		
White	41,987	67.6
Black	14,301	23.0
Asian	1,678	2.7
Hispanic	744	1.2
Other	3,401	
Indication for sonography		
Advanced maternal age	18,772	30.2
Routine anatomic survey	21,989	35.4
Abnormal serum screening results for aneuploidy	4,738	7.6
Abnormal serum screening results for neural tube defects	1,938	3.1
Suspected anomaly	3,007	4.8
Previous child with aneuploidy	603	1.0
Family history of birth defects	3,888	6.3
Drug/teratogen exposure	1,258	2.0
Other	5,918	9.5

Discussion

Our study provides definitive risk estimates for patients with the finding of an EIF on sonographic scans of the fetus. For all fetuses with an EIF, including those with other sonographic markers and risk factors, the risk of T21 was increased, with a positive LR of 4.4. In the entire cohort when an EIF was an isolated finding, the LR was less pronounced (2.0). Importantly, however, the presence of an isolated EIF in patients younger than 35 years and those without an increased risk for aneuploidy on serum screening did not have an increased risk for T21. Although the positive LRs for these groups were 1.7 and 1.6, respectively, both had CIs that crossed 1, and the results for these "low-risk" groups were not statistically significant at the 5% probability level.[9]

Maternal race did not significantly affect the results of our study. There were 2107 EIFs found in the 60,433 non-Asian patients (3.4%). In contrast, there were 1678 Asian patients in the study cohort, and 116 had an EIF (6.9%). There were 6 cases of T21 in the Asian population, and only 1 of these had an EIF. Therefore, despite the knowledge of an association between EIFs and Asian race,[10] there were not enough T21 cases to comment on the risk of T21 in the Asian population with EIFs.

The detection of an EIF is based on multiple factors.[11] The experience of the sonographer and the thoroughness of the examination are vital for

Table 2. Association of Other Fetal Sonographic Abnormalities in T21 Cases With an EIF

Sonographic Finding	n	%
Thickened nuchal fold	20	6.56
Cystic hygroma	4	3.31
Any major CNS anomaly	27	5.38
Congenital heart disease	16	3.88
Hyperechoic bowel	19	6.53
Renal pyelectasis	77	6.17

CNS indicates central nervous system.

Table 3. Screening Efficiency of an EIF and T21

EIF Type	Patients With Sonographic Finding, n	Cases of T21 in Patients With This Finding, n	Sensitivity, %	Specificity, %	PPV, %	NPV, %	LR+	LR–	P (χ^2)
EIF (all)	2223	34	15.6 (11.1–21.1)	96.4 (96.3–96.6)	1.5 (1.1–2.1)	99.7 (99.6–99.7)	4.4 (3.2–6.0)	0.88 (0.79–0.94)	<.0001
EIF (isolated)	1998	14	6.4 (3.6–10.5)	96.8 (96.6–96.9)	0.7 (0.4–1.2)	99.7 (99.6–99.7)	2.0 (1.2–3.3)	0.97 (0.91–0.99)	.007
iEIF (<age 35 y)	1541	5	6.3 (2.1–14.0)	96.4 (96.2–96.6)	0.3 (0.1–0.8)	99.8 (99.8–99.9)	1.7 (0.74–4.08)	0.97 (0.91–0.99)	.20
iEIF (–IRSS)	1856	8	5.2 (2.2–9.9)	96.8 (96.6–96.9)	0.4 (0.2–0.8)	99.7 (99.7–99.8)	1.6 (0.81–3.14)	0.98 (0.93–1.00)	.17

Values in parentheses are 95% CIs. EIF (all) includes fetuses with other markers of T21; EIF (isolated), only marker of T21; iEIF, isolated EIF; and iEIF (–IRSS), isolated EIF with the increased risk on serum screening (IRSS) group removed.

accurate diagnoses. Also, as ultrasound equipment and technology improve, there may be an increase in the rate of EIF detection. A common indication for further imaging and diagnostic testing, an EIF also has the potential to generate considerable anxiety in parents. Therefore, it is essential to accurately counsel patients on the basis of the best available evidence.

The LR is useful in calculating posttest probabilities for patients undergoing a sonographic examination. By taking a person's pretest odds (eg, risk for T21) and multiplying them by the positive LR, we can derive a patient's posttest odds for the disease in question.[9] The results of our study show that for patients younger than 35 years and those with normal serum screening results for aneuploidy, the finding of an isolated EIF does not significantly adjust their risk for T21 before the sonographic findings.

The definitive prenatal diagnosis of fetal chromosomal abnormalities is accomplished only through invasive diagnostic testing, and these techniques should be available to all women regardless of maternal age.[12] However, both amniocentesis and chorionic villus sampling are associated with small but real risks of fetal loss and other complications.[13] Screening strategies that use second-trimester sonographic findings can help with this counseling process.

Strengths of our study included the large sample size and the use of a single institution. The use of a single center allowed standardization of the definition of an EIF and ensured that karyotype testing could be offered to all patients with an increased risk for T21. Further strengthening our results was the finding of cases of T21 in our low-risk population, which allowed us to more accurately compute contingency table analyses.

Our study was not without its limitations. It was a retrospective design, and additionally, there was a possibility that some cases of EIFs were not coded. Given that fetuses with normal karyotypes constituted 99.6% of our overall cohort, a noncoded EIF would likely be a false-positive result and thus would have potentially increased both our PPV and specificity.

In addition, there was potential overlap in the study populations of the patients younger than 35 years and those without evidence of abnormal serum screening results for aneuploidy. However, sonographic markers should be used to modify a patient's a priori risk for aneuploidy. Regardless of age, if a patient has a low risk of T21 based on serum screening, it can be conferred that the presence of an isolated EIF does not substantially modify this risk. Conversely, patients younger than 35 years who have an increased risk of T21 based on serum screening and an isolated EIF should use the serum screening results for their a priori risk. Future studies could address the potential for overlap in the study populations.

The rate of major anomalies also differed between the groups analyzed. Although biologically there should have been no difference between the groups being evaluated, that the women older than 35 years and those with abnormal serum screening results had different prevalence rates for major abnormalities may have confounded the sensitivity for EIFs in these groups.

The discovery of an EIF should prompt a detailed anatomic survey. However, the finding of an isolated EIF on prenatal examination does not appreciably increase the risk for fetal T21 in populations not already at increased risk for this disorder. An isolated EIF should be considered an incidental finding in patients younger than 35 years and those without abnormal serum screening results for aneuploidy. The risk to benefit ratio does not favor invasive genetic testing in these subgroups.

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