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An isolated intracardiac echogenic focus as a marker for aneuploidy

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KEY WORDS
Intracardiac echogenic focus
Fetal aneuploidy
Ultrasound

Objective: This study was undertaken to evaluate the relationship of an isolated fetal intracardiac echogenic focus in a population of patients with a mixed risk for aneuploidy when presenting for prenatal diagnosis.

Study design: All women referred to our institution for screening ultrasound were prospectively evaluated for the presence of an intracardiac echogenic focus in the fetal heart. Each patient was evaluated for the presence of clinical risk factors including ultrasound findings, biochemical screening, and maternal age. The population of patients was then described and neonatal outcomes were obtained.

Results: A total of 10,875 patients were referred and 176 cases of fetal intracardiac echogenic foci were evaluated. There was an overall prevalence of 1.6% in our population. The patients with other ultrasound findings and/or maternal age older than 35 years who underwent amniocentesis had 3 abnormal karyotypes identified and had identifiable risk factors. In the group less than 35 years, the relative risk was 2.55 of having an amniocentesis for an isolated echogenic focus (with no cases of fetal aneuploidy found) in comparison with our referred group of nonadvanced maternal age patients without any ultrasound markers or findings.

Conclusion: This isolated echogenic finding appears to be a benign variant and not an increased risk for fetal aneuploidy. The chromosomal abnormalities were seen in the group with risk factors including maternal age and/or other ultrasound findings. Evaluation of maternal age, biochemical markers, and ultrasound markers should be used together to help determine the risk of patients with an isolated echogenic focus.

The significance of the ultrasound identification of an isolated echogenic focus in the fetal heart remains controversial. The initial description by Allan in 1986 concluded that this was a benign finding.[1] Pathologic correlation by Brown in 1994 showed that the finding of an echogenic intracardiac focus at ultrasound correlated with mineralization within a papillary muscle.[2] However, several more recent articles have suggested a possible association of an intracardiac echogenic focus with fetal aneuploidy.[3-6] In the most cited article, Bromley et al[4] described an association of Down syndrome with echogenic foci of the heart in her high-risk patient population. In that retrospective study, there were 4 fetuses with echogenic foci associated with Down

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Table I Referral indications

Indication	n (%)
Structural/anatomy survey	95 (54%)
Maternal age $\geq$35 y	63 (35.8%)
Abnormal triple marker screen	15 (8.5%)
Second opinion ultrasound	3 (1.7%)

syndrome in a review population of 22 fetuses with the prenatal diagnosis of trisomy 21. However, only 2 of those 4 had this as an isolated finding. The association of intracardiac echogenic focus and maternal age, biochemical markers, or other ultrasound findings has not been clearly addressed in previous studies. The purpose of this study is to describe the relationship of an intracardiac echogenic focus with or without other associated risk factors in a prospective population referred to our tertiary care prenatal diagnosis program over a 2.5-year period. Our null hypothesis is that an isolated intracardiac echogenic focus without other risk factors is a benign finding.

Material and methods

All second trimester (14-26 weeks) patients referred to our institution for an ultrasound examination were eligible for this study. This study was performed over 2.5 years and no changes in method of ultrasound evaluation or equipment took place during that time that could have impacted the findings. Referring indications included a screening ultrasound evaluation, abnormal triple marker screening, advanced maternal age, or suspicious ultrasound findings. All patients were prospectively evaluated by 1 of 6 Maternal-Fetal Medicine specialists using high-resolution ultrasound equipment (ATL 3000, ATL 5000, upgraded Acuson 128XP) with transabdominal transducers. Each study was documented by videotape and hardcopy image. In all cases each patient underwent a detailed examination that included the standard biometric measurements (biparietal diameter, head and abdominal circumference, femur and humeral lengths). Subtle markers including nuchal-fold thickness, brachycephaly, ventriculomegaly, choroid plexus cysts, pyelectasis, echogenic bowel, hand and foot abnormalities, shortened extremities, mandibular length, and intracardiac echogenic focus were evaluated as potential markers for fetal aneuploidy. Assessment for major structural defects was also performed. In addition, all fetal hearts were evaluated with a full cardiac evaluation, including identification of a normal 4-hamber view, left and right outflow tracts, short-axis view and, when possible, aortic and ductal arches. Color flow and pulsed wave Doppler evaluation was also performed.

We defined an intracardiac echogenic focus as a small structure within the fetal ventricular chamber that had an echogenicity similar to or greater than that of the surrounding bone. When an echogenic focus was found, the number, location and movement with the atrioventricular valve were documented as well as the ventricular chamber size and evaluation of cardiac function. This was evaluated in the transverse and lateral views of the heart as well. In each patient in whom an intracardiac echogenic focus was identified, a more detailed fetal heart echocardiographic examination was carried out. If an abnormality was found, or could not be ruled out, a fetal-pediatric cardiologist repeated the fetal echocardiogram.

If an intracardiac echogenic focus was identified, patients were advised of the finding and informed about the association of this finding with aneuploidy (up to 1% risk).[7] In addition, where appropriate, the patients were also counseled about their risk of aneuploidy based on other available data, including advanced maternal age, biochemical screening results, and other associated ultrasound markers. Patients with isolated intracardiac echogenic focus were offered the option of genetic counseling and fetal karyotype if desired. Patients with intracardiac echogenic focus and any other risk factor (maternal age $>$35, positive triple marker, additional ultrasound markers) received genetic counseling and were offered fetal karyotype.

We obtained medical records of all identified cases of intracardiac echogenic foci. Outcomes of each of these cases were determined either with a combination of amniocentesis and pregnancy outcomes at termination or delivery. If amniocentesis was not carried out, birth records were reviewed for any suspicious findings or neonatal dysmorphic features. Statistical analysis included determination of the P-value derived with χ^2 testing.

Results

There were 10,875 patients referred during the study period, and there were 175 women and 176 (1.6%) fetuses with an intracardiac echogenic focus (including 1 set of twins). Table I describes the indications for referral for the patients with the intracardiac echogenic foci. The majority of patients (54%) were referred for fetal structural survey. The mean maternal age was 31.8 years and the mean gestational age at the time of the study was 19.1 weeks. Table II describes the number of patients with intracardiac echogenic foci stratified by maternal age (patients $<$35 and $\geq$35 years). In addition, it details the proportion of patients with isolated intracardiac echogenic foci as well as intracardiac echogenic foci with accompanying clinical risk factors (biochemical screening and ultrasound findings) and amniocentesis results.

Table II Maternal and ultrasound characteristics

	Maternal age < 35 y (107 patients) n (%)	Maternal age ≥ 35 y (69 patients) n (%)	Total opulation (176 patients) n (%)
Isolated echogenic foci	90 (84%)	51 (74%)	141 (80%)
Other ultrasound findings	17 (16%)	18 (26%)	35 (20%)
Isolated focus + risk factors			
≥35 y	0	69 (100%)	69 (39%)
Positive triple marker	12 (11%)	3 (4.3%)	15 (8.5%)
Ultrasound findings	17 (16%)	18 (26%)	35 (20%)
Ultrasound findings and positive triple marker	1 (0.9%)	1 (1.4%)	2 (1.1%)
Amniocentesis done (% yes)	40 (37%)	57 (83%)	97 (55%)
Isolated focus	27 (25%)	43 (62%)	70 (40%)
Ultrasound findings	13 (12%)	14 (20%)	27 (15%)
Had amnios performed	13/17 (76%)	14/18 (78%)	27/35 (74%)
Positive triple marker	12 (11%)	3 (43%)	15 (85%)
Ultrasound findings and positive triple marker	2 (1.9%)	0	2 (1.1%)
Abnormal karyotype	0	3 (4.3%)	3 (1.7%)

Of these 176 cases, there were 3 with abnormal karyotypes. All 3 of these patients were referred to our prenatal diagnostic center because of maternal age older than 35 years at time of delivery. Their mean maternal age was 38.1 years.

An isolated intracardiac echogenic focus as the sole marker was seen in 141 (80%) of the patients. Of the women older than 35 years, 74% had isolated intracardiac echogenic focus, which is similar to the women younger than 35 years. In the women older than 35 years, 26% had other ultrasound findings compared with 16% of women younger than 35 years ($P = .114$). The location of the foci varied but was similar for both groups. Fifty-five percent of the patients (97/175) underwent amniocentesis: 83% of those older than 35 years underwent amniocentesis, whereas 37% of those younger than 35 years underwent amniocentesis ($P < .05$). This *P*-value was calculated from these 4 groups of patients, all women with isolated intracardiac echogenic foci and in association with other ultrasound findings suggestive of aneuploidy. There were 3 cases of trisomy 21 identified through amniocentesis and all occurred in the group older than 35 years.

With regard to the risk factor of advanced maternal age in the patients with trisomy abnormal karyotypes, only 1 patient had an isolated echogenic focus. The other 2 patients had additional risk factors of ultrasound findings and a positive triple marker screen for the other 2 trisomy 21 karyotypes. Eighteen patients had another ultrasound marker in addition to the intracardiac echogenic focus. Two of these women had trisomy 21 fetuses, each with 1 additional ultrasound finding, pyelectasis and increased nuchal fold. Three patients with multiple ultrasound findings were also screen positive with the triple marker. None of these patients had trisomy 21.

Overall, 77.6% of patients younger than 35 years had triple marker results recorded. In this group, there were 12 patients (11%) with isolated echogenic foci and positive triple marker screen. All these patients elected to have amniocentesis with normal results. Seventeen patients had additional ultrasound markers in addition to the intracardiac echogenic focus and these included clinodactyly, nuchal fold, prominent stomach bubble, pyelectasis, short femurs, echobright bowel, choroid plexus cysts, heart defects, and foot abnormality. One of these patients had 2 additional markers seen. Thirteen of these patients had fetal karyotyping with normal results.

Twenty-seven patients (30%) had an isolated intracardiac echogenic focus finding and underwent amniocentesis with all having normal karyotypes. The relative risk for women younger than 35 years of having an amniocentesis caused by an isolated intracardiac echogenic focus is 2.55 (with 95% CI of 1.69-3.85). Young women with echogenic focus and any additional ultrasound findings are 2.5 times more likely to have an amniocentesis in comparison with those without any additional risk factors. Because none of these karyotypes were abnormal, this exposed these women to the potential for pregnancy loss caused by the procedure in fetuses with a low risk of aneuploidy.

All patients with intracardiac echogenic foci underwent fetal echocardiography. Four patients (2.3%) were identified with congenital heart disease. Fetuses with congenital heart disease had intracardiac echogenic foci that were reported as atypical in their location, or movement with the atrioventricular valves and configuration

in the fetal heart. In addition, there were 15 patients (8.5%) who had a small perimembranous ventricular septal defect identified by the fetal pediatric cardiologist. These patients underwent serial fetal echocardiography and the lesions were found to be of no hemodynamic significance. In most cases, the defect resolved with advancing gestational age and is probably related to a normal developmental variant. Our detection rate of congenital heart defects was greater because fetal echocardiography was performed by a single pediatric cardiologist with expertise in identification of fetal congenital heart disease therefore improving our current perinatal detection rate.

Comment

Overall, the incidence of echogenic foci identified in the fetal heart in our series was 1.6%. This is not significantly different from previously reported studies.[8-13] The lowest reported incidence was 0.13% and the highest was 20%.[14,15] The 4 larger series have reported an incidence between 3% and 6.9%.[6,7,16,17]

Our low rate, relative to other studies, can be explained by several factors. First, we used strict criteria for diagnosing an intracardiac echogenic focus, and therefore may not have included some patients who would have screening positive in other studies. In addition, we routinely use 3.5 to 5.0 MHz transabdominal linear array transducers when evaluating fetal hearts. We can only speculate why some authors report a higher incidence. Many authors may overcall papillary muscle hypertrophy as an echogenic focus in the fetal heart. Likewise, the higher reported incidences in other studies may be due to a smaller number of patients, patient referral indications, use of higher frequency transducers, vaginal versus transabdominal examination, scanning in the early second trimester, maternal body habitus, and methods of data acquisition. For example, it has been shown in evaluating echogenic bowel, the frequency of the transducer plays a very important role. Higher frequency transducer is associated with increased likelihood of echogenic bowel. Transducer frequency may also impact the identification of intracardiac echogenic foci. The gestational age and method of scanning (transabdominal vs transvaginal) as a contributor to the prevalence of intracardiac echogenic foci has yet to be determined. In contrast to the study by Achiron et al,[16] the current study was skewed to late second trimester ultrasounds, all of which were performed transabdominally. The study by Achiron et al included patients at an early gestational age and almost all evaluations were performed transvaginal. It is interesting to note that on follow-up examinations, 60% of the patients in his study no longer had an echogenic focus identified. This is in contrast to our observations. Intracardiac echogenic foci noted during second trimester transabdominal ultrasound examinations persisted throughout gestation and did not resolve on subsequent evaluations. Whether this is a different marker than first identified at less than 14 to 16 weeks remains to be determined. We did not follow the natural history from the first-trimester screening to late second-trimester screening to see if what we are calling echogenic focus is identical to that which is described earlier in pregnancy. As first-trimester screening and scanning becomes more prevalent, this would be an important observational study to do, particularly noting the exact location and evolution or resolution of the echogenic focus with serial ultrasounds. Furthermore, we did not measure the size of the focus identified and included patients in whom multiple foci were seen. It is speculated that this increased our case ascertainment. Lastly, it is possible the fetal position (spine anterior or posterior) at the time the procedure is performed as well as the amount of time spent evaluating the fetal heart may play a role in the ability to identify the presence or absence of intracardiac echogenic foci.

The variation in the rate of fetal aneuploidy in patients with intracardiac echogenic foci can be explained by different background patient risks such as maternal age, ethnicity,[18] biochemical markers, and the presence of other sonographic markers. As demonstrated in this article, the risk of fetal aneuploidy in a patient with an isolated intracardiac echogenic foci is most likely to occur in women at high risk, specifically advanced maternal age, positive biochemical screens, or additional ultrasound findings. The extent to which the risk factors coexist is an important predictor, although the exact mathematical relationship remains to be determined. Previous reports support this contention. Many of the articles reporting an association with fetal aneuploidy occurred in patients at high risk for aneuploidy, based on other clinical risk factors, whereas the low association with fetal aneuploidy occurred in the low-risk population.[4-6,17]

Unlike previous studies, we attempted to describe the risk of trisomy 21 in patients with isolated intracardiac echogenic focus compared with the risk of trisomy 21 in patients with foci and other clinical risk factors (maternal age, biochemical results, and ultrasound findings). We found that for patients younger than 35 years, the isolated echogenic focus in the heart does not appear to be associated with an increased risk for fetal aneuploidy. This fact, although different from the initial reports by Bromley et al[4] is consistent with earlier work reported by the same group.[19] Benacerraf et al[19] proposed the concept of a scoring system that assigned points for various ultrasound findings. When using their reported system, they found that for patients who are younger than 35 years and only 1 marker such as echogenic intracardiac focus was present, there was not an increased

risk of fetal aneuploidy.[19,20] Although this has been corroborated by other investigators Nicolaides et al[21] and Rotmensch et al,[22] a prospective study by Simpson et al[7] reported on 228 patients with isolated echogenic focus without any other sonographic abnormalities, and found 2 chromosomal abnormalities. There was no attempt to evaluate these findings in the context of maternal age or serum biochemical results. For women younger than 35 years, the relative risk for amniocentesis and its associated complication rate may not be warranted. In this study, 30% of women underwent an amniocentesis on the basis of isolated echogenic foci solely, with normal karyotype results.

This study suggests that there is not an increased risk of aneuploidy in patients with isolated intracardiac echogenic foci for women younger than 35 years. Although we are unable to determine whether a similar conclusion can be reached in a higher risk group, specifically women who are older than 35 years. It is difficult to delineate from this study or currently available studies whether there is a cumulative effect of multiple markers and maternal age.

One group has attempted to provide relative risk and positive predictive values to improve counseling for these patients.[4,6] The numbers of patient in this study, although large, still do not provide sufficient numbers of abnormal outcomes to provide adequate calculations of odds ratios. Power calculations reveal the need to identify 648 patients with 540 having isolated echogenic foci and 108 with other ultrasound findings and the need to screen approximately 40,000 patients. It is unlikely that a single institutional study will ever achieve these numbers. A multicenter collaborative trial will be needed to make meaningful conclusions to provide for policy recommendations in this controversial area.

In conclusion, in the patients younger than 35 years, with whom there is an isolated echogenic intracardiac focus and no other clinical risk factors (normal serum biochemistry and no other ultrasound markers), amniocentesis may not be indicated. It is likely that our future trends in prenatal diagnosis involving complex calculations taking into account maternal age, biochemical markers, with first- and second-trimester ultrasound findings to adjust the a priori risk of a patient with regard to her absolute individual risk for fetal aneuploidy will be routinely available and implemented. Further studies are needed to evaluate the potential relationship between any isolated ultrasound marker in women whom the biochemical screen with multiple markers raised their background risk but not to the critical cutoff level to offer invasive prenatal testing.

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Editor's note: This manuscript was revised after these discussions were presented.

Discussion

Dr Roger Rowles, Yakima, Wash. The presence of ultrasound markers for fetal aneuploidy, most commonly trisomy 21, has been known since the early work of Benacerraf and others[1] 20 years ago. These markers early on included, cystic hygromas, major cardiac defects, and shortened long bones. As technology has advanced, many more findings have been described, including such subtle ones as the sandal gap foot and absent nasal bone.

The presence of an intracardiac echogenic focus (IEF) was described by Schecter et al[2] in 1987 and was thought to be a benign finding, reflecting thickening of the papillary muscles and chordae tendinae in the fetal heart, secondary to varying degrees of excavation of the ventricle wall, the means by which these structures form. Pathologic correlates at autopsy have shown microcalcifications in these structures. Initially, this was thought to be a normal anatomic variant, but multiple studies since that time have suggested that it is a marker for aneuploidy, increasing the likelihood ratio or risk by a factor anywhere from 1.4 to 2.8.

Dr Bradley and her colleagues, in this prospective study, attempt to show what has not yet been conclusively demonstrated in other studies. That is, that an IEF by itself, absent the risk factors of advanced maternal age, other ultrasound markers, and an abnormal serum screening, does not increase the baseline risk for fetal aneuploidy.

Their patient population includes more than 10,000 women seen at a large referral center. At least 45% of these women were referred because of other markers that would increase their risk of aneuploidy. Among this group, 176 women (1.6%) were found to have an IEF, a lower percentage than most studies report and surprisingly low, given the presence of other risk factors at the time of referral. This low rate may be explained by technique, and by the late gestational age at which these women were scanned. For 80% of these women, the IEF was the only sonographic marker suggestive of aneuploidy.

Dr Bradley's significant finding is that, of these 176 women, only 3 were found to have aneuploidy fetuses, all trisomy 21, and these 3 all were over 35 years. In addition to age as an additional risk factor, 2 of these 3 also had positive serum screens and other ultrasound findings.

Given these findings, Dr Bradley suggests that women under 35 years with an isolated IEF, and no other risk factors, be counseled that their risk for fetal aneuploidy is not increased, and that their decision for further testing be made on the a priori risk on the basis of maternal age and serum screening results. By her conclusion, a patient with an isolated IEF is 2.5 times more likely to have an amniocentesis than cohorts in the general population with the same a priori risk. These women are therefore subjecting themselves to a potential procedure related pregnancy loss with no apparent benefit.

Dr Bradley and her colleagues have assembled one of the largest prospective studies looking at isolated IEF, but, as she has acknowledged, the numbers are still too small to accurately calculate the odds ratio for this finding or to make definitive recommendations. Others have looked at isolated ultrasound markers and have attempted to calculate likelihood ratios. Bromley et al,[3] in an extensive prospective review in the *Journal of Ultrasound Medicine* 2 years ago, assigned a likelihood ratio of 1.4 to an isolated IEF. They suggested that the a priori risk be multiplied by 1.4 to give these women an accurate risk assessment. However, their large study was not done on a high- risk population, whereas Dr Bradley and her colleagues' study includes both high-risk and low-risk patients.

Coco et al,[4] in the largest study to date, reported earlier this year on more than 12,000 patients who were prospectively evaluated for an IEF. They found this focus present in 3.8% of the patients, and 90% of the time it was an isolated finding. Their findings were very similar to Dr Bradley's in that, of the 3 fetuses with an IEF found to have trisomy 21, 2 had other ultrasound markers, and the 1 in which it was an isolated finding was in a patient 35 years old.

I have several questions for Dr Bradley. We will be hearing next on this program from Dr Platt about first-trimester screening for fetal aneuploidy. Where does the second-trimester genetic sonogram, which may or may not include the IEF, fit into the scheme of either sequential or integrated screening for fetal aneuploidies?

A recent review by Seeds[5] in the *American Journal of Obstetrics and Gynecology* suggested that the procedure-related pregnancy loss rate after mid-trimester amniocentesis, performed with ultrasound guidance, is 1 in 166, higher than has been thought in the past. Did you have any procedure-related fetal losses from amniocentesis, and what figure are you currently using as your loss rate in counseling these women before amniocentesis?

One study has suggested that Asian women are almost 4 times more likely to have a fetus with IEF