Isolated choroid plexus cyst or echogenic cardiac focus on prenatal ultrasound: is genetic amniocentesis indicated?

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OBJECTIVE: The purpose of this study was to determine whether or not genetic amniocentesis is warranted when isolated choroid plexus cysts (CPC) or echogenic cardiac foci (EF) are noted on prenatal ultrasound.

STUDY DESIGN: We performed a retrospective analysis on patients from our perinatal database. All obstetric patients with CPC or EF noted on second-trimester perinatology ultrasound from April, 1998 to November, 2004 were included. Information regarding ultrasound findings and neonatal outcome were analyzed.

RESULTS: During the study period, 515 patients with CPC or EF were evaluated. Of these, 429 (83.3%) had isolated CPC or EF and 86 (16.7%) had additional risk factors. The incidence of abnormal karyotype was 0 versus 2.3%, respectively ($P = .03$). The additional risk factors considered were: advanced maternal age, abnormal serum triple marker screening, and/or other abnormal ultrasound findings. Furthermore, during the study period there were 20,122 live births and 27 (0.1%) cases of aneuploidy diagnosed postnatally. Of these, none had isolated CPC or EF on prenatal ultrasound.

CONCLUSION: CPC or EF noted on prenatal ultrasound warrants referral for careful consultative ultrasound evaluation. In the absence of other risk factors, however, genetic amniocentesis for isolated CPC or EF does not appear to be necessary.

Key words: amniocentesis, choroid plexus cyst, echogenic cardiac foci, prenatal ultrasound

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The clinical significance of ultrasound markers for aneuploidy remains an area of active investigation in perinatal medicine. Echogenic intracardiac foci (EF) of the fetal heart and choroid plexus cysts (CPC) of the fetal CNS are 2 such markers that have been studied extensively in this regard. While an EF within 1 of the fetal ventricles was described initially as a normal variant in the 1980s,[1,2] since that time other studies have associated the finding with an increased incidence of Down syndrome.[3-10] Choroid plexus cysts are thought to form physiologically due to entrapment of cerebrospinal fluid within the villi of the lateral ventricle and have no pathologic importance.[11,12] However, like EF some studies have demonstrated an association between CPC detection on prenatal ultrasound and aneuploidy.[13-18]

While detection of EF or CPC can be useful in managing patients at high risk for aneuploidy, their value in the management as isolated findings in low risk women remains unclear. In many cases patients are counseled regarding the isolated findings and subsequently undergo genetic amniocentesis which, in and of itself, entails additional risk. Thus, our purpose was to determine whether or not genetic amniocentesis is warranted when isolated EF or CPC is noted on prenatal ultrasound.

Materials and Methods

We performed a retrospective cross-sectional analysis of patients from the Kaiser Permanente, Baldwin Park, Calif, perinatal database. This study was approved by our Institutional Review Board and complied with all standards, including patient privacy protection stipulations, contained therein. All patients referred for consultative ultrasound to our perinatology center for EF or CPC noted on routine second trimester obstetric ultrasound examination from April, 1998 to November, 2004 were included in this study.

The patients were evaluated by 1 of 2 attending Maternal-Fetal Medicine specialists. Data were collected prospectively and then analyzed retrospectively for the purpose of this study. Where appropriate, information was also abstracted from maternal and neonatal hospital charts and other computerized data sources. The ultrasound examinations consisted of a comprehensive assessment of fetal biometry and anatomy using either a Siemens Aspen (Malvern, PA) or Sequoia high-resolution ultrasound machine. In addition to undergoing a complete anatomic survey pursuant to guidelines set forth by the AIUM,[20] all patients were evaluated for additional markers for aneuploidy, including nuchal skinfold thickness, ventriculomegaly, limb anomalies, pyelectasis, and cardiac defects. In addition to these ultrasound findings, advanced maternal age and abnormal serum triple marker screening (risk greater than

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TABLE 1
Outcome results of study patients

	Isolated EF/CPC	EF/CPC ± risk factors*	*P* value
N (%)	429 (83.3%)	86 (16.75%)	
Amniocentesis performed	158 (36.9%)	37 (43.3%)	.93
Abnormal karyotype	0	2 (2.3%)	.03

* Risk factors included: advanced maternal age, abnormal serum triple marker screening, and/or other abnormal ultrasound findings.

1:190) were considered risk factors for aneuploidy. EF was diagnosed when an echogenic structure on or around the papillary muscle in either fetal ventricle appeared brighter than surrounding bone. CPC was diagnosed when a distinct cystic structure was noted in the area of the choroid plexus within the fetal lateral ventricle. Both unilateral and bilateral EF and CPC of any size were included in the study. The finding was considered "isolated" when no other anatomic abnormality other than the EF or CPC was noted. Data regarding cases of aneuploidy diagnosed postnatally were also analyzed.

Patients were stratified based on the presence or absence of risk factors and the groups compared. To calculate statistical power, we assumed an incidence of EF/CPC of 5% in the general population, a baseline risk for aneuploidy of 0.5% in the general population, and a 15-fold increase in Down syndrome relative risk with prenatal detection of EF/CPC.[4] As such, with 95% significance and 90% power, 207 cases of EF/CPC are required to detect a statistically meaningful difference. Statistical tests used included χ^2 test, 2-tailed *t* test, and Fisher exact test, as appropriate. All analyses were 2-sided, with a P value $< .05$ considered statistically significant.

Results

During the study period, 515 total patients with CPC or EF were evaluated. Of these, 240 had EIF (46.6%) and 275 had CPC (53.4%). Patients with isolated EF/CPC were compared to those with EF/CPC and additional risk factors. These results are summarized in Table 1. For the entire study population, the mean maternal age was 29.4 + 3.2 years. For the subgroup with advanced maternal age, the mean maternal age was 37.3 + 2.1 years. Mean gestational age for perinatology ultrasound evaluation was 19.3 + 0.7 wks. The racial distribution of study patients was as follows: 57% Hispanic, 18% Caucasian, 16% Asian, 6% African American, 3% other. We did not note a significant difference in EF or CPC distribution based on racial background. Additionally, genetic counseling was only offered to these patients if the EF or CPC was not an isolated finding (that is, an additional abnormality was detected on the consultative ultrasound). Patients without second trimester maternal serum screening were not managed differently.

Additional data were analyzed with regard to cases of aneuploidy diagnosed postnatally. For the period studied, there were 20,122 live births and 27 (0.1%) cases of aneuploidy diagnosed postnatally. These were all cases of Down syndrome. Two cases with trisomy 18 with known multiple major anomalies diagnosed in utero were excluded from analysis. Of the 27 Down syndrome cases, none had isolated EF/CPC noted on prenatal ultrasound ($P = .95$). Isolated EF/CPC in the absence of additional risk factors had a 0% positive predictive value in detecting aneuploidy.

Comment

So-called ultrasonographic "soft-markers" for aneuploidy can be useful in mitigating genetic risk and counseling patients, but those markers with low predictive values can result in unnecessary anxiety in parents and practitioners with limited clinical yield at best. While findings such as true structural cardiac defects (eg, ventriculoseptal defects, and endocardial cushion defects), duodenal atresia, and cystic hygroma portend a risk for aneuploidy ranging from 20-80%,[21-23] the predictive value of isolated "soft" findings like EF or CPC remains extremely low.

In a recent study by Bradley et al,[5] EF was noted in 1.6% of patients referred for consultative ultrasound and was shown to be a benign variant not associated with an increased risk for aneuploidy in patients without additional risk factors (abnormal maternal biochemical screening, advanced maternal age, etc). Similarly, Coco and Jeanty[11] demonstrated in their study of isolated CPC that amniocentesis is not acceptable if CPC is an isolated finding. Other reports have demonstrated similar results.[4,13,19]

In the present study, we have shown that in patients with isolated EF/CPC and no other risk factors, the risk for aneuploidy is not increased. As such, we propose that these patients be advised that these findings are normal variants that do not require additional invasive testing. Our findings are further corroborated by the postnatal outcomes data we analyzed, which again demonstrated no cases of isolated EF/CPC in a population of newborns with aneuploidy diagnosed postnatally.

We recognize the limitations of the present study, including the retrospective design and potential interobserver variability inherent in diagnosing either EF or CPC on ultrasound. However, we have reported on a large number of patients from a single center with a study that had adequate power to detect a statistically significant difference.

Furthermore, our study design was unique in that we augmented our results by reviewing antepartum ultrasound data from cases of aneuploidy diagnosed postnatally. Thus, genetic amniocentesis does not appear to be indicated in low risk patients with isolated EF/CPC noted on prenatal ultrasound. ■

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Discussion

Kimberly D. Gregory, MD, MPH. Dr Ouzounian and his colleagues have written a concise paper addressing the low yield of genetic amniocentesis in the setting of an isolated choroids plexus cyst (CPC) or echogenic cardiac focus (ECF) in low risk women (age $<$ 35, normal serum screening, no other ultrasound findings). Using a retrospective institutional perinatal database encompassing 6 years (1998-2004), they identified 515 patients with these findings. There were no cases of aneuploidy identified prenatally or postnatally in the 429 patients who had isolated findings, whereas there were 2 cases of aneuploidy among the 86 patients who had additional risk factors. Furthermore, during the entire study period, there were 20,122 live births and 27 (0.1%) cases of aneuploidy diagnosed postnatally at this center. None of the postnatal cases had isolated ECF or CPC at the time of second trimester ultrasound. The authors concede the limitations of their retrospective study. They state that they had 90% power (95% significance with 207 cases), based on the following assumptions: 5% prevalence of ECF/CPC, and increased risk of Down syndrome to 15% from background risk in this setting.

Isolated CPC and echogenic foci were first reported in the late 80s.[1,2] Numerous authors report an association of these findings with aneuploidy; however, upon further review—it is argued that these findings in isolation, without other risk factors are likely normal variants.[3,4] Risk factors associated with increased likelihood of aneuploidy include AMA, abnormal serum marker screen, or additional ultrasound findings suggestive of aneuploidy. Several prominent colleagues advocate that genetic amniocentesis is not warranted with these isolated findings. And, in fact, some authors have gone so far as to propose that the patient not even be told about the findings due to the potential for harm (anxiety, amniocentesis, and potential miscarriage).[5]

I commend you for addressing a common clinical problem with significant personal, professional, and health policy implications.

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