

Association between echogenic intracardiac focus in first trimester and biochemical screening-an analysis

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Abstract

Introduction: to analyze the relation between presence of EIF in the first trimester, nuchal translucency (NT) and combined biochemical screening.

Methods: a total of 1245 viable low-risk singleton pregnancies was scanned from 11 to 14 weeks gestation. The presence of echogenic intracardiac focus (EIF) in the fetal heart was noted. The ultrasonography was performed by a Fetal Medicine Foundation (FMF) accredited Fetal Medicine Consultant, using recommended guidelines transabdominally and transvaginally when required, by Voluson E6 (GE Healthcare, Kretztechnik, Zipf, Austria). Patients were assessed for the estimated risk of aneuploidy based on their combined first trimester screening report, that included Maternal serum Beta HCG, PAPP-A and nuchal translucency (NT) scan using LifeCycle software. Nasal bone was not included for calculation of risk. An analysis was then performed between the presence of EIF, combined first trimester screening and NT scan reports.

Results: in 26 patients among the 1245, echogenic intracardiac focus was identified. Ductus venosus and tricuspid flow was assessed and were found to be normal. The biochemical screening for all patients were screen-negative. NT value of the EIF and combined first trimester screening fetuses were retrospectively analyzed. Taking this into consideration, all the fetuses identified with EIF, were observed to fall under low-risk category.

Conclusion: presence of EIF in the first trimester does not necessarily mean increased risk for ane-

uploidy. Larger multivariate studies incorporating ultrasound soft markers identified in first trimester scan in detecting aneuploidy will assist physicians in adequate counseling of mothers and thus help in better guidance and management.

Key words: perinatal ultrasound, EIF, echogenic intracardiac focus.

Introduction

A number of soft markers, also known as major structural defects have been reported in about 70-75% of Down syndrome cases. These soft markers usually identified during second trimester sonography include increased nuchal-fold thickness, renal pyelectasis, short femur, short humerus, hyperechogenic bowel and echogenic intracardiac focus (EIF) (1). However, with improvements in ultrasound imaging techniques and the universal use of first trimester scan and screening, the focus of Down syndrome screening has shifted from second to first trimester in the recent years. There is also an increased possibility of detection of these ultrasound soft markers, specially the EIF in the first trimester.

A study by Whitlow et al. has shown that although majority of aneuploidies were detected by nuchal translucency (NT) and the presence of structural abnormalities, the detection rate increased further by 3% with the usage of ultrasound soft markers in the first trimester (2). Dagklis et al. has suggested that the use of soft markers in first trimester can improve the accuracy of screening but has not analyzed its relationship with biochemical screening (3).

A study by Thilagnathan showed that in a low risk population screened by NT or biochemical screening, there is no significant association between isolated EIF in second trimester scan and Downs syndrome (4). According to Prefumo et al., EIF in 20 weeks scan does not alter the first trimester NT based risk. These studies have shown the relationship between first trimester risk assessment and EIF seen in second trimester scan (5). But, the prevalence of EIF in first trimester seems to be 2-3 times lower than in second trimester (3). This indicates the need to systematically analyze the relation between presence of EIF, in the first trimester, nuchal translucency (NT) and combined biochemical screening. Thus, this was the aim of our study.

Materials and method

This is a retrospective study that included a total of 1245 viable low-risk singleton pregnancies, scanned from 11 to 14 weeks gestation. The study period was 2 years, from March 2015 to December 2017, carried out at a Fetal Medicine Center in South India. The details of the scan and investigations were provided to patients, prior to the each procedure. The ultrasound was performed by a Fetal Medicine Foundation (FMF) accredited Fetal Medicine Consultant, using the recommended guidelines. The ultrasonography was performed transabdominally and transvaginally when required, by Voluson E6 (GE Healthcare, Kretztechnik, Zipf, Austria). During routine first trimester scan, presence of echogenic intracardiac focus in the fetal heart was noted. It was identified in 26 of 1245 patients. Thereafter, in all patients in with EIF biochemical screening was performed.

Patients were assessed for the estimated risk of Trisomy 21 based on their combined first trimester screening report, that included maternal serum Beta HCG and PAPP-A and nuchal translucency (NT) scan using Life Cycle software. Nasal bone was not included for calculation of risk.

Thereafter, an analysis was performed between the presence of EIF, combined first trimester screening and NT scan reports.

Results

First trimester scan was performed in 1245 singleton pregnancies, from 11 to 14 weeks of gestation and EIF was identified in 26 of them. The average age of the women was 27. Median NT was 2.1. Ductus venosus and tricuspid flow was assessed and were found to be normal. Nasal bone was present in all these fetuses. However nasal bone was not included for risk calculation. Combined first trimester screening and NT reports of the EIF fetuses were analyzed. The biochemical screening for all patients were screen-negative and were observed to fall under low-risk category (Table 1).

Discussion

An echogenic intracardiac focus (EIF), also known as

a “golf ball”, is defined as a small structure within the fetal heart with similar or greater echogenicity to the surrounding bone. This has been a subject of discussion for more than two decades, in antenatal ultrasound. It was first reported as a normal variant in 1987 by Schechter et al. (6). EIF or microcalcification within the papillary muscle, with echogenicity similar to or greater than that of surrounding bone, without acoustic shadowing. They are usually single, measuring up to 1-2cm in diameter. In 6-11% of the cases, it can be multiple. It is more commonly seen within the left ventricle but its presence in right ventricle (0-25%) and in both ventricles (1.5-7.6%) have also been reported (7). Various Authors have suggested that calcification within the papillary muscle might be the cause of EIF noted at prenatal ultrasound examinations. Apart from this, early ischemic changes in papillary muscle due to abnormal vasculature and incomplete fenestration of the papillary muscle or the chordae tendinae are also possible explanations for the cause of this finding. The general course of EIF is that it disappears as the gestation age advances in 95% of the cases. At times, the EIF may just be a false positive finding, because even the papillary muscles are often visible as echogenic points (8). Reduction of the current gain ensures that it does not fade prior to echogenicity of the ribs. This minimizes the possibility of a false positive test.

In chromosomally normal fetus, EIF is not associated with congenital heart defects. Since these fetuses did not show any signs of cardiac dysfunction, the presence of isolated EIF is not an indication for fetal echocardiography in low risk population (9). With regards to the prevalence of EIF, it varies widely among populations; that is from 0.5 to 20% at anomaly scan. At 11-14 weeks, 0.7% of fetuses have echogenic focus in the ventricle of the heart. In our study that comprised of 1245 Asian women, it was noted that approximately 2% of the total number of fetuses scanned turned out to have an EIF in first trimester. In a study by Shipp et al., it was noted that Asian mothers had an odds ratio of 3.8 for having a fetus with EIF, as compared to white mothers (10). Also, in an Indian study, the prevalence of EIF represented 17.2% of the total number of fetuses scanned (6).

A study by Prefumo et al. has suggested that there is no risk adjustment to maternal age and NT based risk is required if isolated EIF is found in second trimester (5). According to Huang et al., the first-trimester com-

Table 1. Risk of aneuploidy based on maternal age, combined first trimester screening test and nuchal translucency (NT) in fetuses identified with EIF.

Risk	Trisomy 21	Trisomy 18	Trisomy 13
1 in < 250	None	None	None
1 in <1000	14	None	None
1 in 1001 - 5000	12	None	None
1 in >5000	None	26	26

bined screening result appears to be a much more powerful marker for Trisomy 21 than the presence of EIF in second trimester (11). In low risk women the LR of Trisomy 21 for fetuses with EIF was not different from that of fetuses without EIF in this study. Our study has shown presence of EIF in first trimester is not associated with increased biochemical risk. Dagklis et al. has suggested that using first trimester sonographic markers are associated with lower detection rate and higher false positive rate when compared NT and biochemistry (3). Many studies have been performed till date with regards to the presence of EIF and its relation to aneuploidy, but data comparing the widely used first trimester combined screening tests and the identification of isolated EIF in the first trimester is limited. Although our series is too small to draw any major conclusion concerning the fetal heart EIF and its contribution in the risk calculation of Down syndrome, a general analysis of the relation between these showed that isolated EIF was found as an isolated finding in otherwise normal fetuses. These identified fetuses were screen negative and had normal NT scan reports. In our study there is no evidence of presence of tricuspid regurgitation and abnormality of ductus venosus.

First trimester NT scan and biochemical screening are established parameters with high sensitivity that contribute to the risk assessment of Down syndrome and other aneuploidies. Association between NT and EIF is also controversial. Migulez et al. failed to associate between increased NT and EIF in second trimester. He said that including soft markers would improve the accuracy of screening (1). Prefumo et al. in 2003 showed there was an association between increased nuchal translucency in first trimester and the presence of echogenic intracardiac focus in second trimester (5). So it was suggested that both couldn't be used independently for risk assessment. In our study, the nuchal translucency was within normal limits in fetuses identified with EIF in first trimester. With various studies supporting the fact that the rate of identification of EIF in first trimester is lower than its identification in second trimester, this truly questions the theory of Perfumo et al. but goes in favor of Dagklis et al. who derived that there is no significant association soft markers in first trimester and nuchal translucency thickness.

Thus, a definite association of presence of EIF as a soft-marker for trisomy 21 is arguable. Morphologic variations, which may be transient and have little or no pathologic significance but commonly seen in anomalous fetuses especially chromosomal abnormalities are called as soft-markers. They are important because of their statistical association with chromosomal abnormalities. In certain studies for example according to Whitlow et al. in 1998, soft markers increased the detection rate of aneuploidy in the first trimester by 3% (2). A recent meta-analysis by Agathokleus et al. has shown that the LR of isolated EIF in the second trimester (14- 24 weeks) for Trisomy 21 is 0.95. The study also points the uncertainty of whether LR for categorical variables like EIF is constant

across the gestational age of 14-24 weeks (12). However, in the first trimester no likelihood ratio (LR) for identifying soft markers is available.

"*Primum non nocere*" meaning "first, do no harm" is the fundamental ethics of medicine. A rapid advance in imaging technology has led to increased identification of minor anatomical variations (soft markers) in fetal ultrasound. A prenatal screening test reporting the presence of soft markers can significantly increase the risk of anxiety and distress to the mother. Neuropsychological impact of this to the fetus is not known. Because the use of such soft markers may be associated with more harm than benefit, it is necessary to be cautious to counsel women about their risk of having a fetus with Down syndrome when they are used. The probability of litigation also determines the extent of reporting and counseling of such soft markers. In addition there is variation in management of such markers from one unit to another. Even expert examiners have faced confusion, uncertainty and counseling dilemmas due to the ambiguity in relation to the marker's clinical significance, particularly as examiners working with low-risk populations had to make comparisons with data collected on high-risk pregnancies at referral centers (13, 14), when such findings of unclear significance especially when there are no clear consensus available it leaves both the providers and the patients under stress. Moreover in low-risk women, the chance of giving birth to a trisomy 21 baby is significantly less than the chance of having a miscarriage as a result of an unwarranted amniocentesis (15). Hence EIF detection in such cases is merely a bane than a boon.

This stresses the need for large studies regarding the application of first trimester soft markers especially in the era of availability of highly sensitive test like NIPT. Availability of consensus to modify the risk based on soft markers and counsel the patient regarding the same will be beneficial to both USG service provider and the patient. It is recommended that extensive studies be conducted to derive the likelihood ratio (LR) of isolated EIF in the first trimester scan (11- 14 weeks) for Trisomy 21. Evidence of a low LR can avoid the many patient-physician apprehensions evolving during this period.

Conclusion

In conclusion, our study has brought to light that presence of EIF in the first trimester does not necessarily mean increased risk for aneuploidy. They were associated with low risk for aneuploidy in biochemical screening with normal range of NT and normal Tricuspid and ductus venosus flow. Further, performance of elaborate studies showing low likelihood ratio of isolated EIF in first trimester scan in detecting aneuploidy will assist physicians in adequate counseling of mothers and thus help in better guidance and management. Highly anxious women may be given the option of non-invasive prenatal testing (NIPT),



Figure 1. Echogenic Intracardiac Focus(EIF) seen in first trimester ultrasound

which is a risk free procedure that has a high sensitivity and specificity of greater than 99%.

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