Original Article

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Relationship between Maternal Serum Calcium and Magnesium Levels and Isolated Fetal Echogenic Intracardiac Focus Encountered During Second-trimester Ultrasound Screening

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Abstract

Aim: As a frequent finding of prenatal second trimester ultrasound screening, echogenic intracardiac focus (EIF) may have a relationship with serum calcium and magnesium levels instead of major fetal abnormalities. This study was conducted to assess the relationship between the EIF and serum calcium and magnesium levels in women who had undergone mid-trimester screening ultrasound and had no other soft markers or fetal malformations.

Methods: This cross-sectional study was performed in a tertiary center experienced in maternal, fetal, and neonatal care, and included 206 patients who had undergone prenatal screening at 18-25 weeks of pregnancy with isolated EIF or without other laboratory abnormalities from July 2020 to June 2021. Serum calcium and magnesium levels were collected from the electronic health records of our institution.

Results: Overall, although there were remarkable changes in some of the clinical characteristics of patients with or without EIF, in general, the study groups were found comparable in terms of these variables. No significant differences were found between the study groups regarding serum calcium and magnesium levels.

Conclusions: Serum calcium and magnesium levels did not show a significant increase in cases with EIF. Therefore, measurement of serum calcium and magnesium levels in EIF cases was not found to be explanatory of the cause.

Keywords: Fetal heart, muscle, papillary, ultrasonography, prenatal, calcium, magnesium

Introduction

Echogenic intracardiac focus (EIF) is recognized when a bright spot is observed in the heart muscle during fetal ultrasound examination and is accepted as due to calcium deposition in the heart tissue. EIFs can be determined as single or multiple echogenic structures as bright as bone seen in the papillary muscle of the ventricles on routine four-chamber images that move synchronically with the atrioventricular valves (1,2). In fetuses with EIF, mineralization in the papillary muscles can be demonstrated histologically (3). In 90% of cases, microcalcification of papillary muscles is found in the left ventricle. Because the sensitivity of the EIF is low, further investigations, as well as counseling and information, are necessary to address parental anxiety (2). Although the pathogenesis of this finding is unclear, its presence does not cause structural or functional cardiac problems.

Although EIF is seen in 3% to 5% of healthy pregnancies and in 15% to 30% of trisomy 21 fetuses in mid-trimester ultrasound, they do not pose a problem when isolated. The presence of EIF increases the risk of chromosomal abnormality in the fetus, but most

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often increases the risk of trisomy 21 (4). Based on this finding, follow-up ultrasound, fetal echocardiography, and postpartum evaluation are not recommended in pregnant women with isolated EIF with negative serum or cell-free DNA screening results, as EIF diagnosed prenatally is not associated with childhood cardiac dysfunction (5,6).

Magnesium and calcium are essential for fetal development. A number of physiological changes occur during pregnancy for maternal adaptation and to meet fetal nutritional needs. Maternal serum calcium levels change with gestational age during pregnancy. Many studies have reported that total serum calcium levels are significantly reduced in normal pregnancy, especially in the third trimester of pregnancy (7).

There was a lack of information regarding serum calcium and magnesium levels and an isolated EIF during mid-trimester screening ultrasound. Since in the pathogenesis of EIF, the role of microcalcifications is considered, the knowledge about the status of serum calcium and magnesium in the development of EIF needs to be clarified. The finding of EIF, which is known as a soft marker for congenital anomalies, is associated with serum calcium and magnesium, which may increase alertness to accompanying electrolyte metabolism disorders in these infants. The aim of this study was to assess the relationship between the EIF and serum calcium and magnesium levels in women who had undergone mid-trimester screening ultrasound and had no other soft markers or fetal malformations.

Methods

Compliance with Ethical Standards and Study Design

The Local Ethics Committee for Human Research approved the study protocol (Bursa City Hospital, approval no: 2021-13/6 and date: 2021). Written informed consent forms were obtained from all participants. This was a cross-sectional study of women, including 206 patients with singleton pregnancies examined for prenatal care from July 2020 to June 2021. The participants included all pregnant women resorting to a tertiary care hospital for the second trimester ultrasonic analysis.

Patient Evaluation

These mothers were examined for ultrasound markers of chromosomal abnormalities, including EIF in the intraventricular spaces of the fetus through second trimester ultrasound screening. A diagnosis of EIF (Figure 1) was made when a discrete area of echogenicity that is as bright as bone, noted in the heart. Fetal ultrasound examinations during the second trimester were performed by one (A.B.O) of the perinatologists using a 3.5-5 MHz probe on a Voluson E8 ultrasound machine (GE Healthcare, USA). Pregnancies with assisted reproductive technology, other soft markers for aneuploidy, and known chromosomal and major congenital anomalies were excluded from the study. Medical records for this study were retrospectively reviewed for baseline clinical, obstetric, and detailed obstetric ultrasound reports.

Five milliliters of venous blood were collected from the antecubital fossa of each woman. The corrected calcium level was calculated by measuring serum calcium, in addition to measurements of serum magnesium and albumin. All tests were performed using standard procedures of a biochemistry laboratory. Corrected calcium was calculated in mg/dL using the following formula: corrected calcium=serum calcium + 0.8 x (4-serum albumin) (http://www.perinatology.com/calculators/Corrected Calcium). In the second trimester, serum total calcium and magnesium levels ranged from 8.2-10.6 mg/dL and 1.5-2.2 mg/dL, respectively, in healthy subjects (8).

Statistical Analysis

The clinical data was analyzed using IBM SPSS Statistics v23 (IBM SPSS, USA). The Kolmogorov-Smirnov test was used to determine the normality of the data. For parametric and non-parametric analyses of variables, t-test and Mann-Whitney U tests were used, respectively. A categorical variable was analyzed using a chi-square test. The statistical difference was set as $p<0.05$.

Results

Table 1 presents the baseline clinical characteristics of the study population. In the study population, there were 105 participants with EIF and 101 participants without EIF. The median age of the women with and without EIF was found to be similar (p=0.583). The study groups were found to be comparable regarding the median gravidity value (p=0.770). There was no significant difference in the median parity of study groups (p=0.382). The mean body

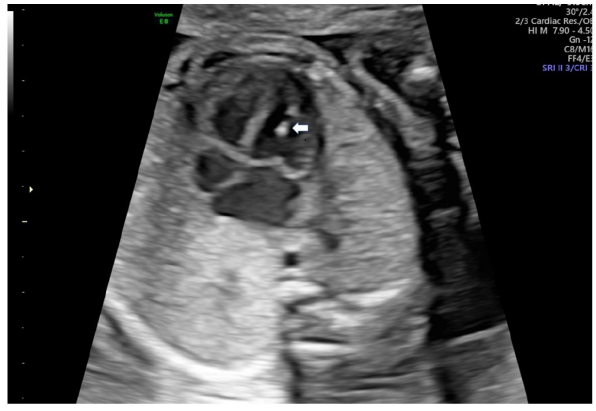

Figure 1. A representative ultrasound image of fetal echogenic intracardiac (arrow) focus in the left ventricle

mass index of the women with and without EIF was found to be similar (p=0.325). The median gestational age of the study groups was found to be comparable (p=0.786). There was no significant difference regarding the median birth weight (p=0.710). Regarding the location of EIF, the rate of being on the right side and bilateral was 4.8% and 1.9%, respectively. Considering the number of EIF, 2 and 3 focuses were found to be 10.5% and 1%, respectively.

Figure 2 displays the serum calcium and magnesium levels of study groups. No significant differences were found between the study groups regarding the serum calcium and magnesium levels (p=0.793 and p=0.938, respectively).

Discussion

In the current study, we aimed to determine the relationship between EIF and the status of serum calcium and magnesium in pregnant women who had undergone mid-trimester screening ultrasound and had no other soft markers of fetal malformations. In accordance with relevant literature, the EIF finding was present mostly on the left side and as a singularity. Serum calcium and magnesium levels had no meaningful relationship with the development of EIF.

Table 1. Baseline clinical characteristics of the study population

	EIF (n=105)	No EIF (n=101)	p-values
Age (years), median (IQR 25-75)	28 (18-43)	29 (17-41)	0.583
Gravidity (n), median (IQR 25-75)	2 (1-7)	2 (1-5)	0.770
Parity (n), median (IQR 25-75)	1 (0-4)	1 (0-4)	0.382
BMI (kg/m2), mean ± SD	26.8±3.9	26.2±4.4	0.325
Gestational age (week), median (IQR 25-75)	21 (18-24)	21 (18-25)	0.786
Female gender (n, %)	48 (46%)	48 (48%)	0.819
Birth weight (g), median (IQR 25-75)	3,240 (1,300-4,295)	3,217 (2,700-4,200)	0.710
Location (n, %)			
Left	98 (93.3%)		
Right	5 (4.8%)		
Bilateral	2 (1.9%)		
Number of EIF (n, %)			
1	93 (88.5%)		
2	11 (10.5%)		
3	1 (1%)		

Data are expressed as mean with standard deviation, median with interquartile range, and count with percentage as appropriate. Statistical analyses were performed with t, Mann-Whitney, and chi-square tests.
EIF: echogenic cardiac focus, BMI: Body mass index, IQR: Interquartile range, SD: Standard deviation

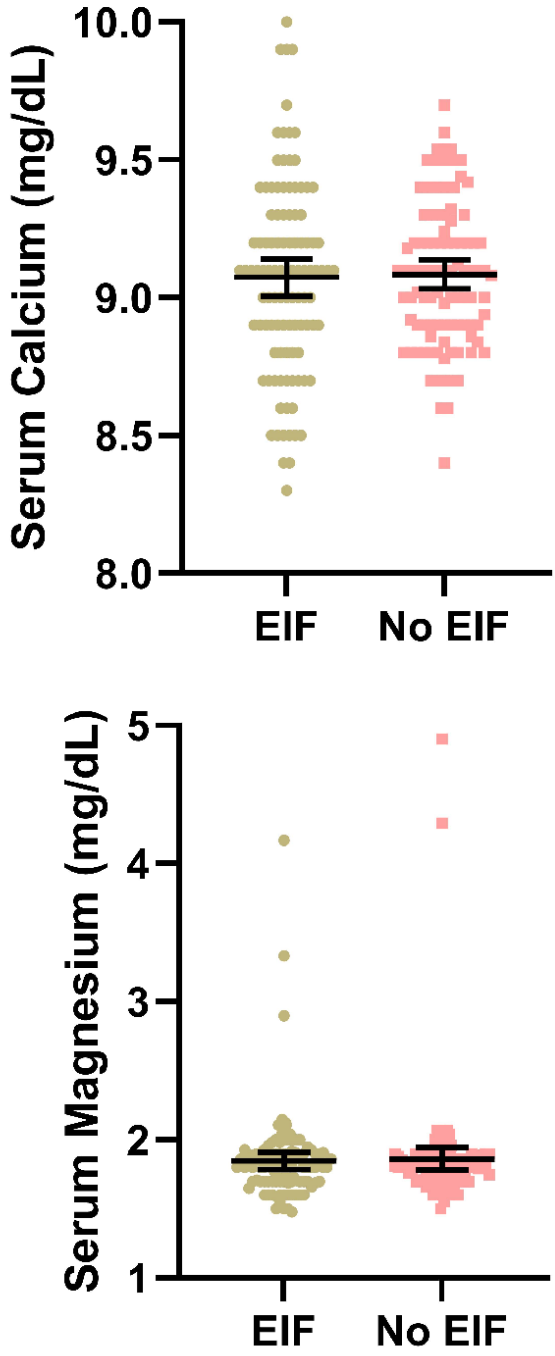

Figure 2. Serum calcium and magnesium levels of the study population. The data are expressed as a median with an interquartile range, and the Mann-Whitney test revealed no significant differences between study groups (p>0.05).
EIF: Echogenic intracardiac focus

During pregnancy and lactation, specific regulatory systems regulate mineral homeostasis according to the needs of the pregnancy trimesters. Intestinal calcium absorption is doubled to meet fetal calcium needs. In comparison, besides calcium release from the skeletal system, renal calcium conservation is also evident. While calcium supplementation during pregnancy causes greater calcium absorption, the effect of calcium supplements on the amount of bone lost during breastfeeding is minimal (7). During the entire pregnancy, the fetus accumulates about 30 g of calcium, 20 g of phosphorus, and 0.8 g of magnesium for mineralization of the skeletal system and for its normal physiological events. Approximately 50% of the total magnesium in the body is found in the bones, the other 50% intracellularly and approximately 1% intravascularly (1). The level of the intravascular compartment is tightly controlled. Serum magnesium levels are between 1.5-2.1 mg/dL (9). Magnesium acts as a cofactor for various enzymatic processes. In some studies, it has been observed that serum magnesium levels decrease with advancing gestational age (10).

The presence of an EIF, when seen isolated in a normal pregnancy, is considered a benign variant that can be interpreted by considering maternal risk factors and other sonographic anomalies, and some authors do not consider karyotyping necessary in mid-trimester fetuses (4,11,12). The finding of an incidental EIF in high-risk pregnancies may increase the risk of echogenic foci of aneuploidic anomalies. Classified as a soft marker for aneuploidic anomalies, there is no recognized direct association with congenital heart disease for an EIF per se (unless there is an aneuploidic anomaly). These are found to have disappeared in the follow-up of infants (13).

Because the presence of an isolated EIF is not associated with a cardiac abnormality, fetal echocardiography is not considered necessary and no specific follow-up is recommended for these pregnancies (14). Index pregnancy should be followed up according to the presence of other clinical indications or the results of the patient's prenatal screening and/or diagnostic tests.

Pavlíček et al. (14) conducted a retrospective study to determine the status of echogenic foci in the fetal heart during prenatal screening and to determine their value for the outcome of offspring. Their findings revealed that the isolated EIF was detected in 3% of the participants. The EIF was located in the left ventricle in 93%, 5%, and 2% of the subjects, mainly in the valvular apparatus of the mitral valve, in both of the ventricles, and in the right ventricle, respectively. No genetic abnormalities were present in the study population. The authors suggested that in their large series, EIF needs to be considered as a meaningfully less important finding without serious consequences in the offspring.

In another study investigating the EIF status, the authors examined the impact of an EIF on the risk of fetal trisomy 21 in a large population. EIF was found in 3.6% of participants and trisomy 21 was diagnosed in 0.4% of fetuses. When EIF, along with other markers, is present, it is associated positively with the presence of trisomy 21. An isolated EIF was not a valuable finding to consider trisomy 21 in patients younger than 35 years old without abnormal serum screening results for aneuploidy (15).

It is possible that the EIF decreases or even disappears with the progression of the gestational week. Huang et al. (11) followed all fetuses with isolated EIF and did not detect any serious disease or symptoms. They stated that these findings were not compatible with the results of previous studies (11,16). The authors noted that their results indicated a low rate of chromosomal abnormalities in fetuses with isolated EIF; however, they pointed to the benefit of performing chromosomal microarray analysis in fetuses with cardiac echogenic focus when other fetal anomalies are found, which facilitates the prediction of fetal outcome during genetic counseling and definitive assessment of prognosis (11).

Study Limitations

Some limitations of the current study also merit consideration before determining the implications of the study results. Although the EIF data were obtained from a single ultrasound examination between weeks 18 and 25, serial ultrasound screening of the EIF after week 25 would be more informative.In the literature, there is no previous study that examined serum calcium and magnesium in terms of the status of EIF. Our results can increase the awareness of serum electrolytes with congenital abnormalities. We think that this aspect of our current work can be considered the strength of this study, and this increases the reliability of our conclusions.

Conclusions

The presence of isolated EIF in the second trimester ultrasound scan causes a serious concern in mothers, and additional laboratory tests and research requests are encountered in this regard. Due to the nature of EIF, the first laboratory tests that come to mind include serum calcium and magnesium measurements. The results of this study revealed that in cases with EIF, serum calcium and magnesium levels did not show a significant increase. Therefore, measurement of serum calcium and magnesium levels in EIF cases was not found to be explanatory of the cause. There is a need to elucidate the pathogenesis of

EIF development with studies examining a wider range of biochemical measurements.

Ethics

Ethics Committee Approval: The Local Ethics Committee for Human Research approved the study protocol (Bursa City Hospital, approval no: 2021-13/6 and date: 2021).

Informed Consent: Written informed consent forms were obtained from all participants.

Authorship Contributions

Concept: F.Y.G., A.B.O., M.E., A.C., Design: F.Y.G., A.B.O., Data Collection or Processing: M.E., A.C., Analysis or Interpretation: F.Y.G., A.B.O., M.E., A.C., Literature Research: F.Y.G., A.B.O., M.E., A.C., Writing: F.Y.G., A.B.O., M.E., A.C.

Conflict of Interest: No conflict of interest was declared by the authors.

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