



Echogenic Intracardiac Focus – Existence in the First Trimester and the Role of MicroRNAs

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Received: 11 May 2020 ♦ **Accepted:** 14 July 2020 ♦ **Published:** 28 Feb 2021

Citation: Koutras A, Fasoulakis Z, Halil A, Kontomanolis EN. Echogenic intracardiac focus – existence in the first trimester and the role of microRNAs. *Folia Med (Plovdiv)* 2021;63(1):142-7. doi: 10.3897/folmed.63.e54171.

Abstract

Echogenic intracardiac focus (EIF) constitutes a finding in the ultrasound study that indicates an area which is echogenically bright in the fetal heart and is as bright as the bone that moves synchronically to the atrioventricular valves. Microcalcifications of the papillary muscles or chordae tendinae are being represented by this echogenicity and are mostly present in the left ventricle (90% of cases). EIF appears usually at the ultrasound that is realized in the mid-trimester in a percentage that reaches 3.5% in euploid fetuses and 15% to 30% in fetuses with trisomy 21. In the current paper, the rare and curious case of a 21-year-old primigravida woman is described, who presented for ultrasound scan at the 12th week of gestation. The scan revealed the presence of EIF, which is very rare, as it is well-known that it usually appears in the second trimester of pregnancy. Counseling and debriefing for dismissing parents' anxiety is necessary as well as further examinations, because EIF has low sensitivity. This specific case report could constitute a beginning in the research of whether investigating EIF in the first trimester of pregnancy is possible and which are the benefits of its detection for the mother, the fetus and the whole family, in clinical practice.

Keywords

echogenic intracardiac focus, Down syndrome, fetal abnormalities, MicroRNAs, proteomics

INTRODUCTION

Fetal abnormalities are detected during a routine diagnostic ultrasound examination. Quite often, scans are performed in an effort to detect an anomaly because of a positive family history, or a positive screening test, such as an abnormal alpha-fetoprotein. Otherwise, ultrasound examinations that reveal anomalies are performed for a variety of reasons. Sonograms are usually ordered when there is a date versus examination discrepancy or traces of vaginal bleeding are reported. When ultrasound reveals a fetus with an unusual appearance many questions come up. Parents may experience different levels of anxiety, im-

patience, guilt, and worry. At the end, no direct relation between concern and ultrasound is proved.¹ Herein, we report the case of a 21-year-old primigravida woman, in which the echogenic intracardiac focus was detected in the first trimester of gestation. EIF is a prognostic tool for detecting fetuses with Down syndrome, along with other prognostic tools such as microRNAs. This report aims to investigate if EIF in the first trimester of pregnancy is possible and which are the benefits of its detection for the mother, the fetus and the whole family, in clinical practice.

CASE REPORT

As EIF or ICEF (echogenic intracardiac focus) is defined a 'golf-ball' sign, a tiny structure found within the fetal heart having similar or greater echogenicity to the surrounding bone. A 21-year-old primigravida woman visited the outpatient clinic of our Department while being in the 12th week of gestation. Her medical history was normal. Her infection control was normal. She was rhesus-positive, a smoker, with a pre-pregnancy weight of 62 kg, no allergies or co-morbidities reported. The serum biochemistry of the mother (free beta hCG: 1.01 MoM, PAPP-A: 0.2 MoM) was within normal ranges. During her nuchal translucency scan, an EIF was detected

in the left ventricle (Fig. 1). The first trimester fetal echo revealed no obvious anomalies. Normal situs solitus was shown by the view of the hearts; thoracic and abdominal organs had normal positions. The relation of great arteries was normal. Cardiac function was well preserved and there were no findings of regurgitation of the atrioventricular (AV) valve, while a normal ductus venosus flow was present (Fig. 2). MicroRNA examination was afterwards suggested, but, due to economical reasons (excessive cost), was not possible to be performed.

Finally, her pregnancy was uneventful, without any complications and she gave birth to a healthy infant after a normal delivery. All clinical and laboratory examinations in both mother and fetus were within normal limits.



Figure 1. The fetal heart with its four chambers with echogenic intracardiac focus (arrow) found within the left ventricle.

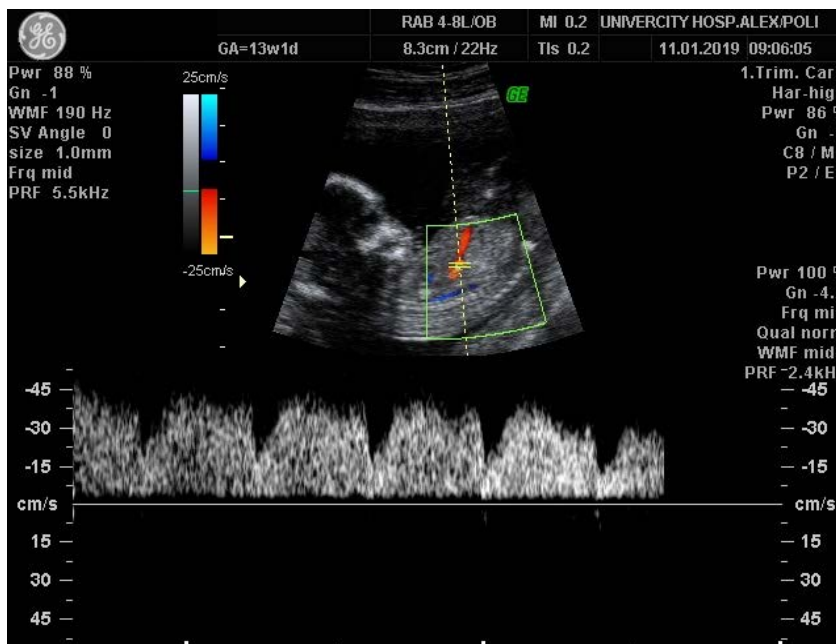


Figure 2. Normal blood flow waveform pattern obtained in the ductus venosus of the fetus by pulsed Doppler.

DISCUSSION

EIF

The present report shows a rare case of an isolated first trimester EIF clearly observable. These tiny white spots move simultaneously with valve cusps along the cardiac cycle. EIF seems to be an accidental finding in prenatal investigation in gestation; the relative rarity of these intracardiac small spots. Based on different series of clinical studies, these tiny foci were not related to any chromosomal or anatomical cardiac and extracardiac abnormalities. The default seems to be of mechanical origin. Despite a number of clinical studies on EIF, its final identity and contribution in prenatal diagnosis remains a mystery. In this article, the aim is to identify the diagnostic benefit of EIF in prenatal ultrasonography. Examination of the 4-chamber-view can be accomplished during the 11th to 14th week's scans. At 12-13 weeks of gestation, the four-chamber-view can be evaluated successfully by trans abdominal ultrasound in 76% of the cases and transvaginally in 95%.¹ By this time, EIF is found in the second trimester of gestation as an early sign of the Down Syndrome. According to the present case report which describes the rare case of detecting EIF in the first trimester, we could note that this case is the beginning of new studies about EIF as they all refer to its detection in the second trimester of pregnancy. Finding EIF in the first trimester could increase sensitivity and accuracy of detecting Down Syndrome earlier with obvious positive outcomes to the fetus' and mother's lives and for the whole family in general.^{1,2} According to Whitlow et al.³ in 1998, in the first trimester, soft markers augmented the rate of detection of aneuploidy by 3%. Agathokleus et al.⁴ conducted recently a meta-analysis in which it was proved that the LR of EIF in the second trimester of gestation (14-24 weeks) is 0.95, instead of not identifying LR for soft markers in first trimester. Thus, finding EIF in the first trimester does not mean necessarily augmented risk for aneuploidy and it must be associated with biochemical screening with normal range of NT and normal tricuspid and dustus venosus flow. The deprival of the likelihood ratio of EIF in the first trimester (11-14 weeks) needs further investigation and studies. These elaborate studies will offer better guidance and management in counseling of mothers. Non-invasive prenatal testing (NIPT) is a risky free procedure with sensitivity and specificity of greater than 99% that could be used in highly anxious women.

More specifically, in terms of frequency, Down syndrome comprises the third leading congenital effect.² Invasive before birth diagnosis relies on the detection of a genetic alteration.⁵ These small structures (EIFs) have approximately same echogenicity to the fetal bone, they do not have a connection to the ventricular wall and we can find them within the ventricles in the anatomic area of the papillary muscle or moving chordally in synchrony with the mitral or tricuspid valve.⁶ A crucial trial to reduce results that are

false positive is reducing the current gain to be certain that it does not discolour prior to rib echogenicity, because of the echogenicity that papillary muscles show.⁷ Concerning the location of EIFs, those which are usually detected (90%) in the left ventricle, are often "one of a kind" and have a dimension between 1 mm and 4 mm. Moreover, a second location in which they can appear is bilaterally or in the right ventricle. The diffuse cardiac echogenic foci and the intra-atrial location are infrequent.⁶ Furthermore, EIF is remarked to an overall of 0.5% – 20% of all fetuses. Additionally, its overall frequency is 5.6%.⁸

On the other hand, the results of the performing ultrasound vary the incidence. Fetal aneuploidy is possibly associated with EIF in some studies, while others remark that EIF is a finding that it is benign in populations that are low-risk.⁷ Thinking from the perspective of the patient, when this marker (EIF) is found, anxiety and neurosis is caused to the patient. In this way, the specialist medical doctor (obstetrician-gynaecologist) must give the proper advice and support, as well as extra invasive tests that, of course, have some risks for both the woman and the fetus. What is important in such cases is the risk of abortion which reaches 0.6%.⁷ A lot of systematic reviews have shown that EIF occurs in 0.5%-20% of the genetic sonograms⁹, by about 11% to 18% of fetuses with DS¹⁰, and in 4%-5% of chromosomally normal fetuses.¹⁰

In most cases, an intracardiac echogenic focus is connected with aneuploidy of the fetus, more precisely trisomy 21, usually when it is found with soft markers, which are other minor abnormalities.¹ On the other hand, EIF when it is found alone in isolation, it comprises a morphologic variation which has minor pathologic importance for the fetus.¹ Of course, there are a lot of cases in which EIF could create worry, that is unnecessary for both women and their partners, connected with the deficiency of preparation concerning ultrasound. Informed decisions about ultrasound and fetal screening can be taken by a variety of tools that providers could use to help pregnant women and their partners.¹

On the other hand, some other studies¹¹ support that EIF is not the most efficient among the markers used for finding if there is a possibility for Down's syndrome; it is only detected in a small percentage of fetuses and, also, it does not increase in a significant way the risk for trisomy 21 in fetuses. The truth is that what is most required is new protocols for the fetal abnormalities detection regarding sonographers. Clinical practice should have new parameters on prenatal diagnosis (i.e. sonographic markers) introduced, which should be more accurate and quantitative.¹¹ MicroRNAs could also constitute a crucial factor, along with EIF, to the diagnosis of Down's syndrome.¹²

MicroRNAs and proteomics

Another important diagnostic tool for checking the normality of fetuses are the microRNAs. These are endogenous, small, single-stranded RNA molecules with a size of

21-23 nucleotides that do not encode proteins. They are found in both plants and animals and are a new class of gene regulators.

It is estimated that there are at least 300 miRNAs in the genome of the human, accounting for approximately 1%-4% of all genes that are expressed in humans, making miRNAs the gene regulators that are mostly found.¹²

In the cell cytoplasm, pre-miRNAs are nucleolyzed from the Dicer enzyme and produce ~21 nucleotide double-stranded fragments that appear to be essential for the growth of an organism since they are involved in many biological processes in the cell, while their expression disorder appears to be involved in many pathological conditions.¹³ MiRNAs can be regarded more as regulators of a cellular function or cellular program rather than just a particular gene. To date, a total of 678 genes of miRNA have been identified in the genome of human and have an important role in stem cell biology, particularly in mechanisms of self-renewal, proliferation and differentiation. MiRNAs, in particular, are essential for the proliferation of embryonic stem cells (ESCs). Research groups showed that mice lacking the Dicer *-/-* gene were unable to process endogenous miRNAs resulting in premature death and, also, that embryonic stem cells lacking the Dicer *-/-* gene showed a low rate of cell proliferation.¹³ So, if used as important markers,

miRNAs could help in checking for trisomy 21 disorders (and not only) and they become important in maintaining the normal function of ESCs and the normal embryonic development. To sum up, the introduction of miRNAs into the cells could facilitate the production of homogeneous cell populations of the desired cell type from stem cells and could be exploited in therapeutic approaches.¹⁴

Last but not least, another important marker that should be taken into account while examining EIF is the whole protein complement of the line of a cell, of a tissue or an organism called “proteomics”. That is a term first met in medicine literature in 1995 and the two most important definitions encountered entail the following according to Pandey and Mann (2000): “The first is the more classical definition, restricting the large-scale analysis of gene products to studies involving only proteins. The second and more inclusive definition combines protein studies with analyses that have a genetic readout such as miRNA analysis, genomics, and the yeast two-hybrid analysis”.¹⁵

The primary target of proteomics consists of giving a further integrated and global way viewing biology via studying proteins (holistic view not studying proteins individually) and, also, to build a 3-D cell map in which the standard location of proteins is indicated; that is depicted in the rubric below (Fig. 3).¹⁴

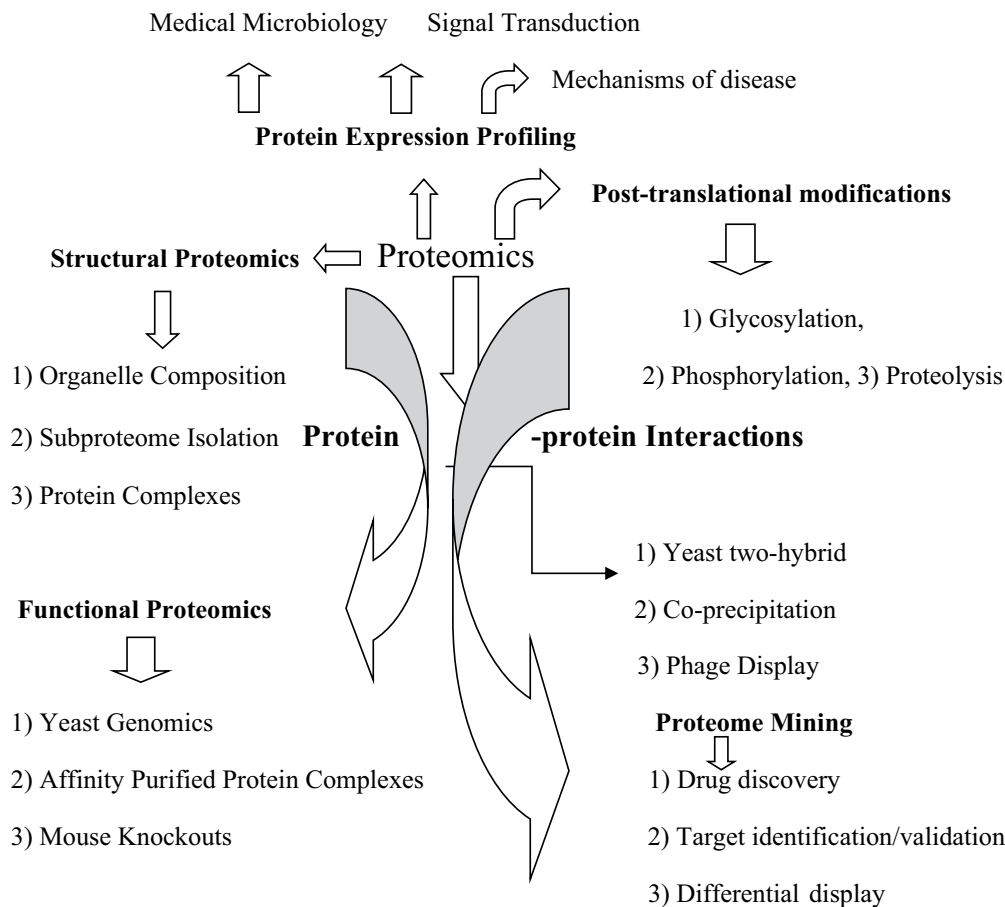


Figure 3. Proteomics rubric (Abbott, 1998).

In the journey to portray the proteome of a given cell or living being, it ought to be recalled that proteomes are dynamic; it mirrors the prompt condition where it is examined. In light of interior or outside signs, post-translational adjustments could change proteins, translocations could be experienced inside the cell, be blended or demoted. Consequently, proteomic assessment resembles a “snapshot” of the environment of a protein at some random time. Thinking about all the conceivable outcomes, all things considered, some random genome can possibly offer ascent to an interminable number of proteomes.^{13,14}

CONCLUSIONS

The objective of the present case report was the finding of a marker (EIF) in a 21-year-old woman in the 12th week of gestation. This marker is specialized in predicting the syndrome of Down in the second trimester of gestation and is remarked to 0.5%-20% of fetuses, with a 5.6% frequency. However, finding this marker in the first trimester of pregnancy could lead to the suspicion that it could be detected earlier, something that could be extremely positive for both the mother and the fetus. But, usually EIF is detected not alone but with other markers which together indicate aneuploidy of the fetus, while when detected alone it has minor pathologic importance. These assistive markers could be microRNAs and proteomics and they are of major importance, as well. There is no doubt that the diagnostic performance of EIF for detecting the Down syndrome in the first trimester of gestation needs further and deeper investigation. However, this specific case report could constitute a beginning in the research of whether investigating EIF in the first trimester of pregnancy is possible and which are the benefits of its detection for the mother, the fetus and the whole family, in clinical practice.

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Эхогенный интракардиальный фокус – наличие в первом триместре и роль микроРНК

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Дата получения: 11 мая 2020 ♦ **Дата приемки:** 14 июля 2020 ♦ **Дата публикации:** 28 февраля 2021

Образец цитирования: Koutras A, Fasoulakis Z, Halil A, Kontomanolis EN. Echogenic intracardiac focus – existence in the first trimester and the role of microRNAs. Folia Med (Plovdiv) 2021;63(1):142-7. doi: 10.3897/folmed.63.e54171.

Резюме

Эхогенный интракардиальный фокус (ЭИФ) – это ультразвуковое обнаружение, которое показывает эхогенно яркую область в сердце плода и яркость такой же яркости, как кость, движущаяся синхронно с атриовентрикулярными клапанами. Микрокальцификации сосочковых мышц или сухожильных хорд обнаруживаются при этой эхогенности и чаще всего присутствуют в левом желудочке (90% случаев). На УЗИ в середине триместра обнаружено, что ЭИФ является нормальным явлением с частотой проявления, достигающей 3.5% у эуплоидных плодов и от 15% до 30% у плодов с трисомией 21. В этой статье описывается редкий и любопытный случай 21-летней первородящей женщины, прошедшей УЗИ на 12 неделе беременности. Обследование выявляет наличие ЭИФ, что является крайне редким явлением, учитывая, что это обычно происходит во втором триместре беременности. Необходимы консультации и обсуждение, чтобы уменьшить беспокойство родителей, а также дальнейшие исследования, поскольку ЭИФ имеет низкую чувствительность. Этот конкретный клинический случай может стать поводом для исследования возможности проведения исследования ЭИФ в первом семестре и того, каковы преимущества его проведения для матери, плода и всей семьи в клинической практике.

Ключевые слова

эхогенный интракардиальный фокус, синдром Дауна, аномалии плода, микроРНК, протеомика
