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Original Article

A re-investigation of the correlation between echogenic intracardiac focus and chromosomal abnormality

Yu Tian[1*], Xinlian Chen[2*], He Wang[2], Hongqian Liu[2]

Departments of [1]Ultrasound, [2]Prenatal Diagnosis, West China Second University Hospital, Sichuan University/ Key Laboratory of Obstetrics & Gynecologic and Pediatric Diseases and Birth Defects of Ministry of Education, Chengdu 610041, China. [*]Equal contributors.

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Abstract: Background: To Re-investigate of the correlation between echogenic intracardiac focus (EIF) and chromosomal abnormality. Methods: Retrospectly 696 women who visited the 2nd West China Hospital of Sichuan University for EIF during January 2013 and June 2015, and were confirmed with amniocentesis and follow-up.696 were divided into four groups: Isolated EIF, complicated with other intracardiac abnormality, EIF complicated with other ultrasonic soft abnormality and EIF complicated with abnormality in other systems. Relationship between the number and size of EIF and the types of chromosomal abnormality were found. Results: The incidence of abnormal chromosome was higher for isolated EIF in left ventricle (0.72%) than that of isolated EIF in right ventricle (0%), and higher for 2 EIF (1.38%) than 1 EIF (0.054%). Furthermore, increase of EIF number in left ventricle (≥3) did not increase the incidence of abnormal chromosome. The incidence of abnormality in both ventricles (1.36%) was higher than that in left ventricle; that in both ventricles with more EIF in left ventricle was the highest (2.63%); The incidence of abnormal chromosomes of EIF complicated with other system (0.88%) was slightly higher than the incidence of isolated EIF (0.85%). Conclusions: Prenatal EIF, particularly for these pregnant women with 2 EIF in left ventricle or with EIF dominant in left ventricle of fetus, should be paid more attention to search the risk of abnormal chromosome. Further prenatal examination like Microarray technology should be performed for these cases complicated with multiple soft ultrasound markers or abnormality in other systems.

Keywords: Echogenic intracardiac focus, chromosomal abnormality, ultrasound

Introduction

Echogenic intracardiac focus (EIF) refers to intraventricular echogenic dots during ultrasound examination in fetus which have similar intensity with bone echo and are free of sound shadow. Most EIFs are adjacent to the papillary orchordaetendineae, having an incidence of 1.5-4% during the second trimester pregnancy [1]. Since 1990s, many researchers have verified that EIF has correlation with fetus aneuploidies, which is still in argument and even in controversyfor Asian because of small samples [2]. The present study re-investigated the location, number and intra-/extra-cardiac complications of EIF and analyzed the outcomes of amniocentesis, which will provide more information for prenatal consulting.

Materials and methods

Retrospective analysis

The subjects of the present study included 1690 pregnant women who visited the 2nd West China Hospital of SiChuan University from January 2013 to June 2015, of which 696 pregnant women for EIF, and were confirmed with amniocentesis and follow-ups. The analysis included the risks of isolated EIF, EIF complicated with other intracardiac abnormality, EIF complicated with other ultrasonic soft abnormality and EIF complicated with abnormality in other systems. The inclusion criteria were: single fetus, EIF, with or without complication of other systems, and low risk of maternal serum prenatal screening for Down's syndrome. The

Table 1. Information of cases with Isolated EIF in left ventricle

EIF number	Cases	Types of chromosomal abnormality	Follow-up cases	Incidence
1	186	45, X	182	0.054%
2	145	47,□□,+21 mos47,XXX[3]/46,XX[29] mos45,XX,rob(15;22)[2]/46,XX[4]	143	1.38%
3	32		32	0
>3	54		54	0
Total	417	4	411	0.72%

exclusion criteria was double or multiple fetuses.

Ultrasound examination

Ultrasound apparatus (Philip IU22 and GE E8) with probe frequency of 4-6 Hz was used to clearly display the sections of 4 cardiac cavities, and the number and size of EIF were calculated. The systemic scanning including brain, face, neck, thoracic cavity, abdomen, spine, limbs, and fetus appendix was performed with detailed recording.

Chromosomal examination

Amniocentesis was performed under the guidance of ultrasound. The fetal cells from 15-20 ml amniotic fluid was cultured for analysis of G-band and chromosomal karyotypes.

Results

Totally, there were 696 women with EIF of all 1690 pregnant women underwent amniocentesis in the hospital. The averages of age of women and gestational week of fetus were 26.9 years (18-42 years) and 24.5 weeks (17-35 weeks), respectively. There was no significant difference in age and gestation week between the cases having isolated EIF, and EIF complicated with other abnormalities. The classification and prognosis were reported as below.

Isolated EIF

There were totally 417 cases with isolated EIF in left ventricle detected by ultrasound examination. These cases included 186 cases with 1 EIF, 145 cases with 2 EIF, 32 cases with 3 EIF and 54 cases with over 3 EIF. The maximal and minimal EIF in size was 0.41×0.24 cm and 0.18×0.1 cm, respectively. There were 411 cases completed and 6 cases lost the follow-up. In the 411 cases completed the follow-up, there were 401 cases with normal labor, 1 case with congenital developmental abnormality of eyes, 5 cases with odinopoeia (4 cases with chromosomal abnormality and 1 case with voluntary odinopoeia), 3 cases with intrauterine fetal death due to intrauterine hypoxia (all with 1 EIF in left ventricle), and 1 case died from severe postnatal pneumonia. The data were listed in **Table 1**.

In these cases with isolated EIF, 19 cases showed EIF in right ventricle. The 19 cases included 1 case with 1 focus, 4 cases with 2 focuses, 1 case with 3 focuses and 1 case with 4 focuses. There was no chromosomal abnormality in these 19 cases including 18 case completed and 1 case lostthe follow-up.

There were 147 cases with EIF in both ventricles. In these 147 cases, there were 38 cases having more focuses in left ventricle than right ventricle, 100 case having same number of focuses in both ventricles and 9 cases having more focuses in right ventricle than left ventricle. Except 5 cases lost the follow-up, 142 cases who completed the follow-up included 1 case died of early labor, 3 cases of odinopoeia (2 cases of abnormal chromosome and 1 cases of voluntary odinopoeia), and 138 cases without any abnormality (**Table 2**).

EIF complicated with other abnormalities

Complications of other intracardiac abnormality: There were 37 cases with complication of other intracardiac abnormality, including 36 cases completed and 1 case lost the follow-up (**Table 3**). The 36 cases included 1 case with odinopoeia due to interventricularseptal defect (0.2 cm) and 35 cases with normal deliver.

Complications of other soft ultrasound markers: There were 57 cases who completed the follow-up and displayed EIF complicated with other soft ultrasound markers. In the 57 cases, 1 case showed 1.12 cm expansion of left brain

Table 2. Information of cases with EIF in both ventricles

EIF number	Cases	Case and type of chromosome abnormality	Follow-up case	Incidence
Left ventricle > Right ventricle	38	46,□□,t(8;12)(p22;q13)mat	37	2.63%
Left ventricle = Right ventricle	100	mos48,XXY,+M[14]/47,XXY[15]	96	1.0 %
Left ventricle < right ventricle	9	0	9	0
Total	147	2	142	1.36%

Table 3. EIF complicated with other intracardiac abnormality

Intracardiac abnormality	Cases	Cases with abnormal chromosomes	Cases completed follow-up
Light tricuspid regurgitation	11	0	10
Interventricularseptal defect	17	0	17
Atrioseptal defect	2	0	2
Other	7	0	7
Pericardial effusion	1	0	1
Expansion coronary sinus, residue of left superior vein	4	0	4
Cortriatriatumsinistrum	1	0	1
Tumor-like arterial tortuosity	1	0	1
Total	37	0	36

Table 4. EIF complicated with other ultrasound soft marker

Ultrasound soft marker	Case	Cases and type of abnormal chromosome	Follow-up case
Single umbilical artery	11	0	11
Separation of bilateral kidney collection system	27	0	27
Widened posterior fossa	7	0	7
Widened lateral ventricle in both sides	8	0	8
Choroid plexus cysts	3	0	3
Echogenic bowel	1	0	1
Total	57	0	57

ventricle and postnatal congenital horizontal nystagmus and ankylodeire, and the other 56 cases showed no obvious abnormality (**Table 4**).

Complications of other system: There were 19 cases had complications of other system and finished the follow-up. In these 19 cases, there were 1 case of odinopoeia due to abnormal chromosome, 1 case of odinopoeia due to abnormal development of bones and 17 cases without obvious abnormality (**Table 5**).

Types of abnormal chromosomes

There were 3 cases having abnormal number in sex chromosome, 2 cases having abnormal number of autosome and 2 cases having abnormal structure of autosome, including 1 case with both abnormal number and structure of autosome. In addition, there was 1 case of chimera of Robertsonian translocation (**Table 6**).

Discussion

Fetal chromosomal disorders are a group of critical diseases seriously threating the quality of newborn. The incidence of fetal chromosomal disorder in China is 0.73% [3]. Prenatal ultrasound examination can find some clues of abnormal chromosomes. Previous study indicated that the abnormal chromosomal disorders in fetus with soft ultrasound markers are significantly higher than normal fetus [4]. Fetal EIF is one of the soft ultrasound marker and is related with trisomy 18 and trisomy 21, having sensitivity of 11% [5, 6]. In the present study, the rate of amniocentesis due to EIF reached 41.18% (696/1690) and ranked number 1. Therefore, it is necessary to further enhance our recognition of EIF in order to provide information for clinical consulting.

Table 5. EIF complicated with abnormality in other systems

Abnormality	Case	Case and type of abnormal chromosome	Case of follow-up	Incidence
Hydramnion	11	46,XX,rob(14;21)+21	11	9.09%
Gallbladder enlargement	2	0	2	0
Hyperechoic liver	2	0	2	0
Delayed development of fetal limbs	2	0,	2	0
Permanent right Persistent right umbilical vein	1	0	1	0
Umbilical cord cyst	1	0	1	0
Total	19	1	19	5.26%

Table 6. Types of chromosomal abnormality

Number	Age	Gestation	Type of chromosomal abnormality	Outcome
1	30	25 weeks	mos47,XXX[3]/46,XX[29]	Odinopoeia
2	33	24 weeks	47,□□,+21	Odinopoeia
3	23	23 weeks	45, X	Odinopoeia
4	30	23 weeks	46,□□,t(8;12)(p22;q13)mat	Odinopoeia
5	26	24 weeks	mos48,XXY,+M[14]/47,XXY[15]	Odinopoeia
6	29	27weeks	mos45,XX,rob(15;22)[2]/46,XX[4]	Odinopoeia
7	28	24 weeks	46,XX,rob(14;21),+21	Odinopoeia

Totally 696 pregnant women with EIF were recruited in this study and performed amniocentesis which detected 6 cases with abnormal chromosomes, and the incidence of 0.86% was similar with literatures. The average of age of pregnant women having abnormal chromosome in fetus was 28.3 years and there was no pregnant woman with age over 35 years. The case with balanced translocation was derived from the mother and was normal after deliver.

The incidence of abnormal chromosome was higher for isolated EIF in left ventricle (0.72%) than that of isolated EIF in right ventricle (0%), and higher for 2 EIF (1.38%) than 1 EIF (0.054%). Furthermore, increase of EIF number in left ventricle (≥3) did not increase the incidence of abnormal chromosome. The incidence of abnormality in both ventricles (1.36%) was higher than that in left ventricle; the incidence of abnormality in both ventricles with more EIF in left ventricle was the highest (2.63%) and was in middle (1%) for these with same number of EIF in both ventricles. These results suggested that the appearance of isolated EIF in both ventricle, particularly for these having more or same number of EIF in left ventricle than right ventricle, results in the highest incidence of abnormality. Furthermore, the incidence of abnormality was the highest when there were 2 EIF for these cases having EIF only in left ventricle and was lower in these cases having EIF dominant in right ventricle.

The incidence of abnormal chromosomes of EIF complicated with other system (0.88%, 1/113) was slightly higher than the incidence of isolated EIF (0.85%, 5/583), which is consitent with literature. There was no abnormal chromosome in 94 cases complicated with intracardiac abnormality and other abnormal soft markers. These results may be related with the small sample and the further examination with *Microarray technology* in these cases to detect minimal defect or repetition of non-euploid abnormality. There was 1 case of trisomy 21 in 11 cases of hydramnios, suggesting that attention should be paid to pregnant women with unclear reason of hydramnios.

The present study detected 6 cases of abnormal chromosomes in pregnant women with 28.3 years of age in average which is not the traditional sense of aged pregnant women. Amniocentesis after detection of soft ultrasound markers with prenatal ultrasound examination can decrease the miss-diagnosis rate. The pregnant women all pass the maternal serum prenatal screening for Down's syndrome and are approved to be the low risk of Down's syndrome in early second-trimester. However, with screening soft ultrasound markers such as EIF, 6 cases of abnormal chromosomes are diagnosed in pregnant women of low-risk screening. So the ultrasonic examination in second-trimester is of great concern and is the key whether more operation should be carried

on such as amniocentesis especially for those women in low-risk maternal serum screening of Down's syndrome. In our study 5 cases were detected with abnormal number of chromosome, including 2 cases with abnormal structure of chromosome, and odinopoeia was performed to terminate the pregnancy. In the fetuses with normal chromosomes, there were 4 cases with other postnatal diseases, including 2 case with abnormal eye, 1 case with severe pneumonia and 1 case died of abortion. These postnatal diseases could not be detected by prenatal amniocentesis and should be informed to pregnant women and relatives. Amniocentesis is a kind of invasive operation and is reported to induce abortion due to infection of amniotic cavity. In our study there is the abortion rate of 0.59% (in 1 of 1690 cases), and being much lower than the rate of finding abnormal chromosome.

In summary, prenatal EIF, particularly for these pregnant women with 2 EIF in left ventricle or with EIF dominant in left ventricle of fetus, should be paid more attention to search the risk of abnormal chromosome. For these cases complicated with multiple soft ultrasound markers or abnormality in other systems, further prenatal examination such as *Microarray technology* should be performed.

Disclosure of conflict of interest

None.

Address correspondence to: Hongqian Liu, Department of Prenatal Diagnosis, West China Second University Hospital, Sichuan University/Key Laboratory of Obstetrics & Gynecologic and Pediatric Diseases and Birth Defects of Ministry of Education, Chengdu 610041, China. Tel: 1398050-2320; E-mail: hongqian.liu@163.com

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