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Echogenic intracardiac focus in fetus and association with maternal respiratory tract infection in Shanghai, China

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Summary

Purpose of investigation: To evaluate the association between fetal echogenic intracardiac focus (EIF) and maternal respiratory tract infections (RTI) during gestation. *Materials and Methods:* Fetal echocardiography was performed on 1,720 pregnant women (1,723 fetuses), and 205 of them showed evidence of fetal EIF. Other 245 pregnancies without fetal EIF were selected randomly as a control group. Comparison was undertaken to evaluate the difference between these two groups, and the possible association between EIF and maternal RTI. *Results:* EIF was present in 11.9% of the examined fetuses, and the presence of fetal EIF with maternal RTI was significantly higher ($p < 0.05$) than those without RTI. Multivariate logistic regression correction of RTI showed that the likelihood of EIF was 49 fold higher in pregnant women with RTI than without it (odds ratio [OR] = 49.958, 95% confidence interval [CI], 25.973~96.092, $p < 0.05$). *Conclusions:* Fetal EIF is suggested to be associated with maternal RTI during gestation in the present study population.

Key words: Ultrasound; Fetus; Echogenic intracardiac focus; Prenatal diagnosis; Respiratory tract infection.

Introduction

Fetal Intracardiac echogenic foci (EIF) are defined as discrete areas of echogenicity in the ventricles first described in 1987 [1]. They are mostly observed in the papillary muscles and the chordate tendinae of the fetus hearts, and appears to be caused by mineralization or small deposits of calcium in heart muscle histologically [2]. Investigations had been conducted to explore the clinical relevance of EIF in fetal hearts at different aspects. It has been reported that fetal EIF is associated with ethnicity, [3, 4] chromosomal abnormalities [5, 6], and maternal body mass index. [7]

Respiratory tract infections (RTI) are acute infections of the respiratory tract [8, 9] caused by over 200 different bacteria and viruses [10]. Among them, certain pathogens such as *Streptococcus pyogenes* has been found to result in rheumatic heart disease [11], which can be detected by echocardiographic screening [12]. Other pathogens, for example, those causing maternal community-acquired pneumonia are found to seriously affect their fetuses, and then increasing the risk of preterm delivery and abortion [13]. The present authors thus hypothesized that maternal RTI might also lead to transient or permanent changes in developing fetal heart, which may be reflected by the presence of EIF.

Materials and Methods

Between May 2009 and April 2010, 1,720 pregnant women with a gestation period of six to 41 weeks underwent prenatal ultrasound examinations in the clinic of the International Peace Maternity and Child Health Hospital, Shanghai, China. Among them, 205 pregnancies were detected to carry babies with EIF. Meanwhile, 245 pregnancies without fetal EIF in the similar gestation period were selected randomly as control. Comparison was done between the maternal RTI before the diagnosis of EIF in EIF group and maternal RTI during the gestation in control group. The differences in the maternal age, gestational period, maternal BMI [maternal weight (kg)/maternal height (m^2)] of the first gestation period, and medication treatment for maternal RTI were also compared between the two groups. All participants were explained the purpose of the study and gave informed consent. The study protocol was approved by the Ethics Committee of the International Peace Maternity and Child Health Hospital.

Fetal ultrasonography was performed using a color Doppler ultrasonic diagnostic apparatus, equipped with a one- to five-MHz transabdominal transducer. During prenatal ultrasound examination, the location of the fetal heart was determined by the appearance of fetal cardiac four-chamber and left/right ventricular outflow tract sections. The atrioventricular connection with the vessels and the internal structure of the fetal heart (including the size of the atrioventricular chamber, valve morphology, and continuity of interval and foramen ovale) were examined.

Fetuses were diagnosed with EIF if a > two mm enhanced echo appeared in the fetal heart, with an echo strength similar to the strength of bone structures, and if the EIF ranged in size from two to five mm. [14] Pregnant women were diagnosed with a RTI if they had a sore throat, running nose, coughing, or fever (< 38.5ºC), with most recovering within a few days. [8, 9, 15] Patients with RTI were recorded only after the diagnosis was confirmed.

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Table 1. — *Association between fetal EIF and time of prenatal ultrasound screening.*

Month and year		Number of fetuses with EIF	Number of fetuses examined	EIF rate (%)
2009	May	16	172	9.3
	June	18	148	12.2
	July	10	137	7.3
	Aug	10	129	7.8
	Sept	9	135	6.7
	Oct	14	127	11.0
	Nov	10	101	9.9
	Dec	16	127	12.6
2010	Jan	26	117	22.2
	Feb	19	145	13.1
	Mar	30	185	16.2
	Apr	27	197	13.7

Note: The EIF rate was defined as the number of fetuses with EIF divided by the total number of fetuses examined.

Table 2. — *Demographic and clinical characteristics of the EIF and control groups.*

Variable	EIF Group (total n = 205)	Control Group (total n = 245)	*p* value
Maternal age (years)			0.0021
≥ 35	70 (34.1)	52 (21.2)	
< 35	135 (65.9)	193 (78.8)	
Gestational period (week) [a]			0.0155
> 24	12 (5.9)	22 (9.0)	
20 - 24	165 (80.4)	209 (85.3)	
≤ 20	28 (13.7)	14 (5.7)	
Maternal BMI			<0.05
> 19.48	57 (27.8)	167 (68.2)	
≤ 19.48	148 (72.2)	78 (31.8)	
Maternal RTI			<0.05
yes	179 (87.3)	50 (20.4)	
no	26 (12.7)	195 (79.6)	
Medication treatment for maternal RTI			<0.05
yes	6 (3.35)	29 (58.0)	
no	173 (96.65)	21 (42.0)	

[a] *p* value of trend test for gestational period is 0.0157.

Statistical analysis was performed using SAS 8.2. Groups of fetuses with and without EIF were compared by the chi square test or Fisher's exact test, as appropriate. Multivariate logistic regression analysis was performed to evaluate the association between clinical factors and fetal EIF. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. A $p < 0.05$ was considered statistically significant.

Results

The study population was Chinese Han ethnic pregnant women underwent routine prenatal ultrasound examinations in the Hospital. Their general health conditions were good during pregnancy.

The present study showed that of the 1,720 pregnancies, 205, including three sets of twins, were diagnosed with fetal EIF, and the incidence of fetal EIF was approximately 11.9% (205/1723). The mothers aged 21 to 42 years (mean 32.4 ± SD4.3), and gestation periods varied from 17 to 38 weeks (mean 22.1 ± SD1.6). No fetal chromosomal abnormality was found in the EIF cases. The control group contained 245 pregnancies without fetal EIF that was randomly selected. The maternal age was from 21 to 43 years (mean 31.1 ± SD4.2), and the gestation period varied from 17 to 38 weeks (mean 22.4 ± SD1.9). The BMIs of the first gestation period of the two groups varied from 15.08 to 23.93 (mean 18.6 ± SD 1.56) and 15.08 to 34.16 (mean 21.11 ± SD 2.83), respectively. The median of the BMIs between the two groups was 19.48.

Of these 205 fetuses with EIF, 91.7% EIF was detected in the left ventricle, 2.9% EIF in the right ventricle, and 5.4% EIF was detected in both ventricles. All fetal hearts had the typical four-chamber structure, with no obvious abnormalities in the inner diameters and courses of the aorta and pulmonary artery, the size of the atrioventricular cavities, in the activities of the atrioventricular valves and the continuity of the ventricular septa, and in the normality of ovale foramen.

EIF was detected as early as 17 weeks of gestation by prenatal ultrasound examination in six fetuses (2.9%). Of the 205 fetuses in which EIF was detected in early gestation, the signal disappeared in 172 cases (83.9%) by 34 weeks of gestation and 199 cases (97.1%) by 38 weeks of gestation. The peak of monthly EIF cases distribution was found in January (Table 1).

The ages, gestational periods, and maternal BMI were all significantly different in the groups of pregnant women with fetal EIF and without fetal EIF ($p < 0.05$ each; Table A trend test for gestational period incidence of EIF revealed a significantly higher occurrence of EIF in the first 20 weeks of pregnancy, compared to 20-24 weeks or over 24 weeks gestation ($p < 0.05$; Table 2).

Moreover, of the pregnant women, 179 out of 205 (87.3%) in the EIF group experienced RTI before the diagnosis of EIF, whereas only 50 out of 245 (20.4%) in the control group had RTI during gestation, with a statistically significant difference ($p < 0.05$; Table 2). Meanwhile, the number of pregnant women who took medication for RTI treatment was only six out of 179 (3.35%) in the EIF group, and 29 out of 50 (58%) in the control group. The difference was also significant between these two groups ($p < 0.05$; Table 2).

Multivariate logistic regression analysis showed that the risk of carrying a fetus with EIF, compared to the gestational period of less than 20 weeks, declined during the gestational period of 20 - 24 weeks (OR = 0.334, 95% CI 0.202~0.553, $p < 0.05$; Table 3), as well as the period over 24 weeks (OR = 0.258, 95% CI 0.080~0.836, $p < 0.05$; Table 3). Meanwhile, compared to maternal BMI of less

Table 3. — *Multivariate logistic regression analysis of risk factors for EIF.*

Risk factor	*p* value	OR value	95% CI
Maternal age (y): ≥35 / <35	<0.581	1.267	0.660 - 2.433
Gestational period (weeks):			
20-24 / ≤20	<0.05	0.334	0.202 - 0.553
>24 / ≤20	<0.05	0.258	0.080 - 0.836
BMI: >19.48 / ≤ 19.48	<0.05	0.164	0.089 - 0.301
Pregnant women with relative to without RTI	<0.05	49.958	25.937 - 96.092
Medication treatment for maternal RTI	<0.05	0.030	0.011 – 0.082

than 19.48, the risk of carrying a fetus with EIF reduced when maternal BMI was over 19.48 (OR = 0.164, 95% CI 0.089~0.301, $p < 0.05$; Table 3). The risk of carrying a fetus with EIF was also 49-fold higher in pregnant women with than without RTI (OR = 49.958, 95% CI 25.973~96.092, $p < 0.05$; Table 3), but the risk could be reduced if medication treatment for maternal RTI was applied (OR = 0.030, 95% CI 0.011~0.081, $p < 0.05$; Table 3).

Discussion

EIF on prenatal ultrasound represents a strong echo reflection caused by thickened ventricle chordae. A previous histological study of six terminated fetuses with EIF confirmed that the strong echoes in the ventricle in their study were caused by myocardial fibrosis or calcified endocardium and papillary muscle [2].

Several mechanisms were considered to cause vascular calcification, such as lipid metabolism, mineral and hormonal balance, or inflammatory cytokines [16, 17]. Some of the inflammatory signalings were also considered to be involved in respiratory diseases [18]. When the pregnant women suffered RTI during pregnancy, although many of them were able to recover from RTI, the responsible pathogens may have affected their fetus [13]. If the certain pathogens were able to attack the fetal hearts [11, 12], along with the maternal body changing in various aspects because of pregnancy, including mineral need and hormone levels [9], the fetus with maternal RTI were possibly more susceptible to form calcification in their circuits. On the cardiac sonographic examination, these calcifications would appear as the strong echo inflections in the fetus heart. In this study the authors found strong association between EIF and maternal RTI. There were more than half of the cases (87.3%) in the EIF group experiencing at least one time RTI before the diagnosis of EIF, only a few amounts of the cases (20.4%) in the control group during gestation, with a statistically significant difference. After adjusted for maternal age, pregnancy period, maternal BMI and medication treatment for maternal RTI, multivariate logistic regression analysis also suggested the strong risk for fetal EIF with maternal EIF.

Two previously studies found the incidence of fetal EIF was higher in Asian ethnicity [3, 4], though others reported no link between fetal EIF and ethnicity [19]. The EIF rate was 11.9% in the present study, similar to previously reported that ranged from 1% to 30% [3, 4, 5, 6, 19, 20]. Since many EIF reported rates were less than 10% excluding Asian ethnicity, and the population of the present study was all Han Chinese, this result also suggests that Asians of Chinese origin may have a relatively high prevalence of echogenic intracardiac foci.

There are studies that showed that low maternal BMI would be an independent risk factor for the development of fetal EIF [7]. The present study also indicated that the risk of fetal EIF declined along with the increasing of maternal BMI, however the present author did not find the incidence of EIF related to chromosomal abnormality, which was considered controversially as the possible risk factor in some previous studies [5, 6].

Furthermore, 91.5% of the cases had EIFs only in the left ventricle, which is in agreement with previous findings [19, 20, 21]. This imbalance in EIF incidence may be due to the characteristics of fetal blood circulation. In fetuses, blood circulation may depend primarily on the right side of the heart, reducing the likelihood of mineral deposits and calcification on that side because of strong blood flow. No correlation was observed between the presence of EIF and congenital structural abnormalities of the fetal heart in many reports [1, 21]. Similarly, none of the fetuses with EIF the present authors assessed had any obvious structural abnormalities in the heart. Moreover, they were able to detect fetal EIF on prenatal ultrasound as early as week 17 of pregnancy. In fact, most of cases (94.2%) were detected before the second trimester, and then the occurrence of EIF declined with the progress of the pregnancies in this study. Statistically the results suggest that gestational period itself may protect fetuses from EIF formation. This finding was similar to previous evidence that the 7.4% prevalence of EIF at 13-16 weeks' gestation decreased to 3% at 20-22 weeks' gestation [20]. The present authors also observed seasonal variations in the occurrence of fetal EIF, with 22.2% occurring in January. This was consistent with flu infection peak in China [22], as well as with the outbreak of H1N1 influenza A virus infection at the end of 2009 [23].

Conclusion

In a specific Chinese population, the present authors found an association between fetal EIF and maternal RTI during pregnancy. The pitfall of this study is that the authors could not follow these children to measure their heart functions during childhood development, so as to gain insights of the EIF pathophysiology.

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