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Research Paper

Prenatal ultrasonographic characteristics and prognosis of isolated redundant foramen ovale flap

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ABSTRACT

Objective: To analyze the prenatal ultrasonographic characteristics and prognosis of the isolated redundant foramen ovale flap (RFOF).

Methods: From January 2014 to December 2021, we collected data on fetal echocardiography analyses and perinatal outcomes for fetuses with isolated RFOF in Peking University People's Hospital.

Results: We found that 0.31% (87/28308) of participants have RFOF. The four-chamber results of the foramen ovale flap (FOF) showed that it was stiff and extended >50% or reached the lateral wall of the left atrium (LA) in diastole. As seen from the foramen ovale(FO) channel and four-chamber views, the hypermobile and redundant flap were observed shrinking and stretching with the fetal cardiac cycle, which is similar to jellyfish. The lateral displacement of flow from LA to the left ventricle (LV) around the FOF on color doppler demonstrated thin linear blood flow from the right to left and a reversal of flow across FO. A uniphasic, but not biphasic, pattern of FOF displacement was observed on M-mode. Stages I (23/87) and II (51/87) had a higher ratio of ventricular disproportion than Stage 0 (11/87) and III (2/87). We observed the RA/LA (right/left atrium) > 1.2 in 53 cases (60.9%), RV/LV (right/left ventricle) > 1.2 in 53 cases (60.9%), PA/AO (pulmonary/aortic artery) > 1.2 in 53 cases (60.9%), and moderate or severe tricuspid regurgitation in 10 cases and moderate pericardial effusion in 2 cases (2.2%). Seventy-four RFOF cases had follow-up data. Neonatal death occurred in 2 cases; 72 fetuses survived with normal or minor heart defects.

Conclusion: RFOF should be considered if the left side of the heart of a fetus is smaller and related to hypermobile FOF. For isolated RFOF cases, a monthly follow-up is recommended to monitor arrhythmia or fetal hydrop status. Prompt treatment is recommended for those with adequate gestational age and lung maturity.

1. Introduction

The foramen ovale (FO) is formed by the septum secundum on the right atrial (RA) side and the septum primum on the left side, and acts as a prenatal communication bridge between the right and left side of the heart.[1] The foramen ovale flap (FOF) is septum primum, which acts as a one-way "valve," with its free rim on the surface of the left septal. As such, the growth or lack of strong supporting tissue of the septum primum will lead to a mobile and redundant foraminal flap.[2] Redundant foramen ovale flap (RFOF) is an abnormal FOF that reaches at least half or more of the LA.[3] Isolated RFOF usually occurs in fetuses with a normal heart, with 0.6%–1.7% frequency based on echocardiographic examinations.[3] RFOF in echocardiography analyses and autopsies have been reported, but reports about antenatal detection of isolated RFOF are still limited.

In this study, we aim to analyze the fetal echocardiographic features of isolated RFOF and identify the risk factors related to adverse outcomes in a large cohorts from a regional and national fetal imaging center.

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2. Materials and methods

2.1. Study population

From January 2014 to December 2021, we examined 32,316 fetuses in Peking University People's Hospital, a regional and national referral center, to identify those with isolated RFOF. Fetuses diagnosed with isolated RFOF constituted the subjects of this review. Exclusion criteria included those diagnosed with congenital heart malformations, premature constriction of the ductus arteriosus, arteriovenous malformations, vein of Galen aneurysm, absent ductus venosus, left diaphragmatic hernia, maternal diabetes, and either increased placental resistance or placental dysfunction. Fetuses diagnosed with isolated RFOF were reexamined with an ultrasound every 2–3 weeks and echocardiography was performed once the baby was born.

2.2. Instruments

All ultrasound examinations were performed by experienced operators using either a General Electric Voluson E8 or E10 ultrasound system with transabdominal RAB-4-8D three-dimensional transducers. Video clips or three-dimensional volume datasets of fetal cardiac tissue were reviewed to perform the measurements. 4D viewer software (version 17; GE Healthcare) was used for the measurement.

2.3. Ultrasound measurements

A complete fetal echocardiographic examination was performed, and the transverse diameter of the left atrium (LA), right atrium (RA), left ventricle (LV), right ventricle (RV), aortic artery (AO), pulmonary artery (PA), ductus arteriosus(DA) and aortic isthmus (AOI) was assessed. We measured the maximum transverse diameters of the LA and RA (inner edge to inner edge) in the four-chamber view just above the atrioventricular valve orifice at the end of the systolic phase of the cardiac cycle. Measurements of the maximum transverse diameters of the LV and RV were made in the four-chamber view just below and parallel to the atrioventricular valve orifice in the end-diastolic phase. The diameters of the AO and PA (inner edge to inner edge) were taken from the outflow tract views of the LV and RV at the end of the systolic phase. The diameter of the AOI and DA were measured from the three-vessel and tracheal view and the sagittal view of the aortic arch. The flow direction across the AOI was recorded as forward, mixed, or reversed. These measurements were compared with the published normal data for the corresponding gestation.[4–6]

The FOF was evaluated in the four-chamber and the FO channel views using 2D and color Doppler echocardiography. A single frame in the four-chamber view that clearly showed the prominence of the FOF was chosen for subsequent investigation and measurements. The maximum diameter of the FOF was measured according to the approach used by Vena et al.[7] A line was drawn along the interatrial septum, and the maximum diameter of the FOF was measured from the outer edge of the more prominent part of the FOF to this short dashed line (Fig. 1). The pulse Doppler value was also recorded.

Additionally, the relative size of the transverse diameters of the RV and LV (RV/LV ratio), the relative size of the PA and AO (PA/AO ratio), the relative size of the AOI and DA (AOI/DA ratio), and the transverse diameter of the FOF and LA (FOF/LA ratio) were also obtained. The redundant and hypermobile flap of the FO and tricuspid regurgitation were assessed.

2.4. The FO channel view

The FO channel view is the sagittal bicaval view. FO is the inlet of the channel, and the upper edge of the free flap constitutes the outlet of the channel. Under the impact of the blood flow shunt, the flap protrudes into the LA and forms a right-to-left shunt channel with the septum secundum. In this channel the blood flow from the RA to the LA can be blocked, regardless of whether stenosis is of the inlet or the outlet. The FO channel view was applied to maximize the display of the FO and the FOF (Fig. 2).

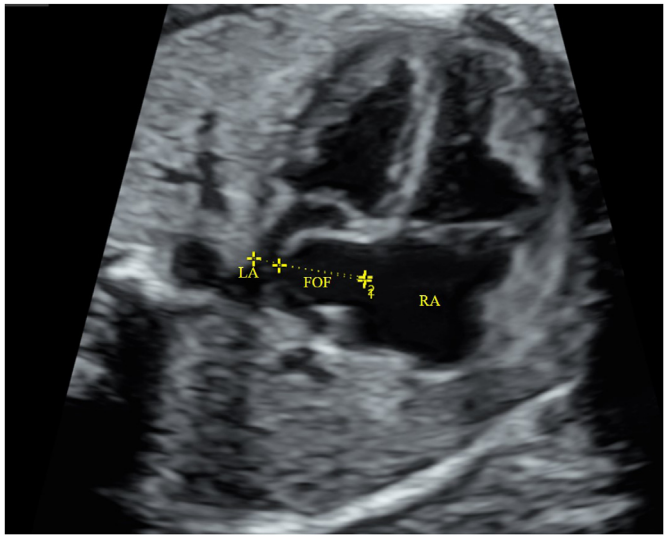

Fig. 1. Four-chamber view of a fetus of 31 gestational weeks. The image shows the methodology for measuring the FOF and LA. The FOF/LA ratio (FOF: short dashed line; LA: long dashed line)was obtained by dividing the maximum diameter of the FOF by the transverse diameter of the LA in the four-chamber view. FOF: foramen ovale flap; LA: left atrium; RA: right atrium.

2.5. Isolated RFOF categories

RFOF is defined as an abnormal FOF that extends at least halfway across the LA.[3] Vena et al.[7] proposed that its association with ventricular disproportion became significant, using a FOF/LA ratio cut-off of $\geq$0.65. They defined four categories of RFOF based on the prominence of the FOF and its hemodynamic effects,[7] which are shown in Table 1.

2.6. Statistics

Data were analyzed using the Statistical Package for Social Sciences version 17 (IBM, Armonk, NY, USA). A Jarque-Bera test was used to test

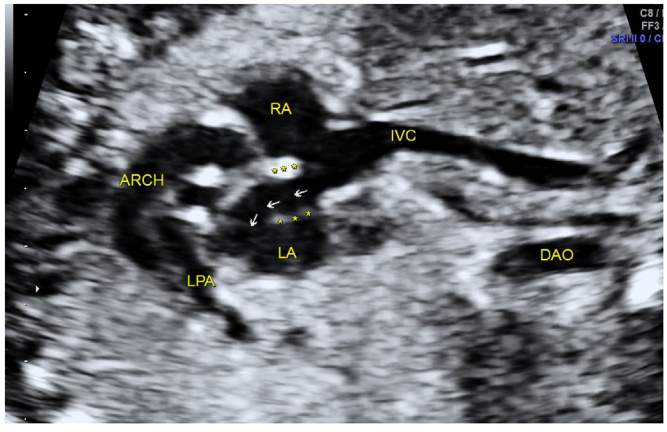

Fig. 2. The section of the FO channel in a normal fetal heart: FO is the inlet of the channel, and the upper edge of the free flap constitutes the outlet of the channel. Septum primum (upper ★★★); the free flap (lower★★★); the FO channel (arrow). ARCH: aortic arch; RA: right atrium; IVC: inferior vena cava; LA: leftatrium; LPA: left pulmonary artery; DAO: descending aorta.

Table 1
Fetal RFOF categories.

Stage	FOF/LA ratio	Ventricular disproportion	Other features
0	<0.65	Absent	–
I	≥0.65	Absent	–
II	≥0.65	Present	–
III	≥0.65	Present	Transient prolapse into mitral valve orifice; pericardial effusion

the s distribution of the variables. Continuous variables are presented as mean ± standard deviation(SD).

3. Results

In this large, single-institution cohort, 32,316 fetal echocardiograms were examined for a cardiac scan (Fig. 2). No structural heart defects or extra-cardiac abnormalities were found in 28308 cases, there were 135 fetuses with RFOF, and 87 cases had no congenital heart disease (CHD). Therefore, the percentage of RFOF in structurally normal hearts was 0.31% (87/28308). When patients were diagnosed with isolated RFOF, the mean maternal age was 34.54 ± 3.65 years (range 22–46 years), and the mean gestational age was 37.47 ± 3.43 weeks (range 28–39).

3.1. Fetal echocardiographic characteristics

Our study shows redundant and hypermobile FOF in 53 cases. After evaluating the four-chamber view, the FOF was stiff without the normal flapping motion. The FOF protruded to the LA in the diastole that extended more than 50% into the LA (Fig. 3A) and even reached the lateral wall of the LA, which was close to the mitral valve in the diastole (Fig. 4A). In the four-chamber and FO channel views (Fig. 3A and C), the hypermobile and redundant flap were observed shrinking and stretching with the fetal cardiac cycle, which is similar to jellyfish.

As shown in Fig. 3B, lateral flow displacement occurred from LA to LV, including a thin linear blood flow from the right to left through the FO and a reversal of flow across FO. Fig. 3D displays a uniphasic mode of the flap excursion. Pulmonary venous return and mitral orifice flow were normal. As seen from fetal echocardiograms, the abnormalities associated with isolated RFOF included redundant flap extending more than halfway to the LA, a smaller left heart, narrowed AO (4C), a narrowed aortic arch (4D), and moderate or severe tricuspid regurgitation.

Echocardiographic findings are listed in Table 2. RA/LA>1.2 in 53 cases (60.9%), RV/LV > 1.2 in 53 cases (60.9%), and moderate or severe tricuspid regurgitation (Fig. 4B) occurred in 10 cases (11.5%). PA/AO>1.2 (Fig. 4C) in 53 cases (60.9%). Moderate pericardial effusion (Fig. 5) occurred in 2 cases (2.2%). AOI/DA<0.74 in 0 cases. The 0.5 < FOF/LA<0.65 (Stage 0) occurred in 11 cases (12.6%). FOF/LA>0.65 occurred in 76 cases (87.3%); Stage I had 23 cases (26.4%), Stage II had 50 cases(58.6%), and Stage III had 2 cases (2.3%), based on the degree of FOF prominence.[7]

3.2. Outcomes of fetuses with isolated RFOF

Neonatal death occurred in two cases, and 13 fetuses were lost during the follow-up period. In the rest of the cohort, 72 fetuses survived with normal or minor heart defects, three had a small secundum atrial septal defect, one had a small perimembranous ventricular septal defect (2.0 mm), one had ductus arteriosus, and three exhibited premature atrial contraction and resolve at birth. Two fetuses with supraventricular tachycardia required treatment; the arrhythmia was resolved in both cases. Two fetuses died after delivery. One showed an RFOF with severe tricuspid regurgitation, decreased systolic function of the right ventricles, moderate pericardial effusion, severe pleural effusion, and severe ascites. The fetus was delivered at 31 gestational weeks and died five days later. The other showed RFOF with severe tricuspid regurgitation, moderate

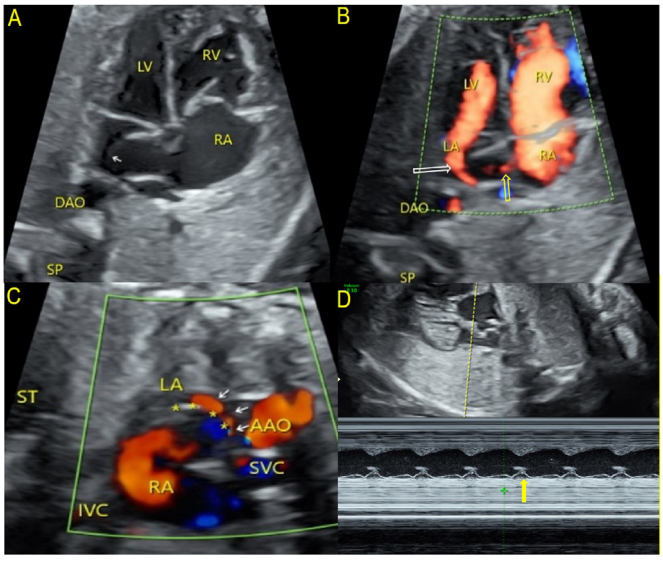

Fig. 3. A 33-week-old fetus with isolated RFOF in category-II. A. The four-chamber view shows the FOF (arrow) significantly protruding to the LA in diastole and a smaller left side of the heart. B. The four-chamber view in CDFI showed lateral flow displacement around the FOF from LA to LV (white arrow) and reversal of flow across FO from left to right (yellow arrow). C. The FO channel (★) view in CDFI showed thin linear blood flow (arrow) from the RA to the LA. D. FOF shows a uniphasic pattern (arrow). LA: left atrium; LV: left ventricle; RV: right ventricle; RA: right atrium; DAO: descending aorta; AAO: ascending aorta; SVC: superior vena cava; IVC: inferior vena cava; ST: stomach; SP: spine. RFOF: redundant foramen ovale flap; FOF: foramen ovale flap; FO: foramen ovale.

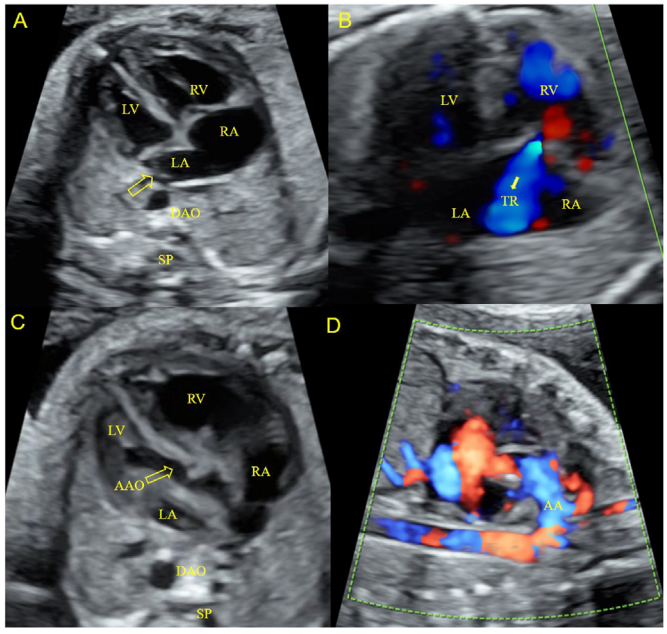

Fig. 4. A 28-week-old fetus with isolated RFOF in category II. A. The four-chamber view shows that FOF reached the lateral wall of the LA (arrow), and the flap was close to the mitral valve in the diastole. B. Color Doppler echocardiogram showed moderate to severe tricuspid regurgitation(TR) (arrow). C. In the left ventricular outflow tract, it showed a smaller AAO(ascending aorta, arrow). D. Sagittal view of the aortic arch(AA) showed a narrow AA. LA: left atrium; RA: right atrium; LV: left ventricle; RV: right ventricle; DAO: descending aorta; AA: aortic arch; AAO: ascending aorta; SP: spine; TR: tricuspid regurgitation; RFOF: redundant foramen ovale flap; FOF: foramen ovale flap.

Table 2
Echocardiographic findings in fetuses with RFOF (87 cases).

Examined cardiac structure	n(%)	Range	Mean ± SD
FOF/LA≥0.65	76(87.3)		
0.5<FOF/LA<0.65	11(12.6)		
Hypermobile and redundant flap	87(100)		
Right/left atrium >1.2	53(60.9)	1.08–2.24	1.52 ± 0.13
Right/left ventricle>1.2	53(60.9)	1.02–2.36	1.56 ± 0.26
Moderate/severe tricuspid regurgitation	10(11.5)		
PA/AO>1.2	53(60.9)	1.02–2.32	1.34 ± 0.27
Aoi/DA<0.74	0(0)	1.02–2.2	1.42 ± 0.33
Moderate pericardial effusion	2(2.2)		

pericardial effusion, and ascites. This fetus was delivered at 29 weeks of gestation and one day later due to FO obstruction.

4. Discussion

FO is covered by a free flap from the septum primum, which extends into the LA. In the fetus, 80% oxygenated blood flows into the LA via FO after it returns from the placenta through the umbilical vein.[8] This shunt ensures flow to the LV part of the heart, providing more oxygenated blood to both cerebral and coronary vascular beds. Typically, FO is unrestrictive during pregnancy.[9,10] After birth, pulmonary vascular resistance decreases and systemic vascular resistance increases. This increased pulmonary venous return increases the left atrial filling pressure, ultimately leading to FOF closure.[10] An echo-free zone near the interatrial septum was observed in the fetus using two-dimensional echocardiography and was considered normal FOF, which is thin, mobile, and unrestrictive, with a smooth curvature extending into the LA. The flow velocity through the normal FO is smooth.[10] If the FOF increases halfway or more across the LA, it will be considered RFOF.[11] The RFOF incidence rate is 0.2%–1% and varies among different study subjects.[12] In our study, we observed a 0.31% rate of isolated RFOF occurrence in 28, 308 normal fetuses. This result is consistent with that of Stewart et al.[12] The exact etiopathogenesis has not yet been explored, but it has been speculated that isolated primary RFOF could be caused by focal dysplasia or intrauterine injuries such as myocarditis.[3,13]

Fetal echocardiography is the best method for identifying isolated RFOF. The four-chamber view and FO channel view are most commonly used for diagnosing isolated RFOF. In these views, the atrial septum and FO are perpendicular in 2D imaging and parallel in Doppler flow. Therefore, it is recommended that FO structure be assessed in these views under the guidance of color Doppler echocardiography. Our study displayed two-dimensional echocardiography of the four-chamber view, and demonstrated that the FOF was stiff without its normal flapping motion. The FOF protruded to the LA in diastole, extended more than 50% into the LA, and reached the lateral wall of the LA, which was close to the mitral valve in diastole. In the FO channel and four-chamber views, the hypermobile and RFOF also contracted and extended when responding to the fetal cardiac cycle. As seen from the color Doppler, there was thin right-to-left linear blood flow through the FO and lateral flow displacement around the FO from LA to LV. In addition, a reversal flow across the FO from the left to right shunt was observed. The flap excursion on M-mode is uniphasic, and the pulmonary venous return and mitral orifice flow were not impaired.

In this study, there were 11 cases with a FOF/LA ratio <0.65 and 76 cases with a ratio ≥ 0.65; of these, 53 showed ventricular disproportion. An FOF/LA ratio cut-off of ≥ 0.65 indicates a significant or extremely significant association with ventricular disproportion.[7] Our results indicate that the degree of asymmetry of the ventricle is associated with the degree of protrusion of the septum primum into LA.

Generally, isolated RFOF should be considered when the left and right heart is disproportionate and there are no other cardiac defects. Typically, a smaller left side of the heart is an initial sign of isolated RFOF. It has been reported that isolated RFOF is one of the most common causes of smaller left hearts in fetuses, excluding congenital or structural heart disease; the RV/LV and PA/AO ratios are 1.23–2.12 and 1.04–2.38, respectively.[1] We obtained a similar ratio, RV/LV1.02–2.36, and a PA/AO ratio of 1.02–2.32. According to the study by Hagen et al.,[14] RA dilation is more common than RV dilation because RA is the first chamber to be affected by overload, and RFOF could reduce blood flow across the FO due to increased RA pressure. Tricuspid regurgitation could further increase RA pressure. In our study, 53 RFOF cases (60.9%) showed dilated RA, and 10 cases (11.5%) had moderate or severe tricuspid regurgitation. RFOF decreased blood flow in the left side of the heart, which could decrease LA and LV dimensions, but systolic LV function remains unaffected compared to the right side of the heart.[2]

Isolated RFOF could be related to ventricular disproportion, especially in type-II and type-III cases. Some fetuses in our study displayed smaller left side of the heart, AO, and AOI. Seven fetuses who could have had coarctation of the aorta (COA) were referred to us. However, none of them had significant COA after their birth, but all had isolated RFOF. A significant amount of systemic venous return is diverted to the RV, depending on RFOF severity. Diminished flow from FO to LV leads to a smaller cavity, while reduced downstream blood flow into the

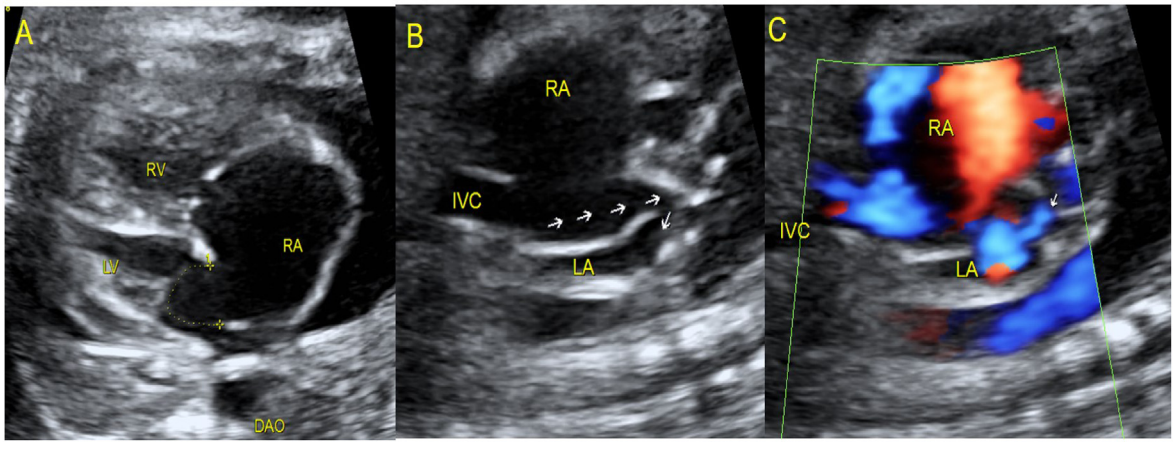

Fig. 5. A-31-week-old fetus with isolated RFOF in category III. A. The four-chamber view shows the FOF (curved dotted line) protruding from the LA and transient prolapse into the mitral valve orifice with moderate to severe pericardial effusion; B, C. The FO channel view in 2D and CDFI shows narrow flow bundles (single arrow) passing through the FO channel (continuous arrows).
RA: right atrium; LA: left atrium; RV: right ventricle; LV: left ventricle; IVC: inferior vena cava; DAO: descending aorta; RFOF: redundant foramen ovale flap; FOF: foramen ovale flap FO; foramen ovale.

descending aorta further decreased the original AOI. No statistical difference was identified between fetuses with isolated RFOF and fetuses with true fetal COA.[7,15] Isolated RFOF and COA can both cause similar morphological and hemodynamic variations in cardiac structures, but there are more fetuses with isolated RFOF than patients without CoA. In fetuses with isolated RFO, the pulmonary venous return will increase LA pressure, the FOF and atrial septum will be repositioned after birth, and LV filling and forward flow in the aortic arch could increase. This indicates that isolated RFOF could be self-limiting but not pathological.[10,15] Early detection of isolated RFOF in a fetus due to suspected COA or ventricular imbalance can minimize the effects of CoA at birth.[15] The combination of AOI/DA<0.74 and the presence of constricted frame and/or isthmus blood flow disturbance can improve diagnostic accuracy.[16] No cases with AOI/DA<0.74 were observed in our study. In clinical practice, a more rigorous assessment of the solitary RFOF bulge in a four-chamber view could reduce false positives and improve the specificity of prenatal COA diagnosis. The FOF/LA ratio can be calculated by measuring the maximum diameter of the RFOF and LA. If FOF/LA > 0.65, CoA should be diagnosed with caution because its indirect signs could be caused by RFOF.[10,15]

In our study, three fetuses had premature atrial contractions and two fetuses had supraventricular tachycardia. The arrhythmia was resolved in both cases. A strong positive association has been reported between RFOF and fetal arrhythmias, the most common of which is the atrial complex of premature (PAC).[17] Papa et al.[18] reported 93 RFOFs in 1223 fetuses, 36% of which were associated with the PAC. They claimed that the pressure exerted on the atria by the redundant primary septum caused the ectopic heart rhythm. After birth, normalization of pulmonary circulation increases LA pressure, which closes FOF and eliminates the cause of these PACs.[17–19]

Isolated RFOF occurs in approximately 1/3 of restrictive FO cases in normal fetus hearts.[2] Isolated RFOF can result in increased and dilated right heart blood flow, congenital heart failure, and fetal hydrops. In our study, there were no obvious cardiac abnormalities after birth, except in two isolated RFOF cases. Case #1 presented with Isolated RFOF with severe tricuspid regurgitation, pleural effusion, and ascites. The fetus was born at 31 weeks of gestation but died five days later. It is speculated that in early FO obstruction, elevated right heart filling pressure could lead to right congestive heart failure, which develops into fetal hydrops and tricuspid regurgitation. Case #2, who had isolated RFOF with moderate pericardial effusion and ascites, was born at 29 weeks of gestation but survived only one day. The presumed cause of death was FO obstruction in the uterus. These two cases represent the potential development of hydrops fetalis and tricuspid regurgitation in the late stages of pregnancy due to FO obstruction. Developments related to antenatal complications should be closely followed, and edema typically completely reverses with timely delivery, when isolated RFOF is the only factor.

5. Conclusion

RFOF diagnosis should be considered if the left side of the fetal heart is small. Fetal outcomes in most isolated RFOFs are favorable, and monthly follow-up is recommended for patients developing arrhythmias or fetal hydrops. Delivery should be performed to save the lives of fetuses with hydrops fetalis, provided they are at the appropriate gestational age and lung maturity.

Limitations of the study

We acknowledge the retrospective nature of this study. Our institution is a regional referral center, meaning there is potential patient selection bias. Therefore, the data and results might not be directly applicable to other centers and populations. The sample size is relatively small, especially for fetal outcomes, which limited the statistical analysis and results of the study.

Ethics approval

This research complied with all relevant national regulations and institutional policies and was conducted in accordance with the principles of the Helsinki Declaration. The study protocol was approved by the Peking University People's Hospital Human Research Ethics Committee (registration number 2018PHB072-01).

Consent to participate

Informed consent was obtained from all individual participants in the study.

Consent for publication

All authors consent to the publication of this manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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