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ORIGINAL ARTICLE

Clinical features and echocardiographic findings of isolated foramen ovale restriction in foetuses

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ABSTRACT

Isolated restrictive foramen ovale (rFO) without complex heart defects is a rare pathology. There may be difficulties in managing this situation, which can lead to right heart enlargement, tricuspid regurgitation and hydrops findings in the foetus. We conducted a retrospective analysis of 8451 foetuses. 7883 (93.2%) had a structurally normal heart or minor heart disease, 18 (0.22%) of which had a diagnosis of isolated rFO. Nine patients with neonatal echocardiographic examination were included in the study. In 8 (88.8%) patients, it was stated that a decision to give birth should be made at the time of presentation. Evaluating postpartum echocardiographic examinations, 7 (77.7%) patients had normal or minor defects. The decision of delivery made at the right time during follow-up is critical to determine the prognosis.

IMPACT STATEMENT

- **What is already known on this subject?** The data about the prenatal diagnosis of isolated rFO is limited.
- **What the results of this study add?** We conducted a retrospective analysis of 8451 foetuses. 7883 (93.2%) foetuses had a structurally normal heart or minor heart disease, 18 (0.22%) of which had a diagnosis of rFO. Nıne patients with foetal and postnatal follow-up and echocardiographic findings were examined in the study. The group's median gestational age at admission was 35.0 weeks (range: 27.0–39.0 weeks). The delivery decision was made in 8 (88.8%) patients at the time of admission. Evaluating postpartum echocardiographic examinations, 7 (77.7%) patients had normal or minor defects. Additionally, one patient was diagnosed with cardiomyopathy, and the other patient was diagnosed with functional pulmonary atresia. No death occurred in any foetus during follow-up.
- **What the implications are of these findings for clinical practice and/or further research?** Isolated rFO, a rare condition in the foetus, is generally well-tolerated in foetal life. However, the right heart enlargement, tricuspid regurgitation, or hydrops findings can be seen in patients. The decision of delivery made at the right time during follow-up is critical to determine the prognosis.

KEYWORDS

Restrictive foramen ovale; fetal echocardiography; prenatal diagnosis; fetal medicine

Introduction

Right ventricle (RV) and left ventricle (LV) widths are expected to be equal in the second trimester of pregnancy and increase in favour of the RV in the following weeks. In the early weeks of pregnancy, ventricular disproportion, and a large RV, is a known early indicator of non-cardiac and cardiac state possible left-sided structural heart disease (Sharland and Allan 1992; Hornung et al. 2001).

Isolated restrictive foramen ovale (rFO) is the possible cause of right heart enlargement in foetal life in patients without structural heart disease. This condition can cause failure to develop the LV, enlargement of the right heart, foetal hydrops, and even neonatal death (Chobot et al.1990; Hagen et al. 2005; Gu et al. 2018).

We aim to present our experience in the foetal and postnatal follow-up of patients not accompanied by complex heart disease and diagnosed with rFO.

Material and methods

We conducted a retrospective analysis of the foetuses referred to the Paediatric Cardiology Department of Çukurova University Hospital between January 2010 and September 2020. Foetal heart examination was performed using Sonos 5500 or 7500 and Philips Epiq 7 echocardiography device, 5 MHz sector transducer, or 3–8 MHz curvilinear transducer. A complete foetal echocardiographic examination, including two-dimensional (2D), M-mode, rhythm analysis, pulse, and

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colour Doppler flow mapping, was performed on the patients who applied to our department, as recommended by the American Echocardiography Association guidelines (Rychik et al. 2004). Examinations were done by two foetal echocardiographers (N.Ö and S.E).

Right ventricle and LV diastolic dimensions were measured just below the atrioventricular (AV) valves, the widest part at the end of the diastole, in the appearance of a four-chamber view. The widest length from each atrium's sidewalls to the atrial septum's edge was measured at end of systole. The dimensions of aorta and pulmonary artery and their relationship with each other were evaluated. The great arteries' dimensions were recorded by measuring their largest diameters at the end of the systole. Ventricular and atrial enlargements were determined based on published standard measurements for gestational age-based dimensional measurements. The ductal view was obtained by aligning the imaging plane with the right ventricular outflow tract and the main pulmonary artery. The ductus arteriosus (DA) was evaluated in sagittal or longitudinal axis views in 2D echocardiography. The ascending aorta's size and shape, the transverse arch, and the descending aorta were visualised. The presence of antegrade blood flow in the aorta and pulmonary artery and velocity was recorded using colour Doppler (Sharland and Allan 1992; Rychik et al. 2004; Donofrio et al. 2014).

Foramen ovale diameter <2.5 mm, FO right to left Doppler$>$ 40 cm/s, FO/right atrium (RA) diameter <0.3, FO/ascending aortic diameter <0.52 are the echocardiographic criteria used in previous studies to identify rFO. In our study, all patients diagnosed with rFO had these findings (Gu et al. 2018). Right ventricle and RA enlargement, tricuspid regurgitation, aneurysmal FO flap, and pericardial effusion were evaluated echocardiographically. If the enlarged septum primum flap is extended to the left atrium (LA) 50% in intrauterine life, this tissue is defined as an atrial septal aneurysm (ASA) (Kachalia et al. 1991; Haddad et al. 1996). Foetuses with complex heart diseases were not included in the study.

The records of the patients delivered at our hospital were examined in terms of associated risk factors. Pregnancy-related risk factors; medications used, smoking and alcohol consumption history, delivery types, and gestation weeks were noted. A detailed echocardiographic examination was performed on the patients immediately after birth.

Informed consent was not required as a retrospective review was performed. Approval was obtained from the ethics committee of Çukurova University.

Results

In this study, records of 8451 foetuses who had foetal echocardiography in our department between September 2010 and September 2020 were examined. 7883 (93.2%) foetuses had a structurally normal or minor heart disease, 18 (0.22%) of which had a diagnosis of rFO. Nine of the 18 patients diagnosed with rFO were excluded from the study because their deliveries did not occur in our hospital, and they did not come for postnatal follow-up. As a result, foetal and postnatal follow-up and echocardiographic findings of 9 patients were examined. The group's median gestational age at presentation 35.0 weeks (range: 27.0–39.0 weeks). The delivery decision was made in 8 (88.8%) patients at the time of admission. The patient with the lowest admission week was 27 weeks old and was followed up for seven weeks. Echocardiographic examination after birth was normal in this patient with significant right heart enlargement in foetal life (Figure 1). The patient's cardiovascular profile score was 10/10 and did not change during follow-up

On postnatal echocardiographic examinations, 7 (77.7%) patients had normal or minor defects. Those with minor defects had patent ductus arteriosus, mild tricuspid regurgitation, and minimal pericardial effusion. Additionally, patient #1 was diagnosed with cardiomyopathy and patient #7 was diagnosed with functional pulmonary atresia. These two children needed treatment in the neonatal follow-up. The patient with an echocardiographic diagnosis of non-compaction cardiomyopathy was treated for heart failure due to mild systolic dysfunction. The other patient diagnosed with functional pulmonary atresia was born by elective caesarean section at 34 weeks. The echocardiography was performed immediately after delivery; there was significant tricuspid regurgitation, no antegrade flow was observed in the pulmonary artery, and started prostaglandin infusion treatment. This patient also had normal anterograde pulmonary artery flow and normal arterial oxygenation within one week. No death occurred in any foetus during follow-up. The patients' characteristics, pregnancy-related risk factors, foetal and postnatal echocardiographic findings were summarised in Tables 1 and 2.

Discussion

The association of congenital heart disease with intrauterine rFO is common and has a poor prognosis (Donofrio et al. 2004). However, isolated rFO is a very rare pathology. GU et al. (2018) found the frequency of isolated rFO as 0.89%. In our study, 18 (0.22%) of 7883 foetuses with structurally normal or minor heart disease had rFO.

Foramen ovale flap with free-edged septum primum on the left septal surface is critical in foetal circulation. Approximately 76% of the total volume of oxygenated blood returning from the placenta through the umbilical vein and inferior vena cava flows from the RA to the LA through the FO. In this way, most of the LV blood flow is maintained and is adequately oxygenated to both the cerebral and coronary vascular beds. Naturally, the FO valve appears freely mobile and non-restrictive. As a result of increased pulmonary venous return after birth, the LA volume and pressure increase. This causes the FO to be covered by the septum primum (Chobot et al. 1990; Uzun et al. 2014).

Two theoretical considerations have been defined as the pathogenesis of rFO. First, increased LA pressure resulted from left heart obstructive pathologies, and finally, functional and anatomical narrowing of FO (Donofrio et al. 2004). This may explain the rFO in the foetus with mitral flow obstruction, mitral insufficiency, and aortic valve obstruction (Chobot

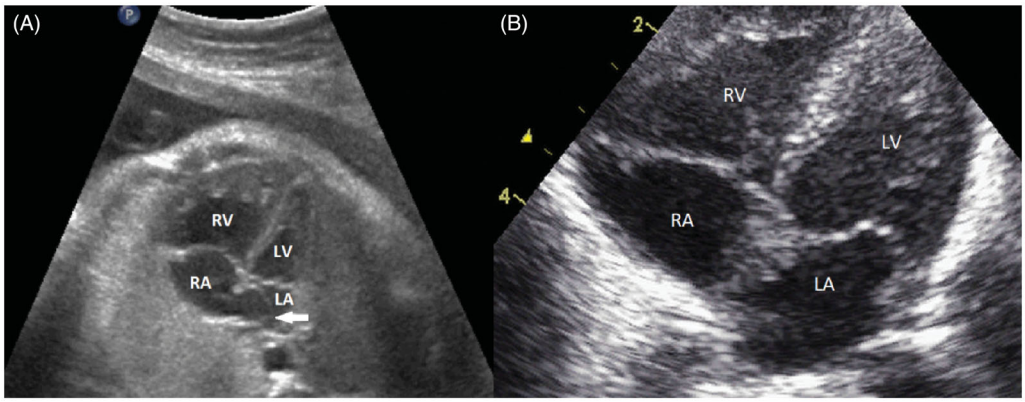


Figure 1. (A) Four-chamber view of 34-wk foetus; atrial septal aneurysm bulging to the left atrium and dilated right heart chambers. (B) In postnatal echocardiography of the same patient, the right and left heart chambers were normal dimensions. RV: right ventricle, LV: left ventricle, RA: right atrium, LA: left atrium.

Table 1. Clinical characteristics and follow-up of patients.

Patient	Maternal age (years)	Referral reason	GA at diagnosis (weeks)	GA at birth (weeks)	Maternal risk factors	Additional findings (echo)	Neonatal echocardiography
1	24	Cardiac abnormality	37	37	–	RV dysfunction, severe TR, MR	Cardiomyopathy
2	29	Cardiac abnormality	27	34	Gestational diabetes mellitus	RA-RV-PA dilatation	Normal
3	21	Cardiac abnormality	34	34	Gestational anaemia	RA-RV dilatation, PE	Minimal PE
4	21	Foramen ovale restriction	39	39	–	RA-RV-PA dilatation, RV dysfunction, severe TR, DC	Pulmonary hypertension
5	33	Hydrops fetalis,	33	33	–	Hydrops findings	Normal
6	26	Cardiac abnormality	36	36	–	RA-RV-PA dilatation	Normal
7	27	Cardiac abnormality	34	34	–	Severe TR, RV hypertrophy	Functional pulmonary atresia, TR
8	25	Cardiac abnormality	36	36	Polyhydramnios	RA-RV dilatation	Normal
9	33	Cardiac abnormality	35	35	–	PA dilatation, RVH	PDA

GA: gestational age, RV: right ventricle, TR: tricuspid regurgitation, MR: mitral regurgitation, RA: right atrium, PA: pulmonary artery, PE: pericardial effusion, DC: ductal constriction, PDA: patent ductus arteriosus.

Table 2. Foetal echocardiographic findings.

Findings	*n* (%)
Right atrium	
Right/left atrium >1.2	4 (44.4)
Trikuspit regurgitation (moderate/severe)	3 (33.3)
Right ventricule	
Right/left ventricle >1.2	4 (44.4)
Hypertrophy	2 (22.2)
Dysfunction	2 (22.2)
Pulmonary artery	
Pulmonary artery/aorta >1.2	5 (55.5)
Pulmonary regurgitation	1 (11.1)
Pericardial effusion	1 (11.1)
Atrial septal aneurysm	6 (66.6)

et al. 1990). We thought that patient #1 developed rFO due to severe mitral insufficiency caused by ventricular dysfunction. The delivery decision was made in this patient. We have seen that ventricular trabeculation increased, and ventricular dysfunction continued in postnatal controls (Figure 2).

The second theory is; rFO causes volume loading on the right side of the heart with a concomitant decrease in the filling of the heart's left side. This is likely to be secondary to excess septal tissue, endocardial disease, or hemodynamics altered by a pre-existing supraventricular tachyarrhythmia (SVT). Left heart hypoplasia is more common in rFO in the early weeks of pregnancy than last weeks (Chobot et al. 1990; Nowlen et al. 2000). The severity of left heart hypoplasia is believed to depend on the length of gestation at which the restriction occurred. This excess blood flow redirected to the RV can cause congestive right heart failure, and at the same time, the left-sided structures may become hypoplastic due to reduced blood flow to the left. However, closure in later pregnancy periods may have a minimal effect on the left heart (Naeye and Blanc 1964; Nowlen et al. 2000).

Isolated rFO is extremely rare in a foetus. Right heart enlargement, tricuspid regurgitation, and pericardial effusion can be seen in foetal echocardiography. Dilation of the RA and RV is often the first sign of restrictive FO. Uzun et al. (2014) concluded that the most common cause (26%) of foetal right heart enlargement was rFO alone. Also, they stated in their study that all patients with rFO had right heart enlargement and secondarily a hypermobile atrial septum. Respectively, our most common foetal echocardiographic findings were ASA, enlargement of the pulmonary artery, and the enlargement of the right heart chambers. A foetal echocardiographic image of patient # 6 with right heart enlargement and the ASA, as shown in Figure 3.

Although foetal ASA is often associated with rFO and foetal cardiac rhythm disturbances (especially SVT), it can also be seen as an isolated condition (Rice et al. 1988; Hung et al. 2008) Isolated ASA is considered a natural transient phase of

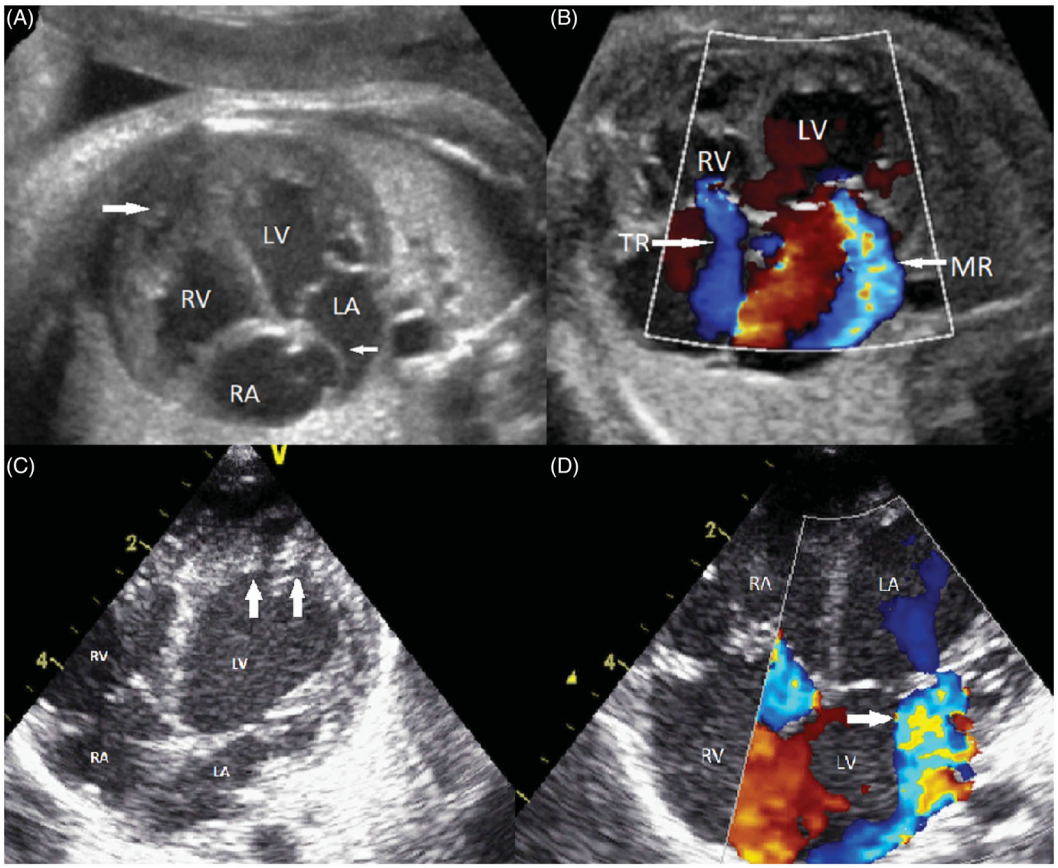


Figure 2. Foetal (A-B) and postnatal (C-D) images of a patient with an echocardiographic diagnosis of non-compaction cardiomyopathy. (A) 2 D image of atrial septal aneurysm bulging to the left atrium and right ventricular hypertrophy in a four-chamber view (B) In a four-chamber view, colour Doppler shows severe tricuspid and mitral regurgitation. (C) Increased trabeculation in the left ventricle (D) Colour Doppler echocardiogram shows severe mitral regurgitation. RV: right ventricle, LV: left ventricle, RA: right atrium, LA: left atrium, TR: tricuspid regurgitation, MR: mitral regurgitation.

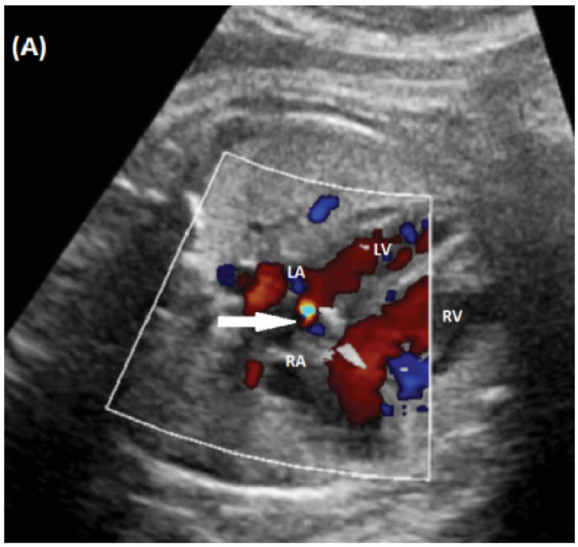


Figure 3. (A) Colour Doppler image of a 36-week foetus; a restrictive flow from the right atrium to the left atrium was seen along with the FO and dilated right heart chambers. RV: right ventricle, LV: left ventricle, RA: right atrium, LA: left atrium.

spontaneous closure of the FO during normal foetal growth. Ozcelik et al. (2006) examined the prevalence and natural history of ASA in newborns. In this study, they reported that all ASAs disappeared at the end of the first year of life, and there were no lesion-related complications in their follow-up.

Another cause of right heart enlargement in patients without structural heart disease is DA constriction. The DA's prenatal constriction leads to increased pressure in the RV, enlargement of right heart structures, pulmonary artery enlargement, tricuspid and pulmonary valve insufficiency, and eventually, right heart failure (Gewillig et al. 2009; Alvarez and McBrien 2018). Patient # 4, both rFO and DA constriction were detected. The most likely cause of DA constriction is nonsteroidal anti-inflammatory drugs used during pregnancy (Siu and Lee 2004). It is well known that feeding the mother with polyphenol-rich foods (e.g. herbal teas, dark chocolate, orange derivatives, strawberries) increases the risk and rarely idiopathic (Trevett and Cotton 2004; Zielinsky et al. 2010). There was no mother's history of drug use or additional risk associated with pregnancy, and this case presented to us at 39 weeks with the suspicion of rFO. Foetal echocardiography showed severe tricuspid regurgitation with right heart cavities and RV dysfunction. The patient was decided to deliver. Postnatal echocardiography showed moderate tricuspid regurgitation, and right heart enlargement was resolved.

The presence of restrictive FO in the late pregnancy weeks is associated with good postnatal outcomes. Gu et al. (2018) showed that none of the 60 foetuses diagnosed with intrauterine restrictive FO had prenatal mortality, and neonatal

mortality was reported only in one foetus. They stated that maternal preeclampsia and placental abruption might cause neonatal death. In our study, prenatal and neonatal mortality did not develop in any of the patients, and the earliest birth week was 33 weeks. Due to the presence of hydrops findings in this foetus, the delivery decision was made.

Consequently, isolated rFO, which is extremely rare, causes different levels of right heart failure in intrauterine life. A careful foetal echocardiographic examination is required for these patients to be diagnosed correctly. The decision to give birth at the right time is critical in these patients' follow-up. (Hagen et al. 2005).

Study limitations

Our study's main limitation is that it is a retrospective study, and our institution is a tertiary-care referral centre south-east of Turkey. We are aware of the limitations inherent in retrospective work. Since patients are referred from many centres, some patients may prefer the centres to which they are referred. Lost follow-up patients have been a limiting factor in our study population.

Disclosure statement

The authors declare that they have no conflict of interest.

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