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REVIEW

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Echocardiographic features and outcome of restrictive foramen ovale in fetuses with and without cardiac malformations: Literature review

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Abstract

Foramen ovale is a small communication between the left and the right atrium and its restriction is a rare congenital heart anomaly. There is no consensus on diagnosis and management of fetal restrictive foramen ovale (RFO). In our paper we included 11 studies about fetuses affected by isolated RFO, RFO with D-Transposition of the Great Arteries (dTGA) and RFO with hypoplastic left heart syndrome (HLHS). While fetuses affected from HLHS and dTGA with RFO have a poor prognosis, premature RFO in an otherwise structurally normal heart, if found in later gestation, have an overall good outcome.

KEYWORDS
dTGA, fetal, foramen ovale, HLHS, restrictive

1 | INTRODUCTION

Foramen ovale (FO) is a small opening in fetal heart between the left and right atrium, which supplies about 76% of left ventricular's output, maintaining an adequate oxygenated blood in cerebral and coronary vascular beds. A restriction of the foramen ovale (RFO) or its premature closure defines a rare cardiac developmental defect, with an incidence ranging from 0.2% to 1.4%.[1–3] RFO includes either a tighted FO orifice or anomalies in shape or motion of the FO valve[4] and could be the consequence of a primary anomalous development of the septum primum or the result of the increased left atrial pressure.[5,6] RFO could lead to fetal hydrops, arrhythmias and low birthweight as a result of progressive circulatory failure due to pulmonary congestion.[6–8] In several cases, the RFO could be associated with other types of cardiac defects, such as ventricular septal anomalies, mitral and aortic atresia, D-Transposition of the Great Arteries (dTGA)[9] and Hypoplastic left heart syndrome (HLHS).[10–14] If untreated, RFO has a poor prognosis and might also lead to death during the intrauterine life[5,11,12,15,16] or immediately after birth,[17] particularly in fetuses with other coexisting congenital heart defects.

The aim of this article is to review the literature on this topic in order to describe the prevalence, pathogenesis, diagnostic ultrasound features, outcomes of RFO in structurally normal hearts and in associations to other cardiac abnormalities and to provide information on how to counsel and manage pregnancies with this ultrasound finding.

2 | MATERIAL AND METHODS OF THE LITERATURE REVIEW

MEDLINE, EMBASE, CINAHL and the Web of Science databases were searched electronically up to December 31, 2021. About the search strategy, were used combinations of the following keywords and medical subject heading (MeSH) terms: "fetal," "foramen ovale,"

"restrictive," "redundancy," "pregnancy," "gestation." Additional sources were identified through cross-referencing. For the analysis were included English language research studies published in scientific journals indexed in the searched databases. Only full-text articles were considered eligible for inclusion; personal communications, case reports, reviews, conference abstracts, and case series with <3 cases were excluded to avoid publication bias.

Sixty-nine articles were identified, 21 were assessed with respect to their eligibility for inclusion and 11 studies were included.

Tables 1–3 shows included studies features. These studies were published between 2004 and 2021: eight were retrospective cohort studies,[1,9–13,18,19] two were retrospective case-control studies[4,20] and one was a prospective cohort study.[14]

Four studies included RFO in the context of a normal heart,[1,4,18,20] while in five studies RFO was associated with HLHS[10–14] and in two studies RFO was found in fetuses affected by TGA.[9,19] Population size ranged from 6 to 65 fetuses. Detailed fetal echocardiography was performed in all the studies. In four studies an ultrasound assessment was also performed postnatally.

3 | RESULTS OF THE LITERATURE REVIEW

3.1 | Diagnostic features of RFO

The diagnosis of this cardiac defect is generally assessed by ultrasound, although the detection is still challenging. Several diagnostic ultrasound findings have been proposed to diagnose RFO by two-dimensional ultrasound (2D-echo), Doppler evaluation and by echocardiographic functional assessment.

By 2D-echo, FO is considered restrictive when its diameter <2.5 mm in normal hearts and <4.0 mm in fetuses with Hypoplastic Left Heart Syndrome (HLHS).[1,10,18] Unfortunately, the paucity of data did not intercept the cut-off to define as restrictive the FO contextually with dTGA. Della Gatta et al. only mentioned the value of FO diameter <6.5 mm as predictive of urgent intervention at birth with a sensitivity of 100% and specificity of 57.1% and <3 mm with a positive predictive value (PPV) of 80%.[19] Moreover, some studies define FO as restrictive when FO to right atrial diameter ratio is <0.3, FO to interatrial septum length ratio is <0.33 and FO to diameter of ascending aorta ratio is <0.52.[10]

By Doppler evaluation, RFO could also be identified by right to left Doppler velocity >40 cm/s.[18]

Moreover, the presence of fetal right heart widening, a hypermobile or redundant FO valve, an increased right ventricular cardiac output (often associated with tricuspid regurgitation) and a posteriorly angulated ductus arteriosus without an evident ductal constriction could be considered as supportive evidence for the diagnosis.[1,4]

Lastly, significant efforts have also been made to functionally assess the foramen ovale as an integral part of cardiac function so far. Not yet validated for the diagnosis of RFO, recent studies have described M-mode echocardiography to study FO flap tracings from 24 weeks of gestation until pregnancy at term in fetuses with structurally normal hearts and with dTGA, but without FO defects. It would be interesting to evaluate with further studies specific functional echocardiographic parameters defining RFO by M-Mode trans-atrial evaluation.[21,22]

3.2 | RFO in fetuses with normal heart

Four studies (4/11) included fetuses with normal hearts affected by RFO (Table 1).[1,4,18,20] Among these, three studies focused on the ultrasound diagnosis of RFO and the other detectable features associated.[1,4,18] The incidence of RFO in fetuses with normal heart was about 0.2%–1.4%[1] and could be caused by a primary abnormal development of the septum primum or by an increased left atrial pressure.[6]

In structurally normal hearts, FO diameter should be <2.5 mm to be defined as restrictive.[1,18]

In a 2018 retrospective analysis of 65 fetuses affected by RFO or complete closure of the FO (cFO), pictures of fetal echocardiogram showed dilation of the right atrium in 73.8% of fetuses, right ventricular dilation in 58.5%, moderate to severe tricuspid regurgitation in 29.2%, mild pericardial effusion in 15.4% and ductus arteriosus premature constriction in 4.6%.[18]

In another retrospective study analyzing the echocardiographic records of 23 fetuses affected by RFO, hypermobile septum showed a sensitivity of 56% and a specificity of 92%, with a PPV of 65% and a negative predictive value (NPV) of 89% ($p = 0.001$) in detecting RFO, while posterior angulation of the ductus arteriosus had a sensitivity of 60% and a specificity of 96% with a PPV of 79% and a NPV of 90% for RFO ($p = 0.001$). Persistent pulmonary hypertension occurred in 30% of infants after birth.[1]

A retrospective case-control study identified 62 fetuses with RFO: 72% of cases had isolated right atrium (RA) dilatation and 18% of cases were associated with right ventricle (RV) dilatation. The study focused on the ratio between FO channel outlet diameter (distance between FO valve's terminal point and the atrial septum) and inferior vena cava diameter (DFO_{out}/D_{IVC}), taken in the sagittal views. DFO_{out}/D_{IVC} is an alternative measure interpreting the severity of RFO and resulted significantly lower in fetuses with RA and RV dilation, compared to the those with isolated RA dilation or normal size chambers ($p < 0.01$). Also, the mean DFO_{out}/D_{IVC} ratio was lower in the RFO group, compared with the group of fetuses with FO valve anomalies without restriction ($p < 0.01$). During follow-up, 17 fetuses with RFO showed evolutive signs of restriction in utero (emerging or progressive RA dilatation; emerging ventricular disproportion; pericardial effusion and tricuspid regurgitation), although the postnatal outcome was good.[4]

Fetal RFO in hearts with otherwise normal structure can lead to right-ventricle volume loading, severe regurgitation through tricuspid valve and hypertension, which may results in congestive heart failure, hydrops or even fetal death. In a retrospective case-control study comparing postnatal outcomes of seven neonates affected by pulmonary hypertension and RFO with seven neonates affected by

TABLE 1 RFO in otherwise structurally normal heart

Study	Design	N. of fetuses)	RFO criteria	Objectives	Time of evaluation	GA at diagnosis	GA at birth	Type of Delivery	Birth weight	Results	Conclusions
Gupta et al (2011)	Retrosp.	14	FO <2 mm Gradient across the septum >5 mmHg	Outcomes of PHT in newborns with RFO compared to ones without RFO (MAS, RDS)	Fetal and postnatal	N.A.[a]	N.A.[a]	N.A.[a]	RFO group 2620 ± 1500 g. NonRFO group 2280 ± 1000 g.	RFO group mean PA pressure was 0.4 ± 0.15 compared with 0.65 ± 0.23 in non RFO group (***p* = 0.03**). Not statistically significant difference in initial PAP.	RFO with PHT had a much better outcome than non RFO fetuses.
Uzun et al (2014)	Retrosp.	23	FO <2.5 mm FO Doppler >40 cm/s FO/RA diameter <0.3 FO/IAS length <0.33 FO/ ascending aorta diameter <0.52.	To determine if a RFO has relevance to the interatrial communication restriction	Fetal	33.0 ± 3.9 weeks	N.A.[a]	19 term VB 2 preterm VB 2 emergency CS	N.A.[a]	The most common ultrasound findings of fetuses with RFO were enlarged RA (100%), hypermobile/ redundant AS (91%) with NPV of 89% for RFO, posteriorly angulated DA (68%) with NPV of 90%. In RFO increased right-to-left ventricular output ratio of 3.42 ± 1.5, greater than normal value of 1.42 (***p* = 0.002**)	Fetal right heart dilatation, hypermobile AS aneurysm and a posteriorly angulated DA can make us suspect of RFO.
Lei et al. (2018)	Retrosp.	659 (62 with RFO)	FO valve characterized by an abnormal shape (aneurysmal/ hypermobile) or motion (thick and flat without a "flapping" motion)	To determine the implications of RFO and its related ultrasound features	Fetal and postnatal	RFO group[b] median GA 30.4 weeks Non-RFO group median GA 32.7 weeks	37 ± 0,9 weeks[b]	10 VB 7 CS	N.A.[a]	The mean DOUT[c]/DIVC[d] ratio was lower in fetuses with RA and RV dilation, compared to the those with isolated RA dilation or normal size chambers (***p* < 0.01**). Also, the mean DFO_{out}/D_{IVC} ratio was lower in the RFO group, compared with the group of fetuses with FO valve anomalies without restriction (***p* < 0.01**). RA/LA was negatively correlated with DOUT/ DIVC ($R^2 = 0.97$, ***p* < 0.01**).	For fetuses with abnormal shape or motion of FO valve, the dilatation of the right heart could be considered as an indicator of RFO. The larger RA/LA ratio indicates a more severe restriction. DFO_{out}/D_{IVC} is another measure interpreting the severity of RFO.
Gu et al. (2018)	Retrosp.	9704 (65 with RFO or cFO)	FO diameter <2.5 mm FO Doppler >40 cm/s, FO/RA diameter <0.3 FO/ascending aorta diameter <0.52.	Characterize FECG features of rFO/cFO in structurally normal hearts, outcome, risk factors for adverse outcome.	Fetal	33.9 ± 4.3 weeks	N.A.[a]	N.A.[a]	N.A.[a]	At FECG: RA dilation in 48 (73.84%), RV dilation in 38 (58.46%), TR in 19 (29.23%), pericardial effusion in 10 (15.38%). No prenatal deaths in the rFO or the cFO group, but neonatal mortality included cases due to maternal or extracardiac conditions.	Premature rFO/cFO is rare in structurally normal hearts. FECG characteristics: dilated RA and RV, TR, and pericardial effusion. Most had good prognosis.

Abbreviations: Ao, aorta; AS, atrial septum; CS, caesarian section; DA, ductus arteriosus; FECG, fetal echocardiography; FO, foramen ovale; cFO, closure of FO; IAS, interatrial septum; LA, left atrium; LV, left ventricle; MAS, meconium aspiration syndrome; NPV, negative predictive value; PHT, pulmonary hypertension; VB, vaginal birth; PA, pulmonary artery; PAP, pulmonary artery pressure; RDS, respiratory distress syndrome; RV, Right Ventricle; Retrosp., retrospective study; RFO, restrictive foramen ovale; TR, tricuspid regurgitation.

[a]N.A. not applicable.

[b]Mentioned only for fetuses with evolutive sign of restriction.

[c]D_{OUT}: distance between the final point of FO valve and the atrial septum.

[d]D_{IVC}: the diameter of the inferior vena cava in sagittal views.

TABLE 2 RFO in hypoplastic left heart syndrome (HLHS)

Study	Design	N. of fetuses	RFO criteria	Objectives	Time of evaluation	GA at diagnosis	GA at birth	Type of Delivery	Birth weight	Results	Conclusions
Donofrio et al. (2004)	Retrosp.	105 CHDs 2/105 fetuses with FO R/C in HLHS	In HLHS fetuses, RFO was defined as a left-to-right atrial peak velocity 1.0 m/s in the presence of a dilated LA and/or rightward septal bowing.	Define the incidence and the outcomes of RFO in fetuses with CHDs, studying also a subgroup with HLHS.	Fetal	N.A.[a]	N.A.[a]	N.A.[a]	N.A.[a]	Fetuses with HLHS and RFO did not have in utero compromise but had severe hypoxia and poor perfusion at birth.	Accurate ultrasound of fetuses with HLHS and FO R/C before delivery is beneficial. A reversed pulmonary vein flow may predict infants that will be hypoxic at birth.
Taketazu et al. (2004)	Retrosp.	45	FO <2.5 mm with a continuous high peak flow >60 cm/s.	Define if FO or PV flow spectra correlate with LA hypertension after birth and post-natal diagnosis of RFO.	Fetal and postnatal	24.6 ± 6.3 weeks	N.A.[a]	N.A.[a]	N.A.[a]	3 PV flow patterns: Type A[b] = VTIR /VTIF <0,18 (normal). Type B[c] = VTIR /VTIF >0,18; Type C[d] = *to and fro*-flow. Neonatal FO size in B was significantly smaller than in type A. All type C had an intact AS postnatally.	Prenatal PV flow patterns in HLHS, with increased a-wave reversal, identify fetuses with postnatal detection of RFO and at risk of severe LA hypertension at birth.
Enzensberger et al. (2012)	Retrosp.	51 16/51 with RFO	FO <2.5 mm with a continuous high peak FO velocity in the 2nd and 3rd trimester	To correlate PV Doppler and FO assessment with the need for EAS.	Fetal postnatal	RFO 31.8 ± 7.9 No RFO 28.2 ± 6.3	RFO 39 ± 1.5 No RFO 39.2 ± 1,7	4/16 CS 9/16 VB 2/16 VE 1 unknown	RFO 3238 ± 411 g No RFO 3330 ± 628 g	Sensitivity and specificity in predicting EAS: Type C[d] PV flow 100%–91.7%. FO evaluation: 100%–72.9%. Type A[b] and B[c] PV flow and absence of cFO have 100% NPV for EAS.	PV Doppler is more accurate than direct assessment of FO in predicting need for EAS in HLHS fetuses with RFO and LA hypertension.
Sokolowski et al. (2019)	Prospective	145[e] Severe planned $N = 91$ Severe urgent $N = 23$ Severest $N = 2$	FO diameter, maximum blood flow velocity through the FO and assessment of the PV flow patterns	Efficacy of FO prenatal features in grading HLHS, according to new classifications of CHD[d]	Fetal	N.A.[a]	Severe planned[e] 38 (37–40) Severe urgent 38 (37–39) Severest HLHS 36 and 39	Severe planned[e] 62% CS Severe urgent 79.2% CS Severest HLHS 100% VB	Severe planned[e] 3110 ± 486 g Severe urgent 3050 ± 425 g Severest HLHS 2820 g and 3100 g	Prenatal diagnosis based on FO features for the group of severe urgent HLHS, that requires urgent treatment in 24 h, was characterized by	Prenatally RFO in HLHS is not an indicator of need for an urgent procedure. We should focus on PV flow to improve prediction of

(Continues)

TABLE 2 (Continued)

Study	Design	N. of fetuses	RFO criteria	Objectives	Time of evaluation	GA at diagnosis	GA at birth	Type of Delivery	Birth weight	Results	Conclusions
										100% sensitivity, 80.6% specificity and a low PPV of 9.5%.	severe urgent HLHS.
Jadczak et al. (2020)	Retrosp.	22 11 Surv 11 NonSurv	FO <4 mm and flow across FO with a maximal velocity > 70 cm/s and reverse flow in the pulmonary veins	To define HLHS survival predictors if associated with RFO	Fetal	Surv 33 (31–36) NonSurv 28 (27–33)	Surv 38 (38–38) NonSurv 38 (38–39)	17/22 CS 5/22 VB	Surv 2849 ± 335.13 g NonSurv 3132 ± 183.59 g	Median time of RFO diagnosis was significantly later in gestation in survivors (33 versus 28 weeks, $p = 0.04$). The average duration of in-utero FO restriction was, therefore, significantly longer in nonsurvivors (9 versus 5 weeks, $p = 0.02$). 2/22 need BAS with VTIF/VTIR <3.	Earlier development and longer time of in-utero FO restriction is associated with higher mortality regardless of the degree of RAS. PV Flow pattern is predictor of BAS rather than FO diameter or flow across FO.

Abbreviations: AS, Atrial Septum; BAS, balloon atrial septostomy; CHD, congenital heart disease; CS, caesarian section; EAS, early atrial septostomy; FO, foramen ovale; FO R/C, foramen ovale restriction or closure; cFO, closure of FO; HLHS, hypoplastic left heart syndrome; LA, left atrium; Non Surv, nonsurvivors; PPV, positive predictive value; PV, pulmonary vein; Surv, survivors; RAS, restrictive atrial septum; RFO, restricted foramen ovale; VB, vaginal birth; VE, vacuum extraction; VTIF, velocity-time integrals for forward PV flow; VTIR, velocity-time integrals for reverse PV flow.

[a]N.A. not applicable.

[b]**Type A**: continuous forward flow during ventricular systole and early diastole with normally limited a-wave reversal during atrial contraction.

[c]**Type B**: continuous forward flow during ventricular systole and early diastole with an increased a-wave reversal.

[d]**Type C**: to-and-fro flow with minimal or no early ventricular diastolic flow.

[e]HLHS classification, severe planned: HLHS does not require urgent postnatal treatment—the newborn is born in good condition and requires only prostaglandin E1 iv infusion, and can be prepared for the first stage of planned cardiac surgery; severe urgent HLHS, HLHS requires, in addition to prostaglandin E1 iv infusion, urgent (first 24 h) treatment in a catheterization laboratory (cath lab); severest HLHS, HLHS during the first minutes of postnatal life is cyanotic, does not respond to iv prostaglandin E1 infusion and is deteriorating within minutes or within the next few hours.

TABLE 3 RFO in dextro-transposition of the great arteries (dTGA)

Study	Design	N. of fetuses	RFO criteria	Objectives	Time of evaluation	GA at diagnosis	GA at birth	Type of Delivery	Birth weight	Results	Conclusions
Tuo et al. (2017)	Retrosp.	40	Maximal angle of flap at attachment point <30° and if it looks hypomobile and thick with a small orifice	Features to predict need for urgent BAS in fetuses with dTGA and RFO	Fetal and postnatal	N.A.[a]	39 weeks (34–39)	30/40 CS, of which 13 for prenatal RFO detection and 17 cases for obstetrical or maternal conditions	3000 g (1600–3900 g)	20/40 fetuses with RFO and dTGA received urgent BAS at birth. Also hypermobile and redundant FO was significantly linked with urgent BAS (***p* < 0.0001**, ***p* = 0.002** and ***p* = 0.0001**, respectively).	The diagnosis of restrictive, redundant and hypermobile FO in fetuses with dTGA in utero is predictor for urgent management at birth.
Della Gatta et al. (2021)	Retrosp.	17	Subjective RFO or FO diameter <6.5 mm	Study correlation between prenatal FECG findings and need of urgent BAS in neonates with dTGA.	Fetal	21.6 ± 4.9 weeks	38.4 ± 1.3 (38–39.5)	N.A.[a]	N.A.[a]	FO <3 mm has a positive predictive value for urgent BAS of 80%.	Cardiac assessment near term in dTGA could improve perinatal management. Positive correlation between FO size and need for urgent BAS.

Abbreviations: CS, caesarian section; BAS, balloon atrial septostomy; dTGA, dextro-transposition of the great arteries; cFO, closure of FO; FECG fetal echocardiography; FO, foramen ovale; Retrosp., retrospective study; RFO: restricted foramen ovale.

[a]N.A., not applicable.

pulmonary hypertension due to respiratory distress syndrome or meconium aspiration syndrome, 86% of neonates who had RFO with pulmonary hypertension did not require any treatment and manifested no clinical symptoms, resulting in significantly better outcomes compared with neonates without RFO, since the increase of blood pressure is strictly related to in utero circulation and often tends to resolve spontaneously after birth.[20]

However, data are too limited to exclude the possibility of adverse post birth outcomes in fetuses affected by RFO with normal hearts, so it's important to diagnose RFO prenatally and monitor them through a postnatal echocardiography.

3.3 | RFO in fetuses affected by HLHS

Five studies (5/11) included fetuses with RFO associated with HLHS, since a minority of fetuses affected by HLHS can develop RFO during gestation (Table 2).[9,11–14]

HLHS is one of the most common types of congenital heart disease (about 4.8%–9%); in this case, FO diameter should be <4 mm to be defined as restrictive.[10] RFO is detected in about 6%–11% of cases. The diagnosis should be done prenatally, but most cases remain undetected until birth.[10] Direct assessments of the atrial septum in fetuses with HLHS could be arduous because of the position of the foramen ovale, that appears high and posterior, as common in this condition.[12] Many Authors have investigated Doppler of pulmonary venous flow patterns that has been observed to indirectly reflect atrial pressures.[12,13]

In a retrospective analysis of 105 fetuses with CHDs, infants affected by HLHS with RFO or cFO (2/105) had the highest mortality rate, requiring an urgent Balloon Atrial Septostomy (BAS) at birth. In the third trimester echocardiography, an increase in the atrial shunt was reported, while the reversed pulmonary vein flow assessed was strictly related to infants' hypoxia at birth.[11]

In a 2019 study, HLHS was classified according to the severity of clinical conditions, assessing FO's diameter and the blood flow through it. The study included 145 fetuses and showed that the prediction of urgent treatment based on the evaluation of the foramen ovale had high sensitivity (100%) and satisfying specificity (80%), but a very low PPV (9%).[14]

Furthermore, a retrospective case-control study on 22 fetuses affected by RFO and HLHS, divided into 11 survivors and 11 non-survivors, showed that Pulmonary Venous Doppler (PVD) of forward/reverse velocity-time integral (VTI) ratio of <3 was the strongest predictor of urgent treatment and postnatal outcome. Moreover, earlier development and longer presence of RFO resulted in higher rate of short-term mortality, regardless of the type of restriction.[10]

Another study reviewed the prenatal and postnatal echocardiograms and outcomes of 45 fetuses with variants of HLHS, in order to define if direct assessment of FO or flow patterns of pulmonary vein (PV) are related with post-natal clinical left atrium hypertension. The study distinguished three different pulmonary vein flow patterns in fetuses with RFO associated to HLHS and showed that the PV flow pattern can be a very helpful predictor of left atrium hypertension's grade and outcome and may supply informations about the pathogenesis of PV pathology observed in affected newborns.[12]

Similarly, a retrospective analysis on 51 fetuses affected by HLHS and RFO showed that the above-mentioned pulmonary flow pattern classification and the measurement of FO could effectively predict the risk of an urgent intervention at birth.[13]

3.4 | RFO in fetuses affected by dTGA

Two studies (2/11) included fetuses with RFO and dTGA (Table 3).[9,19] Both analyzed the relationship between prenatal detection of RFO and the need for urgent treatment with BAS, since the early identification of neonates at high risk is essential for a proper management.[9,19]

The first included study was a retrospective analysis in 40 fetuses with dTGA: the 32.5% was affected by RFO. The study showed that a fetal redundant foramen ovale should be regarded as a BAS predictor as well as RFO and hypermobile foramen ovale.[9]

Similarly, another retrospective study including 60 fetuses affected by dTGA, of which 11 with RFO demonstrated the positive link between FO's dimension and the necessity for urgent BAS, with a measure of <3 mm being associated with a PPV of 80%.[19]

4 | CRITIQUE OF THE LITERATURE: DISCUSSION

This is the first review describing antenatal prevalence, clinical presentation, diagnostic ultrasound characteristics and outcomes of RFO in fetuses with either structurally normal hearts or CHD, and particularly dGA and HLHS.

The pathogenesis of RFO or cFO has not been clearly elucidated yet. Pinette et al. suggested that RFO/cFO may be caused by incorrect development of the connective tissue in the fetal heart, that is, the interatrial septum and atrio-ventricular valves.[23] Furthermore, Uzun et al. found that isolated RFO is the most usual cause (26%) of dilation of right heart in fetuses.[1]

Since the first description of premature RFO in 1982 by Hansmann and Redel,[24] only anecdotal reports and small series have been published, thus leading to a very low-quality evidence concerning all the aspects of RFO.

Premature RFO in a fetus with an otherwise normal heart's structure is rare (0.2%–1.4%)[1–3] and therefore most of the studies focused on RFO in HLHS.

HLHS encompasses fetuses with underdevelopment of left heart structures, with severe hypoplasia of the left ventricle and the left ventricular outflow tract. Defective aortic valve is the most common cause for decreased flow and increased pressure in the left ventricle.[25] The increasing left atrial hypertension can lead to a progressive underdevelopment of the left ventricle, with a meaningful movement

of blood from the left to the right side, and a consequent ventricular disproportion. Even if most fetuses with HLHS have a fully evident interatrial communication, in about 10%–20% of cases there is an intact or highly RFO, with a subsequent worsening of left atrial pressure. The increasing left atrial pressure damages the pulmonary veins and leads to their "arterialization."[14,26] Therefore, newborns with HLHS often shows left atrial hypertension and severe hypoxemia, which can represent a cardiovascular emergency and require urgent treatment with poor prognosis and high perioperative risk.[26–31] Moreover, despite the continuous therapeutic improvements of the last decades, such as the possibility to dilate a FO directly in utero, the survival rate of the patients with severe RFO associated with HLHS after the BAS procedure rages between 33% and 48%, compared with 74% in patients affected only by HLHS.[32–34]

In this scenario, the acknowledgment of this condition in case of HLHS is decisive for both an accurate counseling and the planning of a proper timing of delivery in a multidisciplinary setting including also interventional cardiology and cardiovascular surgery specialists.

Similarly, prenatal finding of RFO in fetuses affected by dTGA is associated with a poorer prognosis and a higher risk of perinatal mortality due to the inadequate intracardiac mixing and the need for urgent BAS.[9,19,35–37]

As a predictor of urgent septostomy at birth, the FO, as well as for its anatomy, can provide crucial insights when studied by functional assessment with fetal M-mode echocardiography. By setting M-mode pointer perpendicularly to the atria, the FO flap tracing index can be derived. This formula is obtained from the ratio of the two atria transverse section measurements in diastole and the maximum valve excursion of the FO. FO index, when multiplied by the FO diameter, especially in fetuses with dTGA, can predict with 100% specificity and PPV the risk of urgent BAS at birth.[21,22]

Premature RFO or cFO in otherwise a structurally normal heart, if found later in gestation, is generally associated with an overall good outcome but there was an association between RFO/cFO and neonatal mortality and morbidity, which is worthy of further discussion.[20] Unfortunately, most of the studies included in our literature review did not mention prenatal diagnosis and genetic associations. Our study has several strengths: this is the first review that includes all retrospective and prospective studies published to date on the topic. The main limitation of the study is the small number of studies present in the literature - and therefore included in our review - with a great number of case report or case series with <3 cases concerning this topic. Another limitation is due to the heterogeneity of the studies given by the coexistence of RFO and other pathologies such as the HLHS and dTGA.

5 | CONCLUSIONS

While fetuses affected from HLHS and dTGA with RFO have a poor prognosis, premature RFO or cFO in an otherwise structurally normal heart if found in later gestation have an overall good outcome. The mentioned ultrasound findings could be usefully implemented in prenatal diagnosis and routine clinical care to identify fetuses affected by CHD at high risk of urgent postnatal BAS. Finally, clinicians should be aware and schedule the best multi specialized care in order to assess the optimal medical or surgery treatment for these patients.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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