Sun et al. Journal of Congenital Cardiology (2021) 5:4
https://doi.org/10.1186/s40949-021-00059-x

Journal of Congenital Cardiology

REVIEW Open Access

Update on fetal cardiovascular magnetic resonance and utility in congenital heart disease

Liqun Sun[1†], Fu-Tsuen Lee[1,2†], Joshua F. P. van Amerom[1], Lindsay Freud[1], Edgar Jaeggi[1], Christopher K. Macgowan[3] and Mike Seed[1,4*]

Abstract

Background: Congenital heart disease (CHD) is the most common birth defect, affecting approximately eight per thousand newborns. Between one and two neonates per thousand have congenital cardiac lesions that require immediate post-natal treatment to stabilize the circulation, and the management of these patients in particular has been greatly enhanced by prenatal detection. The antenatal diagnosis of CHD has been made possible through the development of fetal echocardiography, which provides excellent visualization of cardiac anatomy and physiology and is widely available. However, late gestational fetal echocardiographic imaging can be hampered by suboptimal sonographic windows, particularly in the setting of oligohydramnios or adverse maternal body habitus.

Main body: Recent advances in fetal cardiovascular magnetic resonance (CMR) technology now provide a feasible alternative that could be helpful when echocardiography is inconclusive or limited. Fetal CMR has also been used to study fetal circulatory physiology in human fetuses with CHD, providing new insights into how these common anatomical abnormalities impact the distribution of blood flow and oxygen across the fetal circulation. In combination with conventional fetal and neonatal magnetic resonance imaging (MRI) techniques, fetal CMR can be used to explore the relationship between abnormal cardiovascular physiology and fetal development. Similarly, fetal CMR has been successfully applied in large animal models of the human fetal circulation, aiding in the evaluation of experimental interventions aimed at improving in utero development. With the advent of accelerated image acquisition techniques, post-processing approaches to correcting motion artifacts and commercial MRI compatible cardiotocography units for acquiring gated fetal cardiac imaging, an increasing number of CMR methods including angiography, ventricular volumetry, and the quantification of vessel blood flow and oxygen content are now possible.

Conclusion: Fetal CMR has reached an exciting stage whereby it may now be used to enhance the assessment of cardiac morphology and fetal hemodynamics in the setting of prenatal CHD.

Keywords: Fetal cardiac magnetic resonance, Morphology, Circulation, Oxygen transport, Congenital heart disease

* Correspondence: mike.seed@sickkids.ca
†Liqun Sun and Fu-Tsuen Lee contributed equally to this work.
[1]Division of Cardiology, Department of Paediatrics, Hospital for Sick Children, University of Toronto, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada
[4]Department of Diagnostic Imaging, Hospital for Sick Children, University of Toronto, Toronto, Canada
Full list of author information is available at the end of the article

Background

Since its early development in the 1980s, fetal echocardiography has been widely adopted as a screening technique for the prenatal diagnosis of congenital heart disease (CHD). The benefits of prenatal detection include the prevention of morbidity associated with neonatal hemodynamic instability, as well as providing families with a choice about whether to continue with a pregnancy in which the fetus is affected by a severe congenital heart malformation [1–3]. In a small minority of patients with the most severe forms of CHD, prenatal diagnosis may lead to families being offered fetal interventions aimed at improving the outcome of the malformation [4–6]. Ultrasound generally allows for excellent visualization of cardiac morphology and function, while Doppler can be used to characterize fetal cardiovascular physiology. The widespread availability of ultrasound in maternal fetal medicine clinics and the familiarity of fetal ultrasound techniques amongst perinatologists make it an ideal modality for detecting CHD [7]. However, in late gestation, fetal echocardiography can be hampered by technical limitations resulting from maternal obesity, oligohydramnios, adverse fetal position, multiple gestations and acoustic shadowing by the bony thorax, and this has led to interest in the development of fetal cardiovascular magnetic resonance (CMR) [8]. Of note, the image quality of fetal CMR actually improves in late gestation, especially when oligohydramnios or engagement of the fetus in the pelvis limits fetal body movement, thus limiting motion artifacts. Fetal CMR may therefore have a role as an adjunct to ultrasound when technical factors limit the diagnostic utility of fetal echocardiography [9, 10]. One of the strengths of magnetic resonance imaging (MRI) lies in its versatility in creating contrast between different tissues [11]. This has been exploited to reveal myocardial injury in a fetal sheep model [12]. Although concerns have been raised about the safety of MRI during embryogenesis and gadolinium-based contrast agents are contraindicated in pregnancy due to an increase in the risk of inflammatory conditions in children exposed to these agents in utero, fetal MRI is well tolerated and provided the equipment is used correctly, safe for mother and fetus [13]. To overcome the challenges imposed by maternal breathing and fetal body movements while attempting to image small cardiac structures beating at heart rates that are typically in the 130–150 beats per minute range, a number of modifications have been made to conventional post-natal CMR methods [14]. With the advent of accelerated imaging techniques, motion correction algorithms and a range of techniques for synchronization of image acquisition to the cardiac cycle, it is now possible to capture the anatomy and function of the fetal heart and measure blood flow and oxygen content within fetal vessels. This review aims to provide an update on the latest techniques available for imaging the fetal heart using MRI, emphasizing the unique information fetal CMR provides about fetal hemodynamics. In particular, we will focus on the potential clinical utility of fetal CMR in the setting of CHD.

Techniques and utility in fetal CMR

Fetal cardiovascular morphology and function

The most commonly used static CMR method for imaging fetal cardiac anatomy are balanced steady-state free precession “bright blood” sequences (bSSFP), which are referred to as TrueFISP, bFFE, FIESTA in vendor specific terminology. A single-shot fast spin echo “black blood” with half fourier transformation sequence is also useful for imaging mediastinal vascular anatomy and the airways and lungs (commercial names: HASTE, TSE, SSFSE). These sequences are well suited to fetal MRI because they offer relatively high spatial resolution with short acquisition times. However, they are subject to artifacts arising from cardiac motion, and provide no information about cardiac function [14]. In conventional postnatal CMR, high resolution cine imaging of the beating heart is achieved by triggering the image acquisition to the different phases of the cardiac cycle using the electrocardiographic (ECG) signal [15]. However, the fetal ECG is difficult to detect, particularly in the MRI environment. Non-invasive approaches to acquiring triggered cardiac imaging in the fetus include metric optimized gating (MOG), strategies based on “self-gating”, and Doppler Ultrasound gating (DUS) [16–22]. When gating is applied to cine bSSFP imaging, it is possible to obtain stacks of dynamic images of the heart that capture the details of cardiac structures and provide an assessment of ventricular contraction. However, each slice of gated bSSFP cine imaging requires several seconds of scan time, and this approach is therefore susceptible to artifacts arising from fetal body motion and maternal breathing movements. To overcome these artifacts, the acquisition can be accelerated using a combination of undersampling approaches such as golden angle radial trajectory k-space filling with an advanced reconstruction algorithm that employs compressed sensing. When combined with strategies for excluding data acquired during gross fetal movements and correcting for minor fetal and maternal respiratory movement using registration techniques, these accelerated imaging approaches result in consistently high quality cine imaging [14, 23–25]. An alternative approach to acquiring triggered fetal cine imaging that is feasible in animal models is to utilize an arterial blood pressure waveform obtained from a catheter placed in the carotid or femoral artery and connected to a blood pressure transducer. In combination with procedural anesthesia, this approach has

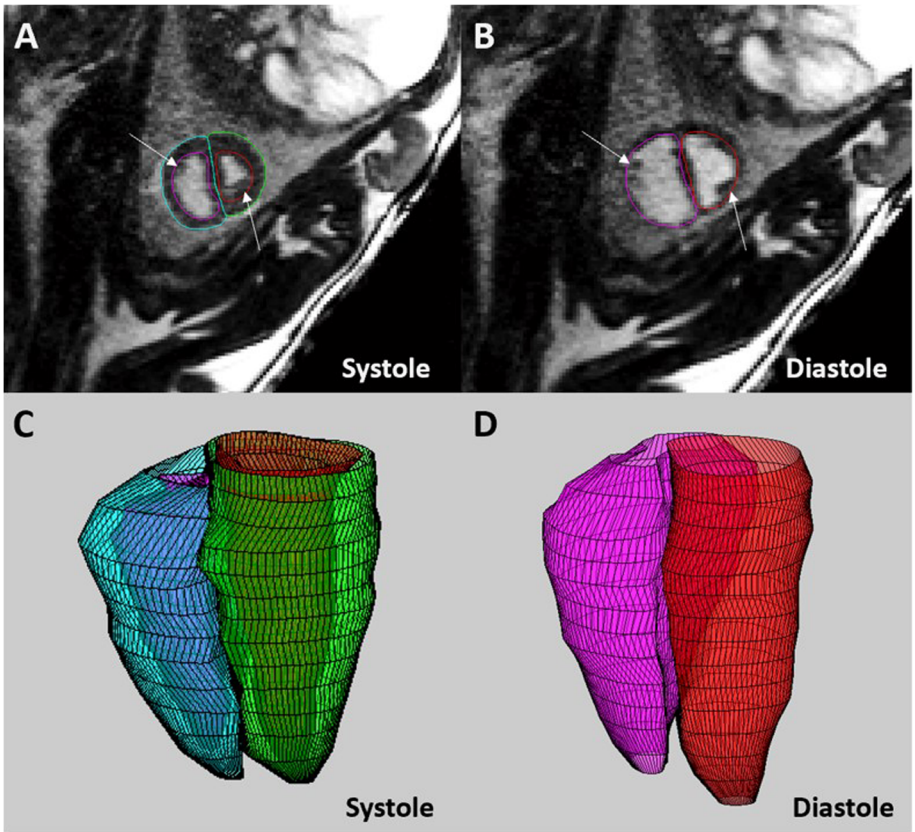

Fig. 1 Ventricular volumetry by post-processing a short-axis cine fetal CMR in fetal sheep. The top picture represents contoured 2-D cine images of the fetal heart and reconstructed into ventricular volumes (bottom picture). Re-produced from Cho et al. (58) with permission from Wiley

yielded novel measurements of right and left systolic and diastolic ventricular volumes and ejection fractions in fetal sheep (Fig. 1) [26].

Fetal circulation

Fetal blood flow

The current gold standard approach to the non-invasive measurement of vessel blood flow in children and adults is by velocity-encoded cine phase-contrast (PC) CMR [27, 28]. Using similar cardiac gating approaches to those described above for myocardial cine imaging, cine PC CMR can be applied to the quantification of flow in fetal vessels, allowing for the measurement of the right and left ventricular output, and pulmonary and umbilical blood flow [16, 29–31]. Quantification of superior vena caval flow provides an approximation of cerebral blood flow [32], while calculations based on the conservation of flow can be used to estimate the shunt across the foramen ovale. Using multiplanar PC CMR, it is also possible to interrogate intracardiac flow dynamics. Thus, fetal MRI can be used to quantify the distribution of the fetal circulation and evaluate the impact of congenital cardiac malformations on fetal organ perfusion [33]. In animal models in which the imaging conditions can be further optimized through invasive gating and procedural sedation, complex flow dynamics such as the streaming of the umbilical venous return across the foramen ovale and the spiral trajectory of ductus venosus flow can be characterized by so-called four-dimensional cine PC CMR [34, 35].

Fetal blood oxygen content

One of the unique properties of the MRI signal is its sensitivity to changes in oxygen saturation and hemoglobin concentration. This can be exploited using quantitative relaxometry techniques known as T1 and T2 mapping to quantify the oxygen content of blood in fetal vessels, providing a completely novel approach to the assessment of fetal hemodynamics. Using modified versions of sequences developed for measuring T1 and T2 in the myocardium it has been shown that the paramagnetic effect of deoxyhemoglobin results in the time constant of the transverse relaxation of blood being proportional to its oxygen saturation, while its longitudinal recovery rate is primarily dependent on hematocrit. Interestingly, oxygen saturation also influences the relationship between T1 and hematocrit, while hematocrit affects the conversion of T2 to hematocrit. However,

using a combination of T1 and T2 measurements from an individual vessel it is possible to calculate a unique solution for both hematocrit and oxygen saturation. Notwithstanding the negligible contribution of oxygen dissolved in plasma, oxygen content can then be quantified as the product oxygen saturation and hematocrit [36–38].

Fetal oxygen transport

The combination of fetal vessel flow and oximetry data provides additional information regarding placental and fetal hemodynamics, fetal oxygen transport and fetal metabolism. Oxygen flow in a vessel is the product of oxygen content and blood flow. When this approach is applied in the umbilical vessel it can be used to quantify fetal oxygen delivery (umbilical vein oxygen content by umbilical vein flow). The combination of fetal oxygen delivery and oxygen content in the umbilical arteries (which is more easily measured in the descending aorta) yields fetal oxygen consumption, a measure of fetal metabolism, and fetal oxygen extraction, which may be increased in low output states [10, 39]. Using a similar approach, oxygen delivery and consumption of individual organs can be estimated using a combination of flow and oximetry measurements in fetal vessels. For example, cerebral oxygen delivery has been measured in fetal sheep using a combination of carotid blood flow measurements and oximetry measurements made in the superior vena cava and ascending aorta [40]. The same principle has been used to study the impact of the abnormal cardiac connections and obstructed blood flow that characterize CHD on fetal streaming, and the associated effect on cerebral oxygenation [41]. Measurements of umbilical vein oxygen saturation have also revealed evidence of subtle placental dysfunction in the setting of fetal CHD [42].

Fetal CMR as a clinical diagnostic tool

Over the past two decades, a number of studies have investigated the utility of fetal CMR for the diagnosis of CHD. Static, non-gated bSSFP imaging has been used to visualize the gross morphological structures of the fetal heart and great vessels. Fetal CMR has been used to define the viscero-atrial situs, cardiac position, atrioventricular and ventriculo-arterial concordance, systemic and pulmonary venous connections, great artery relationship, arch sidedness, and heart, chamber and vessel sizes in healthy and congenitally malformed hearts [43–48]. Studies have indicated there is a high degree of concordance between fetal CMR and echocardiography [44, 49–51]. Fetal CMR has also been used in the setting of cardiac tumours [52, 53]. In one study, fetal CMR had an 88% sensitivity and 96% specificity for the detection of CHD in relation to postnatal imaging, although the authors noted that MRI provided no additional diagnostic value over ultrasound [51]. By contrast, another study found fetal CMR was useful as an adjunct for the diagnosis of CHD when later confirmed by postnatal evaluation. In this cohort, 15% of cases were correctly diagnosed by CMR when echocardiography was incorrect. However, 18% of cases were correctly diagnosed by echocardiography when CMR was incorrect and 3% of cases were misdiagnosed by both echocardiography and CMR [54]. In a large retrospective study comparing fetal CMR with postnatal diagnosis at a single center in patients in whom there was some limitation of the ultrasound diagnosis, fetal CMR correctly diagnosed 99.2% of cases that had normal hearts, 60.6% of cases with CHD, and 87.9% of cases with other heart diseases [55]. Most of the misdiagnoses were attributed to atrial and ventricular septal defects, coarctation of the aorta, and patent ductus arteriosus. Several studies have focused on the diagnostic value of fetal CMR in vascular anomalies, in which it was reported to demonstrate high diagnostic accuracy, provide diagnostic value, and be superior to echocardiography [56–62]. It was suggested that the transverse aortic arch view by fetal CMR is relatively easy to obtain, to reproduce, and to interpret [58]. An alternative technique to visualize the entire fetal vasculature such as non-contrast magnetic resonance angiography using time-of-flight MRI has been feasible in late human pregnancy [63].

More recently, cardiac gated dynamic cine CMR imaging has been reported to deliver improved image quality of the cardiac anatomy while also providing a functional assessment of the fetal heart [18, 20, 23, 24, 64]. When compared to grey-scale cine sweeps by echocardiography, stacks of cine bSSFP CMR were reported to have superior image quality but lacked resolution for outflow tract abnormalities, small pulmonary arteries, and valvular morphology. Difficulties in visualizing the outflow tracts and pulmonary arteries were attributed to fetal movement and could often be shown by a repeat acquisition, which resulted in a longer scan [9]. Comparisons of measurements of various cardiac structures also suggest that cine fetal CMR imaging agrees well with measurements made using conventional echocardiography [19, 65, 66]. In one case report of an unbalanced atrioventricular septal defect, fetal CMR reliably detected significant aortic arch hypoplasia and excluded an interventricular communication, resulting in a more appropriate perinatal management plan [67]. Motion correction techniques have been successfully applied to multiplanar stacks of black-blood imaging to achieve very high resolution three-dimensional datasets, which have been used to generate exquisite volume rendered reconstructions of congenital cardiac abnormalities involving the great vessels and systemic and pulmonary

veins. The motion corrected approach to reconstruction has been reported to improve fetal CMR visualization of the mediastinal vessels from 53 to 97%, with diagnostic imaging achieved in 90% of cases and good agreement with echocardiographic findings [25]. In one case, this approach to fetal CMR was used to successfully diagnose a double aortic arch with atresia of the aortic isthmus of the smaller arch [61].

The supplemental file 1. shows an example of how fetal CMR was helpful in the management of a fetus presenting in late gestation with a large congenital diaphragmatic hernia. The echocardiographic windows were extremely challenging, and although there was a suspicion of CHD, no diagnosis could be made. Fetal CMR was performed at 35 weeks and provided reasonable views of the heart, confirming the presence of balanced ventricles with a large ventricular septal defect and a single outlet to an overriding aorta with no central pulmonary arteries. Postnatal echocardiography in this case confirmed the presence of tetralogy of Fallot with pulmonary atresia and major aorto-pulmonary collateral arteries. Given the complexity of the cardiac diagnosis combined with the severity of the diaphragmatic hernia, the family opted for palliative management, and the infant died soon after birth. In this example, the fetal CMR provided additional information over the echocardiogram which helped with fetal counselling and helped the family in their decision making about the postnatal management.

Assessment of the fetal circulation

Our modern understanding of fetal circulatory physiology is largely based on experiments performed in fetal sheep. Adopting techniques for catheterizing exteriorized fetal sheep developed by Barcroft and Dawes [68, 69], Rudolph et al. developed an approach to measuring the distribution of the fetal sheep circulation using radioactive microspheres injected into the different venous compartments, the concentrations of which could then be measured where they become lodged in the microcirculation of each organ supplied by the right and left heart [70]. This approach was combined with conventional blood gas samples and pressure measurements obtained from intravascular catheters to define the hemodynamics of the fetal circulation. A number of human ultrasound studies have since provided estimates of the distribution of the human fetal circulation [71–75]. However, through a combination of blood flow and oximetry measurements, fetal CMR has provided a more definitive picture of late gestational human fetal hemodynamics, confirming many similarities with the fetal sheep [29, 76]. In the human fetal circulation, just as in the sheep, the circulation operates in parallel, with shunts and the foramen ovale and the ductus arteriosus which allow blood to bypass the lungs. This is tolerated in fetal life because gas exchange occurs at the placenta. Thus, the highest oxygen saturations in the fetal circulation are found in the umbilical vein (85%). As a result of streaming of the umbilical venous return via the ductus venosus and foramen ovale, the oxygen saturation in the left heart and aorta is higher (68%) than in the right heart and main pulmonary artery (49%). The oxygen saturation in the descending aorta lies between these values (57%), being derived from both right and left ventricles, giving an arteriovenous difference across the fetal side of the placenta of 28%. The combined ventricular output (CVO) in the late gestation human is 465 ml/min/kg, which is comprised of contributions of 57% from the right ventricle and 43% from the left ventricle. Pulmonary blood flow is higher in the human than the sheep, accounting for 16% of the CVO, while umbilical flow is 29% and foramen ovale shunt is 27%. Despite the lower umbilical flow (135 ml/min/kg) present in the human fetal circulation, fetal oxygen delivery (25 ml/min/kg) and consumption (6.8 ml/min/kg) are very similar to sheep, due to the higher hematocrit present in the human (15.5 g/dL) [40]. The unique streaming mechanism responsible for relatively well-oxygenated blood reaching the left heart and being supplied to the metabolically active heart and brain, while more deoxygenated blood is delivered to the lungs and placenta via the right heart, ductus arteriosus can clearly be visualized in fetal sheep using a “four dimensional” cine phase contrast CMR acquisition, often referred to as 4D flow (Fig. 2) [34]. This approach has also revealed a spiral trajectory of blood flow through the ductus venosus, which may account for the lack of mixing between the two streams as they flow towards the right atrium in the inferior vena cava (Fig. 3) [35]. With the advent of increasingly sophisticated approaches to image acquisition and processing, approaches similar to 4D flow are now being used to interrogate complex flow dynamics in human fetuses [77, 78].

The application of cine PC CMR and MR oximetry in fetuses with CHD has provided an opportunity to confirm many of the observations made about the impact of the abnormal cardiac anatomy on fetal cardiovascular physiology. For example, in the setting of obstruction of blood flow across one side of the heart, the output of the contralateral ventricle increases. However, in the setting of single ventricle physiology, the increase does not entirely compensate, resulting in a reduction in combined ventricular output [79]. This is most profound in the setting of severe atrioventricular valve regurgitation such as in fetuses with severe forms of Ebstein’s anomaly, in which reductions are seen in pulmonary, cerebral and umbilical perfusion [80]. In other forms of CHD, cerebral blood flow appears to be preserved, or even

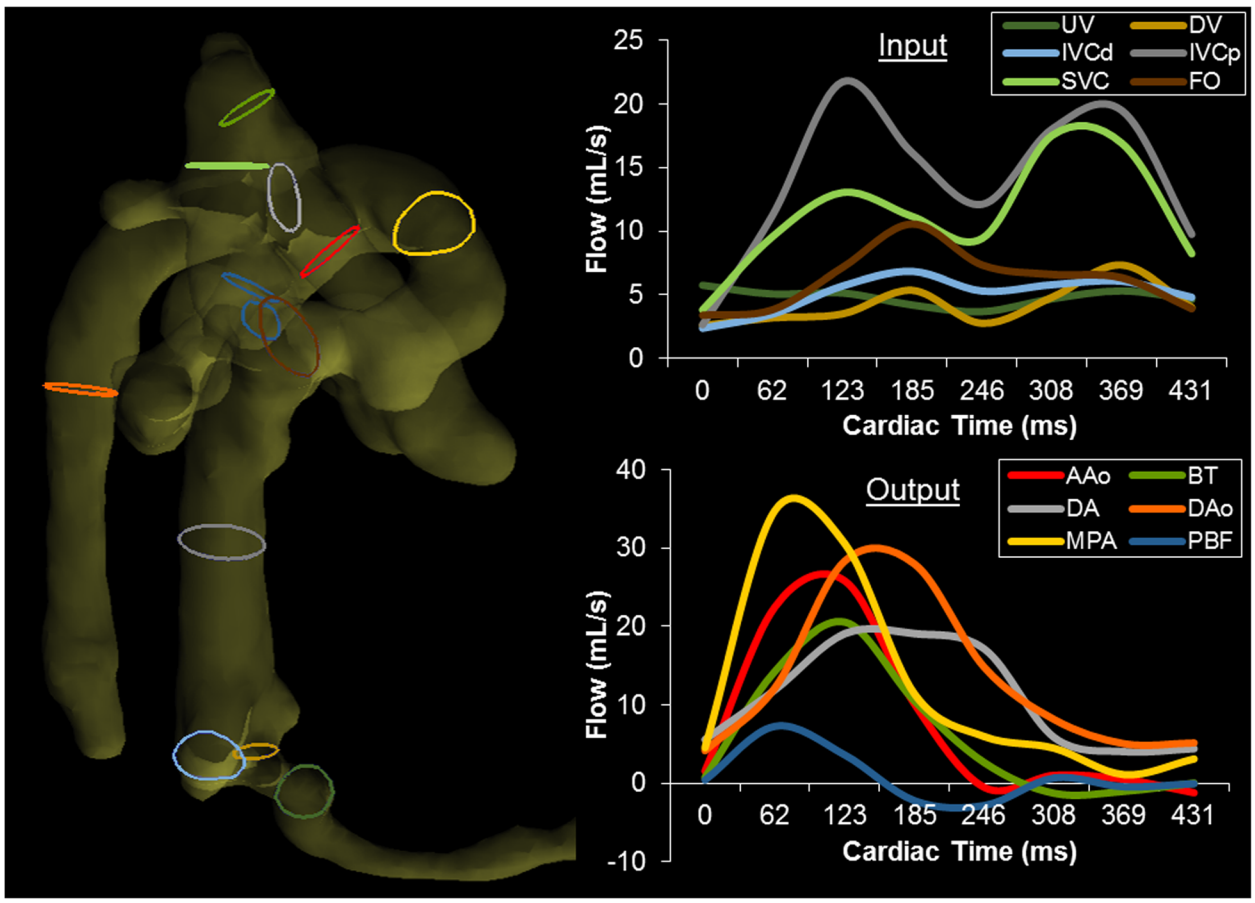

Fig. 2 Blood flow through a 3-D reconstructed cardiovascular system using 4-D flow CMR in fetal sheep. The left picture represents the 3-D reconstruction of the major fetal vessels and cardiac shunts with rings representing where blood flow was assessed. The top left graph represents the blood flow of inflow vessels and cardiac shunts of the heart. The bottom left graph represents the blood flow of outflow vessels and cardiac shunts of the heart. UV, umbilical vessel; DV, ductus venosus; IVCd/p, distal/proximal inferior vena cava; SVC, superior vena cava; FO, foramen ovale; AAo, ascending aorta; BT brachiocephalic trunk; DA, ductus arteriosus; DAo, descending aorta; MPA, main pulmonary artery; PBF, pulmonary blood flow. Re-produced from Schrauben et al. (27) used under CC BY 4.0

increased in the setting of transposition of the great arteries [81]. However, in severe forms of left heart obstruction, perfusion of head and neck vessels is achieved via retrograde arch flow via the ductus arteriosus [79]. The interruption of the normal streaming mechanism in all major forms of CHD results in more desaturated blood reaching the cerebral and coronary circulations, which may account for the impaired brain growth and development that is typical of newborns with CHD [41]. In fetuses with CHD associated with left atrial hypertension, such as hypoplastic left heart syndrome with an intact or highly restrictive atrial septum, pulmonary blood flow is impaired [79]. Similarly, pulmonary blood flow is reduced in fetuses in which the pulmonary circulation is supplied retrograde via the ductus arteriosus including those with pulmonary atresia and severe forms of Ebstein's anomaly [80]. Umbilical blood flow is reduced in the setting of fetal CHD that is associated with lower cardiac output, and this further impacts fetal oxygen delivery [41]. The presence of CHD also appears to be associated with subtle decrements in placental function which result in reduced umbilical venous oxygen saturations [42]. Thus, the fetus with CHD is subject to a suboptimal fetal environment, while individual organs may be underperfused and hypoxemic as a result of the heart disease, potentially leading to issues with fetal development included brain dysmaturation and pulmonary vascular disease.

Development and monitoring of fetal interventions

The demonstration of reduced fetal oxygen delivery and cerebral hypoxemia in fetuses with CHD has led to interest in the potential of maternal hyperoxygenation as a neuroprotective strategy in fetuses with CHD [41]. It has long been known that increasing maternal fraction of inspired oxygen (FiO_2) results in an increase in fetal

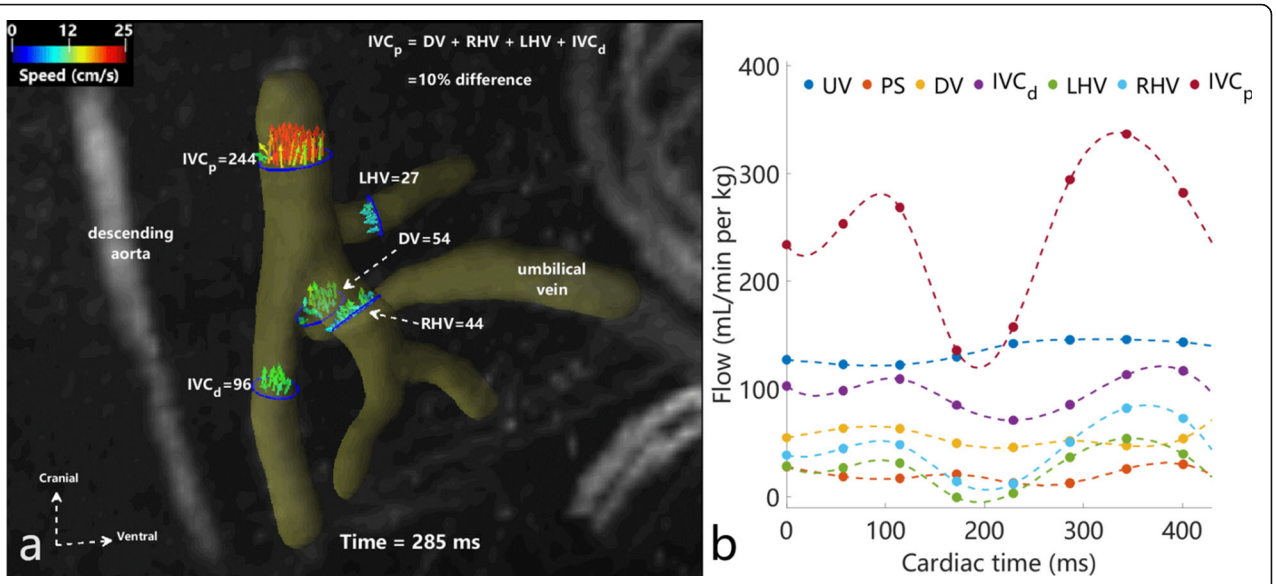

Fig. 3 Blood flow through a 3-D reconstructed ductus venosus – inferior vena cava junction using 4-D flow CMR in fetal sheep. The left picture represents the 3-D reconstruction major hepatic veins and inferior vena cava with rings representing where blood flow was assessed. The right graph represents the blood flow across each vessel interrogated. UV, umbilical vein; PS, portal sinus; DV, ductus venosus; L/RHV, left/right hepatic vein; IVCd/p. distal/proximal inferior vena cava. Re-produced from Schrauben et al. (61) with permission from Wiley

PaO_2 and SaO_2, and several randomized controlled trials performed in the 1990s suggested that chronic maternal hyperoxygenation was associated with improved outcomes in growth restricted fetuses [82]. Acute maternal hyperoxygenation results in an increase in umbilical vein oxygen saturation in fetuses with normal hearts, and in those with CHD [42]. In pregnant sheep ventilated with an FiO_2 of 1.0, we observed no change in uterine or cerebral blood flow and 20% increase in cerebral oxygen delivery (unpublished data). We are currently conducting a pilot safety and feasibility study of chronic maternal hyperoxygenation in fetuses with single ventricle CHD (NCT03136835). The pulmonary vasodilator effect of maternal hyperoxygenation has also resulted in interest in intermittent doses as an approach to increasing venous return to the underdeveloped left ventricle [83–85]. In one case of borderline left ventricular hypoplasia, the impact of acute maternal hyperoxygenation was assessed by PC-CMR, revealing no increase in ascending aortic flow despite a doubling of pulmonary blood flow, which may explain why the response to chronic maternal hyperoxygenation is inconsistent and likely related to the degree of anatomical restriction imposed by morphologic abnormalities versus underfilled left heart structures [86]. In cases of Ebstein Anomaly with circular shunting, fetal CMR revealed an improvement in systemic and cerebral blood flow following constriction of ductus arteriosus flow induced by transplacental treatment with non-steroidal anti-inflammatory drugs (NSAID) [80]. In this case series, severely diminished cardiac output and cerebral oxygen delivery and consumption identified by CMR contributed to decision making about the timing of delivery, highlighting the potential clinical value of fetal CMR in cases of severe hemodynamic compromise.

An example of how fetal CMR can be used to aid decision-making around fetal cardiac intervention, and monitor the impact of an in utero procedure is provided in the case illustrated in Table 1 and Fig. 4. The

Table 1 Fetal PC-CMR blood flow assessment demonstrating the hemodynamic changes in TGA with IVS and RAS before and after fetal balloon atrial septostomy. *TGA* transposition of the great arteries, *IVS* intact ventricular septum, *RAS* restricted atrial septum, *MPA* main pulmonary artery, *AAo* ascending aorta, *SVC* superior vena cava, *DAo* descending aorta, *UV* umbilical vein, *DA* ductus arteriosus, *PBF* pulmonary blood flow, *CVO* combined ventricular output, *FO* foramen ovale

	TGA IVS RAS			
	Flow (ml/kg/min)		Oxygen Saturation	
	Before	After	Before	After
MPA	129	128	68	72
AAO	266	210	77	71
SVC	76	129	65	60
DAO	207	216	73	74
UV	119	111	88	86
DA	11	41		
PBF	68	50		
CVO	407	407		
FO	17	135		

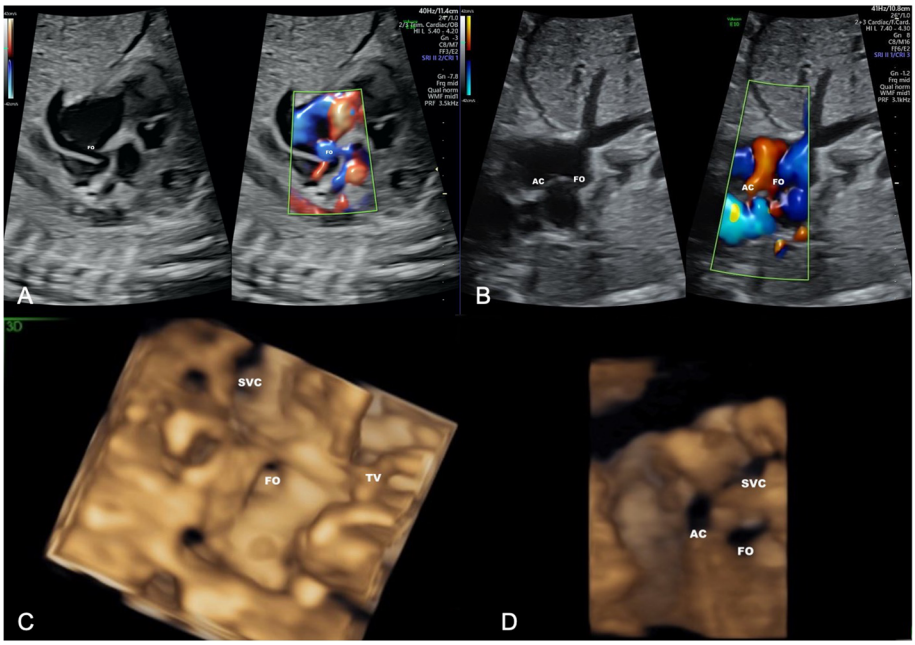

Fig. 4 Echocardiography of the fetal heart in TGA IVS and RAS before and after fetal balloon atrial septostomy (BAS). Panel A and C represents limited blood flow across the small FO prior to BAS. Panel B and D represents blood flow across the restrictive FO and additional superior atrial communication (AC) after BAS. Panel A and B were acquired using 2-D echocardiography and Panel C and D were acquired using 3-D echocardiography. TGA, transposition of the great arteries; IVS, intact ventricular septum; RAS, restricted atrial septum; FO, foramen ovale; SVC, superior vena cava; TV, tricuspid valve

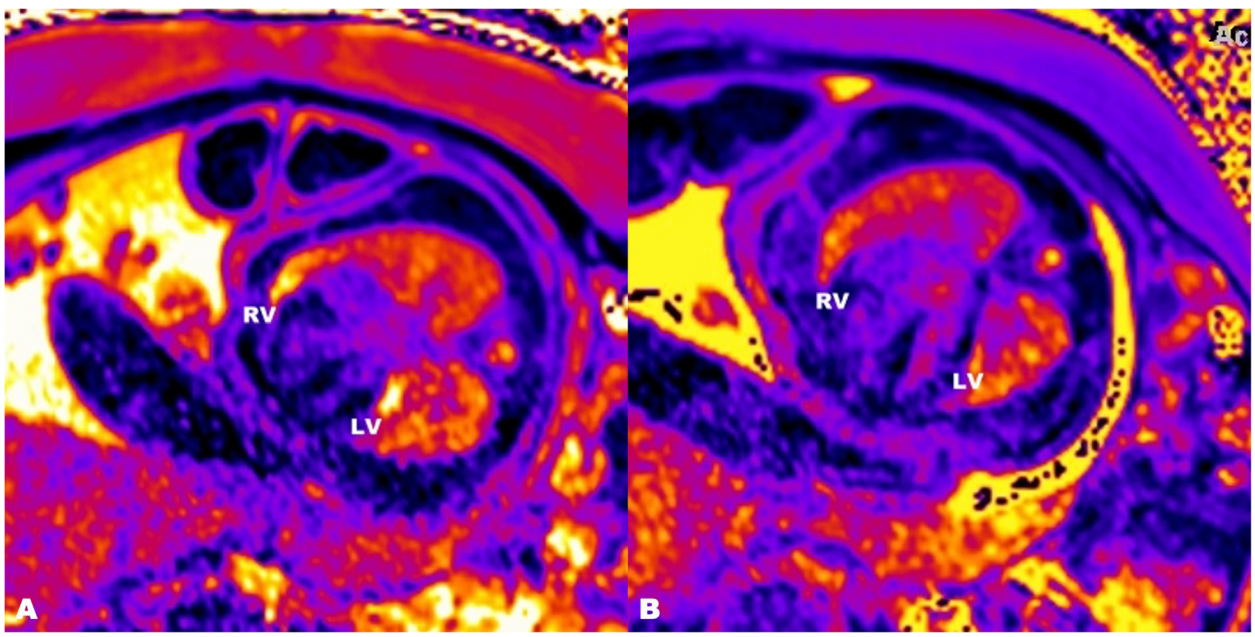

Fig. 5 Oxygen saturations of the four-chamber view in TGA with IVS and RAS before intervention (**a**) and after intervention (**b**) by fetal CMR Color T2 mapping. TGA; transposition of the great arteries; IVS, intact ventricular septum; RAS, restricted atrial septum

presence of an intact or highly restrictive atrial septum has been shown to be an important prognostic factor in fetuses with transposition of the great arteries [87]. In recognition of the potential for severe hypoxemia following birth in this setting, we have reported the use of late gestational balloon atrial septostomy to achieve a more stable transition from fetal to postnatal circulation [88]. In a second fetal case of transposition in which we suspected a restrictive atrial communication we recently performed fetal CMR. The results of the CMR revealed that unlike in most fetuses with TGA, in which streaming results in higher oxygen saturations in the left heart and main pulmonary artery than the right ventricle and aorta, in this fetus the oxygen saturations were actually slightly higher in the right ventricle than the left (Fig. 5a), while the PC CMR assessment of the distribution of blood flow indicated there was a diminutive shunt across the foramen ovale (Fig. 6). Following percutaneous in utero balloon atrial septostomy, the flow assessment indicated a significant increase in flow across the atrial septum with equalization of oxygen saturations in the right and left heart (Fig. 5b). The supplemental files 2 and 3 shows the application of PC-CMR and cine imaging to assess fetal blood flow and the four-chamber view heart structure, respectively, after intervention. The baby was born 7 days later with arterial oxygen saturations of 70% and successfully underwent repeat balloon atrial septostomy and arterial switch. Of note, the pre-procedural flow assessment was also suggestive of significant aortopulmonary collateral flow, which may account for the relative preservation of oxygen saturations in the left ventricle despite the lack of shunting at atrial level. The presence of significant aortopulmonary collaterals has previously been reported in fetuses with transposition with atrial septal restriction and could be a contributing factor to the development of pulmonary vascular disease in these patients [81, 89].

Fetal CMR has also been used to investigate the impact of potential fetal pharmacologic strategies aimed at improving fetal development in animal models. Examples include the investigation of the impact of an umbilical vein infusion of prostaglandin I_2 (PGI_2) on fetal circulatory physiology, which revealed an increase in ductus venosus shunting of substrate-rich blood from the placenta to the heart. However, the administration of PGI_2 was also associated with vasodilation of the pulmonary circulation, which decreased FO shunting, resulting in no increase in cerebral oxygen delivery [90].

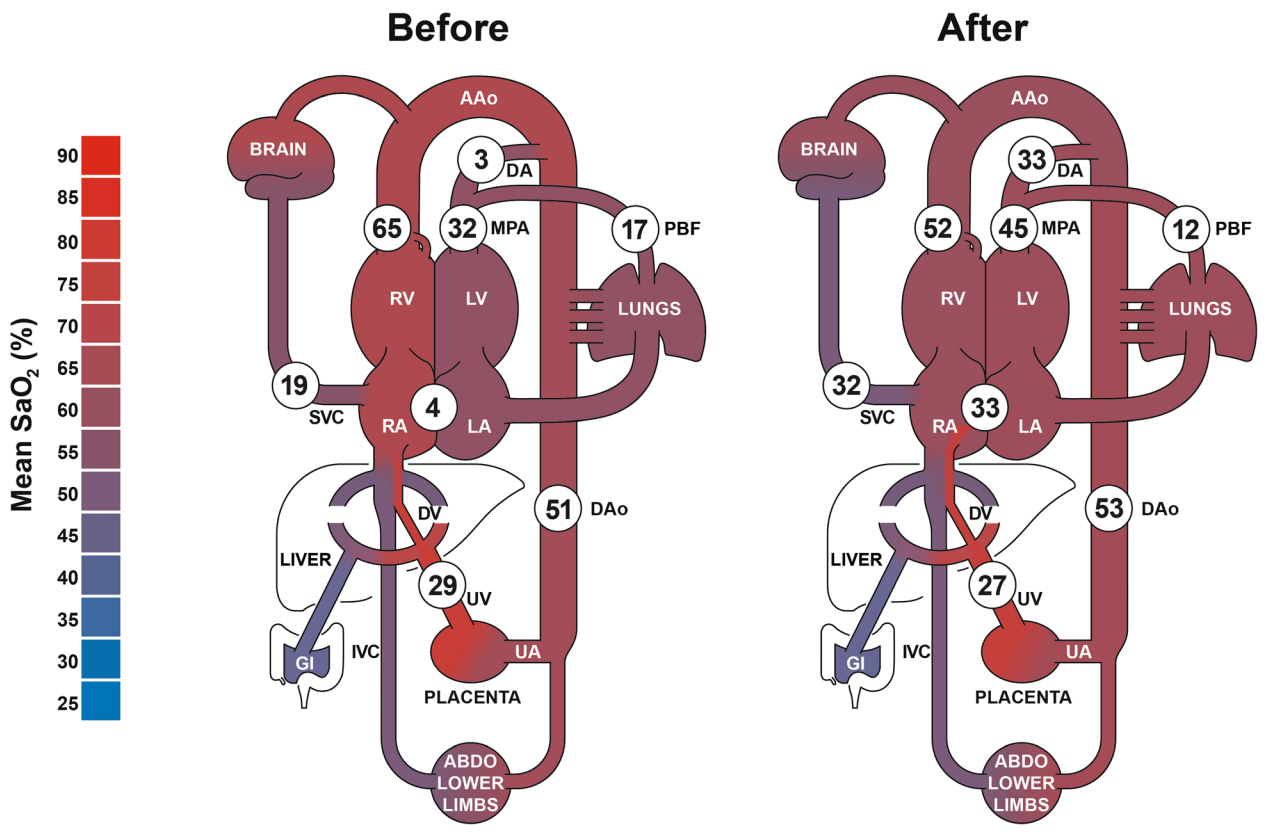

Fig. 6 Fetal blood flow distribution and oxygen content before and after fetal balloon atrial septostomy in TGA with IVS and RAS by fetal CMR. TGA; transposition of the great arteries; IVS, intact ventricular septum; RAS, restricted atrial septum

In another set of experiments, CMR was used to measure uterine blood flow in pregnant sheep exposed to resveratrol to demonstrate an increase in uterine blood flow and fetal weight (unpublished data).

Future directions and current limitations

The examples provided above give a sense of how, in a few academic centers, fetal CMR is beginning to find a role in selected fetal congenital heart disease cases. It would appear possible that just as postnatal CMR is now used by most large paediatric units caring for patients with CHD, fetal CMR may ultimately be used in specialist centers for rare cases like those described above, when echocardiography is so limited that additional diagnostic information is required in order to determine a safe perinatal management plan, or when a fetal intervention is being contemplated or followed up. It is also possible that fetal CMR will continue to be used by researchers interested in studying fetal cardiovascular physiology or developing new fetal treatments.

However, despite our enthusiasm for an increased role for fetal CMR, we recognize there remain significant limitations and barriers to wider adoption of the technique. Importantly, fetal CMR is currently only useful in the third trimester, while many of the critical management decisions about a fetus with CHD are often made during the second trimester. Even in late gestation, current fetal CMR techniques continue to be degraded by motion artifacts, and while substantial advances have been made in overcoming these artifacts, the techniques required currently involve several postprocessing steps and significant investments in terms of computer science and manual analyses steps. Indeed, any form of MRI remains relatively expensive and inaccessible in comparison to ultrasound. Further work and collaboration with the MRI vendors is needed to make these postprocessing steps more automated and less time consuming before they are feasible for most clinical settings.

Conclusion

In summary, fetal CMR represents an exciting new imaging modality for characterizing the morphology and physiology of fetal CHD. Many of the initial barriers to imaging the fetal heart and cardiovascular system have been overcome through technical innovations involving accelerated imaging strategies and approaches to motion correction. As a result, fetal CMR is providing new insights into the impact of cardiac malformations on fetal development, and may be helpful for visualizing the anatomy when conventional echocardiographic imaging is limited, and in patients requiring a sophisticated approach to perinatal management.

Abbreviations

CHD: Congenital heart disease; CMR: Cardiac magnetic resonance; MRI: Magnetic resonance imaging; bSSFP: Balanced steady-state free precession; ECG: Electrocardiographic; MOG: Metric optimized gating; DUS: Doppler Ultrasound; PC-CMR: Phase-contrast cardiac magnetic resonance; CVO: Combined ventricular output; FiO_2: Fraction of inspired oxygen; NSAID: Non-steroidal anti-inflammatory drugs; TGA: Transposition of the Great Arteries; FO: Foramen ovale; PGI_2: Prostaglandin I2

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40949-021-00059-x.

Additional file 1.
Additional file 2.
Additional file 3.

Acknowledgements

We acknowledge Luke Itani for his work on Fig. 6.

Authors' contributions

The study was conceived by LS, FTL, JvA, LF, EJ, CM and MS. LS and FTL performed the literature review and drafted the manuscript, contributed equally. JvA and CM reviewed the manuscript and added changes. LF EJ and MS reviewed and modified the manuscript. All authors contributed to writing and reviewing of the final manuscript.

Authors' information

Not applicable.

Availability of data and materials

All data generated during this study are included in this published article [Table 1].

Declarations

Ethics approval and consent to participate

TGA IVS case.
Approved by Research Ethics Board, The Hospital for Sick Children.
REB# 1000060514.
TOF PA case.
Approved by Research Ethics Board, The Hospital for Sick Children.
REB# 1000062939.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Division of Cardiology, Department of Paediatrics, Hospital for Sick Children, University of Toronto, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada. [2]Department of Physiology, Temerty Faculty of Medicine, University of Toronto, Toronto, Canada. [3]Department of Medical Biophysics, Hospital for Sick Children, University of Toronto, Toronto, Canada. [4]Department of Diagnostic Imaging, Hospital for Sick Children, University of Toronto, Toronto, Canada.

Received: 2 February 2021 Accepted: 12 March 2021
Published online: 26 March 2021

References

1. Peyvandi S, De Santiago V, Chakkarapani E, Chau V, Campbell A, Poskitt KJ, et al. Association of Prenatal Diagnosis of critical congenital heart disease with postnatal brain development and the risk of brain injury. JAMA Pediatr. 2016;170(4):e154450. https://doi.org/10.1001/jamapediatrics.2015.4450.
2. Holland BJ, Myers JA, Woods CR. Prenatal diagnosis of critical congenital heart disease reduces risk of death from cardiovascular compromise prior to

planned neonatal cardiac surgery: a meta-analysis. Ultrasound Obstet Gynecol. 2015;45(6):631–8. https://doi.org/10.1002/uog.14882.
3. Kovacevic A, Simmelbauer A, Starystach S, Elsässer M, Müller A, Bär S, et al. Counseling for prenatal congenital heart disease—recommendations based on empirical assessment of Counseling success. Front Pediatr. 2020;8:26.
4. McElhinney DB, Tworetzky W, Lock JE. Current status of Fetal Cardiac intervention. Circulation. 2010;121(10):1256–63. https://doi.org/10.1161/CIRCULATIONAHA.109.870246.
5. Marshall AC, van der Velde ME, Tworetzky W, Gomez CA, Wilkins-Haug L, Benson CB, et al. Creation of an atrial septal defect in utero for fetuses with hypoplastic left heart syndrome and intact or highly restrictive atrial septum. Circulation. 2004;110(3):253–8. https://doi.org/10.1161/01.CIR.0000135471.17922.17.
6. Freud LR, Mcelhinney DB, Marshall AC, Marx GR, Friedman KG, Nido PJ, et al. Syndrome : postnatal outcomes of the first 100 patients. Circulation. 2015;130(8):638–45.
7. Donofrio MT, Moon-Grady AJ, Hornberger LK, Copel JA, Sklansky MS, Abuhamad A, et al. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the american heart association. Circulation. 2014;129(21):2183–242. https://doi.org/10.1161/01.cir.0000437597.44550.5d.
8. Gholipour A, Estroff JA, Barnewolt CE, Robertson RL, Grant PE, Gagoski B, et al. Fetal MRI: a technical update with educational aspirations. Concepts Magn Reson Part A Bridg Educ Res. 2014;43(6):237–66. https://doi.org/10.1002/cmr.a.21321.
9. Roy CW, Marini D, Lloyd DFA, Mawad W, Yoo SJ, Schrauben EM, et al. Preliminary experience using motion compensated CINE magnetic resonance imaging to visualise Fetal congenital heart disease. Circ Cardiovasc Imaging. 2018;11(12):e007745. https://doi.org/10.1161/CIRCIMAGING.118.007745.
10. Marini D, van Amerom J, Saini BS, Sun L, Seed M. MR imaging of the fetal heart. J Magn Reson Imaging. 2020;51(4):1030–44. https://doi.org/10.1002/jmri.26815.
11. Saleem SN. Fetal MRI: An approach to practice: a review. J Adv Res. 2014;5(5):507–23.
12. Duan AQ, Lock MC, Perumal SR, Darby JR, Soo JY, Selvanayagam JB, et al. Feasibility of detecting myocardial infarction in the sheep fetus using late gadolinium enhancement CMR imaging. J Cardiovasc Magn Reson. 2017;19(1):1–11.
13. Patenaude Y, Pugash D, Lim K, Morin L, Bly S, Butt K, et al. The use of magnetic resonance imaging in the obstetric patient. J Obstet Gynaecol Canada. 2014;36(4):349–55.
14. Roy CW, van Amerom JFP, Marini D, Seed M, Macgowan CK. Fetal Cardiac MRI: A review of technical advancements. Top Magn Reson Imaging. 2019;28(5):235–44. https://doi.org/10.1097/RMR.0000000000000218.
15. Nacif MS, Zavodni A, Kawel N, Choi EY, Lima JAC, Bluemke DA. Cardiac magnetic resonance imaging and its electrocardiographs (ECG): tips and tricks. Int J Cardiovasc Imaging. 2012;28(6):1465–75. https://doi.org/10.1007/s10554-011-9957-4.
16. Jansz MS, Seed M, van Amerom JFP, Wong D, Grosse-Wortmann L, Yoo SJ, et al. Metric optimized gating for fetal cardiac MRI. Magn Reson Med. 2010;64(5):1304–14. https://doi.org/10.1002/mrm.22542.
17. Roy CW, Seed M, van Amerom JFP, Al Nafisi B, Grosse-Wortmann L, Yoo SJ, et al. Dynamic imaging of the fetal heart using metric optimized gating. Magn Reson Med. 2013;70(6):1598–607. https://doi.org/10.1002/mrm.24614.
18. Haris K, Hedström E, Bidhult S, Testud F, Maglaveras N, Heiberg E, et al. Self-gated fetal cardiac MRI with tiny golden angle iGRASP: a feasibility study. J Magn Reson Imaging. 2017;46(1):207–17.
19. Chaptinel J, Yerly J, Mivelaz Y, Prsa M, Alamo L, Vial Y, et al. Fetal cardiac cine magnetic resonance imaging in utero. Sci Rep. 2017;7(1):15540. https://doi.org/10.1038/s41598-017-15701-1.
20. Roy CW, Seed M, Kingdom JC, Macgowan CK. Motion compensated cine CMR of the fetal heart using radial undersampling and compressed sensing. J Cardiovasc Magn Reson. 2017;19(1):29. https://doi.org/10.1186/s12968-017-0346-6.
21. Kording F, Schoennagel BP, de Sousa MT, Fehrs K, Adam G, Yamamura J, et al. Evaluation of a portable doppler ultrasound gating device for fetal cardiac MR imaging: initial results at 1.5T and 3T. Magn Reson Med Sci. 2018;17(4):308–17. https://doi.org/10.2463/mrms.mp.2017-0100.
22. Kording F, Yamamura J, De Sousa MT, Ruprecht C, Hedström E, Aletras AH, et al. Dynamic fetal cardiovascular magnetic resonance imaging using Doppler ultrasound gating. J Cardiovasc Magn Reson. 2018;20(1):17. https://doi.org/10.1186/s12968-018-0440-4.
23. van Amerom JFP, Lloyd DFA, Price AN, Kuklisova Murgasova M, Aljabar P, Malik SJ, et al. Fetal cardiac cine imaging using highly accelerated dynamic MRI with retrospective motion correction and outlier rejection. Magn Reson Med. 2018;79(1):327–38. https://doi.org/10.1002/mrm.26686.
24. Haris K, Hedström E, Kording F, Bidhult S, Steding-Ehrenborg K, Ruprecht C, et al. Free-breathing fetal cardiac MRI with doppler ultrasound gating, compressed sensing, and motion compensation. J Magn Reson Imaging. 2020;51(1):260–72. https://doi.org/10.1002/jmri.26842.
25. Lloyd DFA, Pushparajah K, Simpson JM, van Amerom JFP, van Poppel MPM, Schulz A, et al. Three-dimensional visualisation of the fetal heart using prenatal MRI with motion-corrected slice-volume registration: a prospective, single-Centre cohort study. Lancet. 2019;393(10181):1619–27. https://doi.org/10.1016/S0140-6736(18)32490-5.
26. Cho SKS, Darby JRT, Saini BS, Lock MC, Holman SL, Lim JM, et al. Feasibility of ventricular volumetry by cardiovascular MRI to assess cardiac function in the fetal sheep. J Physiol. 2020;598(13):2557–73. https://doi.org/10.1113/JP279054.
27. Fratz S, Chung T, Greil GF, Samyn MM, Taylor AM, Valsangiacomo Buechel ER, et al. Guidelines and protocols for cardiovascular magnetic resonance in children and adults with congenital heart disease: SCMR expert consensus group on congenital heart disease. J Cardiovasc Magn Reson. 2013;15(1):51. https://doi.org/10.1186/1532-429X-15-51.
28. Buechel ERV, Grosse-Wortmann L, Fratz S, Eichhorn J, Sarikouch S, Greil GF, et al. Indications for cardiovascular magnetic resonance in children with congenital and acquired heart disease: an expert consensus paper of the imaging working group of the AEPC and the cardiovascular magnetic resonance section of the EACVI. Eur Heart J Cardiovasc Imaging. 2015;16(3):281–97. https://doi.org/10.1093/ehjci/jeu129.
29. Seed M, van Amerom JFP, Yoo SJ, Al Nafisi B, Grosse-Wortmann L, Jaeggi E, et al. Feasibility of quantification of the distribution of blood flow in the normal human fetal circulation using CMR: a cross-sectional study. J Cardiovasc Magn Reson. 2012;14(1):79.
30. Salehi D, Sun L, Steding-Ehrenborg K, Bidhult S, Kording F, Ruprecht C, et al. Quantification of blood flow in the fetus with cardiovascular magnetic resonance imaging using Doppler ultrasound gating: validation against metric optimized gating. J Cardiovasc Magn Reson. 2019;21(1):74. https://doi.org/10.1186/s12968-019-0586-8.
31. Bidhult S, Töger J, Heiberg E, Carlsson M, Arheden H, Aletras AH, et al. Independent validation of metric optimized gating for fetal cardiovascular phase-contrast flow imaging. Magn Reson Med. 2018;81(1):495–503. https://doi.org/10.1002/mrm.27392.
32. Fogel MA, Durning S, Wernovsky G, Pollock AN, Gaynor JW, Nicolson S. Brain versus lung: hierarchy of feedback loops in single-ventricle patients with superior cavopulmonary connection. Circulation. 2004;110(11 Suppl 1):147–52.
33. Sun L, Marini D, Saini B, Schrauben E, MacGowan CK, Seed M. Understanding Fetal Hemodynamics using cardiovascular magnetic resonance imaging. Fetal Diagn Ther. 2020;47(5):354–62. https://doi.org/10.1159/000505091.
34. Schrauben EM, Saini BS, Darby JRT, Soo JY, Lock MC, Stirrat E, et al. Fetal hemodynamics and cardiac streaming assessed by 4D flow cardiovascular magnetic resonance in fetal sheep. J Cardiovasc Magn Reson. 2019;21(1):8. https://doi.org/10.1186/s12968-018-0512-5.
35. Schrauben EM, Darby JRT, Saini BS, Holman SL, Lock MC, Perumal SR, et al. Technique for comprehensive fetal hepatic blood flow assessment in sheep using 4D flow MRI. J Physiol. 2020;598(17):3555–67. https://doi.org/10.1113/JP279631.
36. Portnoy S, Seed M, Sled JG, Macgowan CK. Non-invasive evaluation of blood oxygen saturation and hematocrit from T1 and T2 relaxation times: in-vitro validation in fetal blood. Magn Reson Med. 2017;78(6):2352–9. https://doi.org/10.1002/mrm.26599.
37. Portnoy S, Osmond M, Zhu MY, Seed M, Sled JG, Macgowan CK. Relaxation properties of human umbilical cord blood at 1.5 Tesla. Magn Reson Med. 2017;77(4):1678–90. https://doi.org/10.1002/mrm.26231.
38. Portnoy S, Milligan N, Seed M, Sled JG, Macgowan CK. Human umbilical cord blood relaxation times and susceptibility at 3 T. Magn Reson Med. 2018;79(6):3194–206. https://doi.org/10.1002/mrm.26978.
39. Sun L, Macgowan CK, Portnoy S, Sled JG, Yoo SJ, Grosse-Wortmann L, et al. New advances in fetal cardiovascular magnetic resonance imaging for quantifying the distribution of blood flow and oxygen transport: potential applications in fetal cardiovascular disease diagnosis and therapy.

Echocardiography. 2017;34(12):1799–803. https://doi.org/10.1111/echo.13760.
40. Saini BS, Darby JRT, Portnoy S, Sun L, van Amerom J, Lock MC, et al. Normal human and sheep fetal vessel oxygen saturations by T2 magnetic resonance imaging. J Physiol. 2020;598(15):3259–81. https://doi.org/10.1113/JP279725.
41. Sun L, Macgowan CK, Sled JG, Yoo SJ, Manlhiot C, Porayette P, et al. Reduced fetal cerebral oxygen consumption is associated with smaller brain size in fetuses with congenital heart disease. Circulation. 2015;131(15):1313–23. https://doi.org/10.1161/CIRCULATIONAHA.114.013051.
42. Porayette P, Madathil S, Sun L, Jaeggi E, Grosse-Wortmann L, Yoo S-J, et al. CKM and MS. MRI reveals hemodynamic changes with acute maternal hyperoxygenation in human fetuses with and without congenital heart disease. Prenat Diag. 2016;36(3):274–81.
43. Manganaro L, Savelli S, Di Maurizio M, Perrone A, Tesei J, Francioso A, et al. Potential role of fetal cardiac evaluation with magnetic resonance imaging: preliminary experience. Prenat Diagn. 2008;28(2):148–56. https://doi.org/10.1002/pd.1945.
44. Saleem SN. Feasibility of MRI of the fetal heart with balanced steady-state free precession sequence along fetal body and cardiac planes. Am J Roentgenol. 2008;191(4):1208–15. https://doi.org/10.2214/AJR.07.3839.
45. Wielandner A, Mlczoch E, Prayer D, Berger-Kulemann V. Potential of magnetic resonance for imaging the fetal heart. Semin Fetal Neonatal Med. 2013;18(5):286–97. https://doi.org/10.1016/j.siny.2013.05.006.
46. Manganaro L, Vinci V, Bernardo S, Sollazzo P, Sergi ME, Saldari M, et al. Magnetic resonance imaging of fetal heart: anatomical and pathological findings. J Matern Neonatal Med. 2014;27(12):1213–9. https://doi.org/10.3109/14767058.2013.852174.
47. Dong SZ, Zhu M. Pattern-based approach to fetal congenital cardiovascular anomalies using the transverse aortic arch view on prenatal cardiac MRI. Pediatr Radiol. 2015;45(5):743–50. https://doi.org/10.1007/s00247-014-3131-9.
48. Dong SZ, Zhu M. MR imaging of fetal cardiac malposition and congenital cardiovascular anomalies on the four-chamber view. SpringerPlus. 2016;5(1):1214.
49. Gorincour G, Bourlière-Najean B, Bonello B, Fraisse A, Philip N, Potier A, et al. Feasibility of fetal cardiac magnetic resonance imaging: preliminary experience. Ultrasound Obstet Gynecol. 2007;29(1):105–8. https://doi.org/10.1002/uog.3924.
50. Manganaro L, Savelli S, Di Maurizio M, Perrone A, Francioso A, La Barbera L, et al. Assessment of congenital heart disease (CHD): is there a role for fetal magnetic resonance imaging (MRI)? Eur J Radiol. 2009;72(1):172–80. https://doi.org/10.1016/j.ejrad.2008.06.016.
51. Votino C, Jani J, Damry N, Dessy H, Kang X, Cos T, et al. Magnetic resonance imaging in the normal fetal heart and in congenital heart disease. Ultrasound Obstet Gynecol. 2012;39(3):322–9. https://doi.org/10.1002/uog.10061.
52. Zhou Y, Dong S, Zhong Y, Sun A. Prenatal and Postnatal Diagnosis of Rhabdomyomas and Tuberous Sclerosis Complex by Ultrafast and Standard MRI. Indian J Pediatr. 2018;85(9):729–37.
53. Jana M, Gupta AK. Expanding applications of prenatal MR imaging: detection of complex multisystem anomalies made easy. Indian J Pediatr. 2018;85(9):716–7. https://doi.org/10.1007/s12098-018-2726-9.
54. Dong SZ, Zhu M, Li F. Preliminary experience with cardiovascular magnetic resonance in evaluation of fetal cardiovascular anomalies. J Cardiovasc Magn Reson. 2013;15(1):40. https://doi.org/10.1186/1532-429X-15-40.
55. Dong SZ, Zhu M, Ji H, Ren JY, Liu K. Fetal cardiac MRI: a single center experience over 14-years on the potential utility as an adjunct to fetal technically inadequate echocardiography. Sci Rep. 2020;10(1):12373. https://doi.org/10.1038/s41598-020-69375-3.
56. Lloyd DFA, van Amerom JFP, Pushparajah K, Simpson JM, Zidere V, Miller O, et al. An exploration of the potential utility of fetal cardiovascular MRI as an adjunct to fetal echocardiography. Prenat Diagn. 2016;36(10):916–25. https://doi.org/10.1002/pd.4912.
57. Li X, Li X, Hu K, Yin C. The value of cardiovascular magnetic resonance in the diagnosis of fetal aortic arch anomalies. J Matern Neonatal Med. 2017;30(11):1366–71. https://doi.org/10.1080/14767058.2016.1214126.
58. Dong SZ, Zhu M. Magnetic resonance imaging of fetal persistent left superior vena cava. Sci Rep. 2017;7(1):4176. https://doi.org/10.1038/s41598-017-04591-y.
59. Dong SZ, Zhu M. MR imaging of subaortic and retroesophageal anomalous courses of the left brachiocephalic vein in the fetus. Sci Rep. 2018;8(1):14781. https://doi.org/10.1038/s41598-018-33033-6.
60. Dong SZ, Zhu M. Prenatal cardiac magnetic resonance imaging of right aortic arch with mirror image branching and retroesophageal left ductus arteriosus. J Matern Neonatal Med. 2019;32(7):1057–62. https://doi.org/10.1080/14767058.2017.1399116.
61. van Poppel MPM, Pushparajah K, Lloyd DFA, Razavi R, Speggiorin S, Nyman A, et al. Insights from fetal cardiac magnetic resonance imaging in double aortic arch. Ultrasound Obstet Gynecol. 2020;56(4):636–9. https://doi.org/10.1002/uog.22110.
62. Dong SZ, Zhu M. Utility of fetal cardiac magnetic resonance imaging to assess fetuses with right aortic arch and right ductus arteriosus. J Matern Neonatal Med. 2018;31(12):1627–31. https://doi.org/10.1080/14767058.2017.1322951.
63. Neelavalli J, Krishnamurthy U, Jella PK, Mody SS, Yadav BK, Hendershot K, et al. Magnetic resonance angiography of fetal vasculature at 3.0 T. Eur Radiol. 2016;26(12):4570–6. https://doi.org/10.1007/s00330-016-4243-4.
64. Roy CW, Seed M, Macgowan CK. Accelerated MRI of the fetal heart using compressed sensing and metric optimized gating. Magn Reson Med. 2017;77(6):2125–35. https://doi.org/10.1002/mrm.26290.
65. Tavares de Sousa M, Hecher K, Yamamura J, Kording F, Ruprecht C, Fehrs K, et al. Dynamic fetal cardiac magnetic resonance imaging in four-chamber view using Doppler ultrasound gating in normal fetal heart and in congenital heart disease: comparison with fetal echocardiography. Ultrasound Obstet Gynecol. 2019;53(5):669–75. https://doi.org/10.1002/uog.20167.
66. Tavares de Sousa M, Hecher K, Kording F, Yamamura J, Lenz A, Adam G, et al. Fetal dynamic magnetic resonance imaging using Doppler ultrasound gating for the assessment of the aortic isthmus: a feasibility study. Acta Obstet Gynecol Scand. 2021;100(1):67–73.
67. Bhat M, Haris K, Bidhult S, Liuba P, Aletras AH, Hedström E. Fetal iGRASP cine CMR assisting in prenatal diagnosis of complicated cardiac malformation with impact on delivery planning. Clin Physiol Funct Imaging. 2019;39(4):231–5. https://doi.org/10.1111/cpf.12566.
68. Longo LD. Sir Joseph Barcroft: one victorian physiologist's contributions to a half century of discovery. J Physiol. 2016;594(5):1113–25. https://doi.org/10.1113/JP270078.
69. Dawes GS, Mott JC, Widdicombe JG. The foetal circulation in the lamb. J Physiol. 1954;126(3):563–87.
70. Rudolph AM, Heymann MA. The circulation of the fetus in utero. Circ Res. 1967;21(2):163–84. https://doi.org/10.1161/01.RES.21.2.163.
71. Kenny JF, Plappert T, Doubilet P, Saltzman DH, Cartier M, Zollars L, et al. Changes in intracardiac blood flow velocities and right and left ventricular stroke volumes with gestational age in the normal human fetus: a prospective Doppler echocardiographic study. Circulation. 1986;74(6):1208–16. https://doi.org/10.1161/01.CIR.74.6.1208.
72. De Smedt MCH, Visser GHA, Meijboom EJ. Fetal cardiac output estimated by Doppler echocardiography during mid- and late gestation. Am J Cardiol. 1987;60(4):338–42. https://doi.org/10.1016/0002-9149(87)90238-4.
73. St John Sutton M, Groves A, MacNeill A, Sharland G, Allan L. Assessment of changes in blood flow through the lungs and foramen ovale in the normal human fetus with gestational age: a prospective Doppler echocardiographic study. Br Heart J. 1994;71(3):232–7. https://doi.org/10.1136/hrt.71.3.232.
74. Hecher K, Campbell S, Doyle P, Harrington K, Nicolaides K. Assessment of fetal compromise by Doppler ultrasound investigation of the fetal circulation. Arterial, intracardiac, and venous blood flow velocity studies. Circulation. 1995;91(1):129–38. https://doi.org/10.1161/01.CIR.91.1.129.
75. Rasanen J, Wood DC, Weiner S, Ludomirski A, Huhta JC. Role of the pulmonary circulation in the distribution of human fetal cardiac output durin the second half of pregnancy. Circulation. 1996;94(5):1068–73. https://doi.org/10.1161/01.CIR.94.5.1068.
76. Prsa M, Sun L, van Amerom J, Yoo SJ, Grosse-Wortmann L, Jaeggi E, et al. Reference ranges of blood flow in the major vessels of the normal human fetal circulation at term by phase-contrast magnetic resonance imaging. Circ Cardiovasc Imaging. 2014;7(4):663–70. https://doi.org/10.1161/CIRCIMAGING.113.001859.
77. van Amerom JFP, Lloyd DFA, Deprez M, Price AN, Malik SJ, Pushparajah K, et al. Fetal whole-heart 4D imaging using motion-corrected multi-planar real-time MRI. Magn Reson Med. 2019;82(3):1055–72. https://doi.org/10.1002/mrm.27798.
78. Roberts TA, van Amerom JFP, Uus A, Lloyd DFA, van Poppel MPM, Price AN, et al. Fetal whole heart blood flow imaging using 4D cine MRI. Nat Commun. 2020;11(1):4992. https://doi.org/10.1038/s41467-020-18790-1.
79. Al Nafisi B, van Amerom JF, Forsey J, Jaeggi E, Grosse-Wortmann L, Yoo SJ, et al. Fetal circulation in left-sided congenital heart disease measured by

cardiovascular magnetic resonance: a case-control study. J Cardiovasc Magn Reson. 2013;15(1):65. https://doi.org/10.1186/1532-429X-15-65.
80. Torigoe T, Mawad W, Seed M, Ryan G, Marini D, Golding F, et al. Treatment of fetal circular shunt with non-steroidal anti-inflammatory drugs. Ultrasound Obstet Gynecol. 2019;53(6):841–6. https://doi.org/10.1002/uog.20169.
81. Porayette P, van Amerom JFP, Yoo SJ, Jaeggi E, Macgowan CK, Seed M. MRI shows limited mixing between systemic and pulmonary circulations in foetal transposition of the great arteries: a potential cause of in utero pulmonary vascular disease. Cardiol Young. 2015;25(4):737–44. https://doi.org/10.1017/S1047951114000870.
82. Say L, Gülmezoglu AM, Hofmeyr GJ. Maternal oxygen administration for suspected impaired fetal growth. Cochrane Database Syst Rev. 2003;1:CD000137.
83. Kohl T. Chronic intermittent materno-fetal hyperoxygenation in late gestation may improve on hypoplastic cardiovascular structures associated with cardiac malformationsin human fetuses. Pediatr Cardiol. 2010;31(2):250–63. https://doi.org/10.1007/s00246-009-9600-5.
84. Lara DA, Morris SA, Maskatia SA, Challman M, Nguyen M, Feagin DK, et al. Pilot study of chronic maternal hyperoxygenation and effect on aortic and mitral valve annular dimensions in fetuses with left heart hypoplasia. Ultrasound Obstet Gynecol. 2016;48(3):365–72. https://doi.org/10.1002/uog.15846.
85. Lee F-T, Marini D, Seed M, Sun L. Maternal hyperoxygenation in congenital heart disease. J Transl Pediatr. 2020. https://doi.org/10.21037/tp-20-226.
86. Borik S, Macgowan CK, Seed M. Maternal hyperoxygenation and foetal cardiac MRI in the assessment of the borderline left ventricle. Cardiol Young. 2015;25(6):1214–7. https://doi.org/10.1017/S1047951114001802.
87. Maeno YV, Kamenir SA, Sinclair B, van der Velde ME, Smallhorn JF, Hornberger LK. Prenatal features of ductus arteriosus constriction and restrictive foramen ovale in d-transposition of the great arteries. Circulation. 1999;99(9):1209–14. https://doi.org/10.1161/01.CIR.99.9.1209.
88. Mawad W, Chaturvedi RR, Ryan G, Jaeggi E. Percutaneous Fetal Atrial Balloon Septoplasty for Simple Transposition of the Great Arteries With an Intact Atrial Septum. Can J Cardiol. 2018;34(3):342.e9–342.e11.
89. Himeno W, Maeno Y, Kamura T, Matsuishi T. Enlarged bronchial arteries in a fetus with transposition of the great arteries and intact ventricular septum. Pediatr Cardiol. 2003;24(2):172–4. https://doi.org/10.1007/s00246-002-0310-5.
90. Darby JRT, Schrauben EM, Saini BS, Holman SL, Perumal SR, Seed M, et al. Umbilical vein infusion of prostaglandin I2 increases ductus venosus shunting of oxygen-rich blood but does not increase cerebral oxygen delivery in the fetal sheep. J Physiol. 2020;598(21):4957–67. https://doi.org/10.1113/JP280019.

Publisher's Note