Title

Integration of Prenatal Cardiovascular Magnetic Resonance Imaging in Congenital Heart Disease.

Journal

Journal of the American Heart Association, 12(22)

Authors

Desmond, Angela
Nguyen, Kim-Lien
Watterson, Christopher
et al.

Publication Date

2023-11-20

DOI

10.1161/JAHA.123.030640

Peer reviewed

Journal of the American Heart Association

CONTEMPORARY REVIEW

Integration of Prenatal Cardiovascular Magnetic Resonance Imaging in Congenital Heart Disease

Angela Desmond, MD; Kim-Lien Nguyen, MD; Christopher T. Watterson, MD; Mark Sklansky, MD; Gary M. Satou, MD; Ashley E. Prosper, MD; Meena Garg, MD; Glen S. Van Arsdell, MD; J. Paul Finn, MD; Yalda Afshar, MD, PhD

Standard of care echocardiography can have limited diagnostic accuracy in certain cases of fetal congenital heart disease. Prenatal cardiovascular magnetic resonance (CMR) imaging has potential to provide additional anatomic imaging information, including excellent soft tissue images in multiple planes, improving prenatal diagnostics and in utero hemodynamic assessment. We conducted a literature review of fetal CMR, including its development and implementation into clinical practice, and compiled and analyzed the results. Our findings included the fact that technological and innovative approaches are required to overcome some of the challenges in fetal CMR, in part due to the dynamic nature of the fetal heart. A number of reconstruction algorithms and cardiac gating strategies have been developed over time to improve fetal CMR image quality, allowing unique investigations into fetal hemodynamics, oxygenation, and growth. Studies demonstrate that incorporating CMR in the prenatal arena influences postnatal clinical management. With further refinement and experience, fetal CMR in congenital heart disease continues to evolve and demonstrate ongoing potential as a complementary imaging modality to fetal echocardiography in the care of these patients.

Key Words: cardiac magnetic resonance imaging ■ congenital heart disease ■ fetal cardiac gating ■ pregnancy

Congenital heart disease (CHD) affects approximately 8 in 1000 live births, and 1 in roughly 4 cases are considered critical CHD, requiring surgical or procedural intervention within the first year of life.[1] Prenatal diagnosis of CHD often improves neonatal morbidity and mortality through improved anticipatory counseling, multidisciplinary care, and delivery coordination.[2,3] With the increased availability of neonatal CHD intervention and care options, progress in prenatal diagnostic imaging beyond standard of care ultrasonography and fetal echocardiography is needed. Prenatal imaging and the information obtained give the ability to appreciate differences between fetal and postnatal physiology and hemodynamics (Figure 1).

Current prenatal detection rates of CHD are less than 50% on routine obstetric ultrasonography and improve to near 90% with comprehensive fetal echocardiography, albeit with selection bias,[4] and has increased from 26% to 42% between 2006 and 2012 in the United States.[5] Prenatal detection has historically been more challenging for certain lesions including coarctation of the aorta (21.6%) and total anomalous pulmonary venous return (9.1%), both with significant postnatal implications requiring critical medical and surgical care.[5] Imaging these lesions prenatally is inherently difficult due to unique in utero hemodynamics as blood flows in parallel with shunting at levels of the ductus venosus, foramen ovale, and ductus arteriosus; right-sided cardiac output is higher than left-sided structures. Postnatal blood flows in series through pulmonary and systemic circulation; right- and left-sided cardiac outputs become equal. More fetal blood flow bypasses a portion of the aortic arch and less fetal blood flows through the pulmonary veins, as

Correspondence to: Yalda Afshar, MD, PhD, University of California, 200 Medical Plaza, Suite 430, Los Angeles, CA 90095. Email: yafshar@mednet.ucla.edu

This article was sent to Erik B. Schelbert, MD, MS, Associate Editor, for review by expert referees, editorial decision, and final disposition.

For Sources of Funding and Disclosures, see page 12.

JAHA is available at: www.ahajournals.org/journal/jaha

Nonstandard Abbreviations and Acronyms

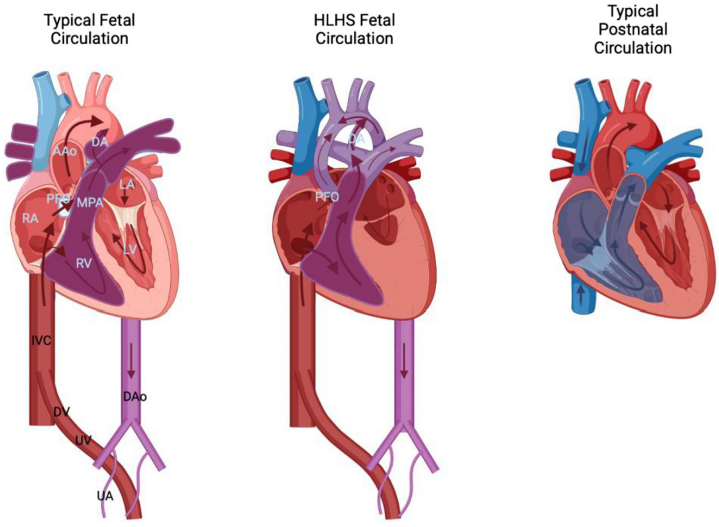
DUS	Doppler ultrasound
IAS	intact atrial septum
MOG	metric optimized gating
SaO_2	oxygen saturation
SV	single ventricle
SVC	superior vena cava

an example, making prenatal diagnosis of aortic narrowing and anomalies of pulmonary veins difficult with standard imaging modalities.

For some fetuses at increased risk for critical CHD, fetal cardiac magnetic resonance (CMR) may complement fetal echocardiography (Figure 2). To date, prenatal magnetic resonance imaging (MRI) has often been technically challenging and underused in part due to intrinsic factors related to the maternal–fetal condition, but advances in imaging technology are rendering it more feasible.[6]

METHODS

This narrative review of fetal CMR incorporates previously published literature related to CMR imaging, diagnostic accuracy of prenatal CHD, applications of fetal CMR, and required technological advances in the field of fetal CMR. The PubMed and Cochrane Library databases were searched with an English language restriction over the past 15 years. We used search



	Typical Fetal Circulation	HLHS Fetal Circulation	Typical Postnatal Circulation
CVO	Typical	20% less than typical	Typical
RV contribution to CVO	60%	78%	50%
LV contribution to CVO	40%	22%	50%
AAo, MPA flow		Less AAo flow, more MPA flow	
SVC flow (surrogate for cerebral flow)	147 mL/min/kg	130 mL/min/kg	130 mL/min/kg

Figure 1. Fetal versus postnatal circulation.
AAo indicates ascending aorta; CVO, combined ventricular output; DA, ductus arteriosus; DAo, descending aorta; DV, ductus venosus; HLHS, hypoplastic left heart syndrome; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; MPA, main pulmonary artery; PFO, patent foramen ovale; RA, right atrium; RV, right ventricle; SVC, superior vena cava; UA, umbilical artery; and UV, umbilical vein.

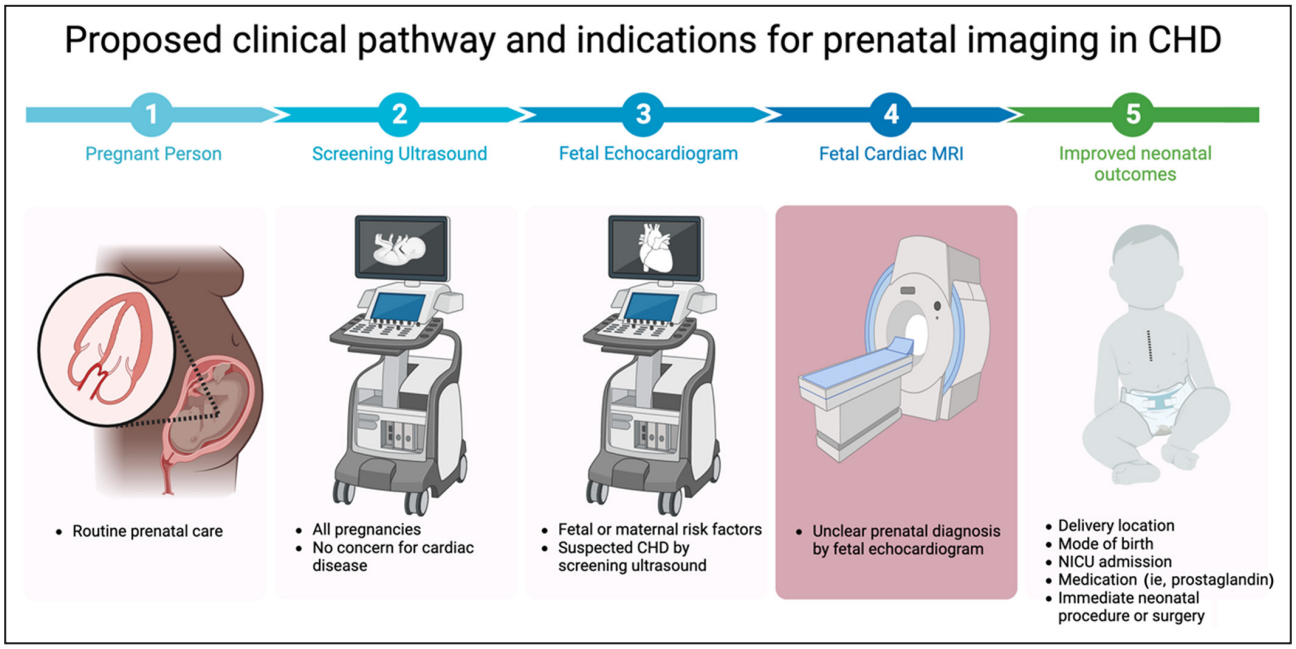


Figure 2. Proposed clinical pathway and indications for prenatal imaging in congenital heart disease.
Figure created with biorender.com. CHD indicates congenital heart disease; MRI, magnetic resonance imaging; and NICU, neonatal intensive care unit.

terms "fetal cardiac magnetic resonance," "fetal congenital heart disease diagnosis," "congenital heart disease magnetic resonance," and "prenatal imaging congenital heart disease." In addition, we searched additional sources such as *Circulation* (www.ahajournals.org/journal/circ), *Pediatrics* (publications.aap.org), American College of Cardiology (www.acc.org), and American College of Obstetricians and Gynecologists (www.acog.org).

RESULTS

The identified publications from our search are listed in Table 1.[7–27] We will review the strengths of CMR and illustrate what has been learned from fetal CMR. We will then present the clinical utility of incorporating CMR into prenatal diagnostics. Finally, we discuss challenges and technological advances made in the field of fetal CMR.

APPLICATIONS OF FETAL CMR

CMR provides excellent soft tissue images of cardiac structures in any plane as well as estimates of vessel blood flow, venous and arterial oxygen content and hematocrit using T1 and T2 mapping, fetal oxygen delivery and extraction, and myocardial perfusion.[7] These measurements are not readily determined using echocardiography. Because many infants (13%–56.6%) with CHD have extracardiac anomalies, performing volumetric imaging with high spatial resolution and a large field of view can facilitate early diagnosis of many associated noncardiac anomalies.[8,28–31] CMR is also quite safe.[32,33] A comparison of ultrasonography, echocardiography, and CMR is summarized in Table 2.

Investigations in fetal CMR have provided significant information about in utero hemodynamics, oxygen content and delivery, cerebral blood flow, and growth. We will review some of these findings and how they contribute to our understanding of CHD. Then, we will turn our focus to how incorporating CMR into prenatal diagnostics influences postnatal management.

In Utero Hemodynamics

In utero (prenatal) blood streaming and hemodynamics are vastly different from postnatal flows. Calculations from CMR allow us to quantify and understand these changes. Oxygenated blood from the umbilical vein (UV) and ductus venosus preferentially shunts across the foramen ovale to the left heart to prioritize supplying the brain and heart with more-oxygenated blood. The ductus venosus streaming mechanism, previously only demonstrated in fetal sheep using 4-dimensional flow MRI, is supported by fetal CMR. Imaging revealed oxygen saturations approximately 15% higher in the left heart and ascending aorta compared with the right ventricle and pulmonary artery.[7] In the setting of CHD, these fetal circulatory changes vary greatly (Figure 1). In transposition of the great arteries, for example, CMR has demonstrated that flow through the ascending aorta is greater than through the main pulmonary artery, which is the reverse of what is typically seen in fetal cardiac

Table 1. Included Publications From Literature Search

Author(s)	Study design	Cohort number	Key outcome measures
Sun et al[7]	Review article		Fetal circulation
Roy et al[8]	Cohort	25	Identification of cardiac structures and lesions
Al Nafisi et al[9]	Case–control	34	Fetal circulation in left-sided congenital heart disease
Sorensen et al[10]	Cohort	8	Fetal brain oxygenation during maternal hyperoxia
Sun et al[11]	Case–control	60	Fetal brain size, oxygen saturation, and blood flow
Porayette et al[12]	Case–control	37	Pulmonary blood flow during maternal hyperoxia
Xu et al.[13]	Cohort	23	T1 and T2 mapping to estimate fetal hematocrit
Lloyd et al[14]	Cohort	22	Evaluating extravascular anatomy
Bhat et al[15]	Case report	1	Impact on delivery planning
Ryd et al[16]	Cohort	31	CMR's influence on clinical decision-making
Dong et al[17]	Retrospective review	1573	CMR's utility as an adjunct to echocardiography
Lloyd et al[18]	Cohort	85	Comparison of 3-dimensional to 2-dimensional MRI image sets of fetal thorax
Lloyd et al[19]	Case–control observational study	72	Quantifying blood flow in fetal ascending aorta and isthmus
Haris et al[20]	Feasibility study	5	Iterative golden-angle radial sparse parallel self-gated images quality
Jansz et al[21]	Methodology paper		Metric optimized gating technique
Roberts et al[22]	Methodology paper		4-Dimensional flow MRI
Berggren et al[23]	Cohort	28	Image quality of superresolution enhanced images
Seed et al[24]	Cohort	12	Blood flow distribution using MOG
Roy et al[25]	Cohort	5	Image quality using MOG
Kording et al[26]	Cohort	15	Image quality using DUS gating
Ryd et al[27]	Cohort	22	Blood flow measurements from DUS gated vs MOG images

CMR indicates cardiac magnetic resonance; DUS, Doppler ultrasound; MOG, metric optimized gating; and MRI, magnetic resonance imaging.

physiology.[7] In another example, hypoplastic left heart syndrome, flow through the ascending aorta is drastically reduced with a compensatory increase in flow through the main pulmonary artery and ductus arteriosus.[7] Despite these altered right and left heart outputs in CHD, organ perfusion appears to be maintained.

In a study evaluating the impact of left-sided CHD on fetal hemodynamics, postnatal outcomes, and lung and brain development, 22 pregnancies carrying fetuses with left-sided CHD and 12 pregnant controls underwent phase contrast CMR. The mean combined ventricular output was 19% lower in CHD compared with controls,[9] consistent with previous fetal echo flow measurements demonstrating a 20% reduction in combined ventricular output in fetal hypoplastic left heart syndrome compared with controls. In controls, the mean contributions of right and left ventricles were 60% and 40%, respectively. In pregnancies with aortic stenosis or coarctation of the aorta, the contributions were 78% and 22%.[9] This differential could be a source of decreased cerebral blood flow.

Superior vena cava (SVC) flow is often used as a surrogate for cerebral blood flow in the fetus. On average, the fetuses with left-sided CHD had an SVC flow of 130 mL/min/kg, similar to 147 mL/min/kg in fetuses without CHD, but with more significant variation. Six of the 22 fetuses with left-sided CHD had brain weights lower than the fifth percentile despite normal fetal and birth weights,[9] with no correlation found between brain weight and combined ventricular output or flow through the SVC or ascending aorta.

A wide range of blood flow through the pulmonary system and foramen ovale in healthy fetuses has been shown. This may be related to the inverse relationship between the 2 competing sources of venous return to the left ventricle in the setting of constant ascending aortic flow. As well, changes in placental function may lead to changes in pulmonary vascular resistance, which can lead to a variation in streaming of umbilical venous return at the ductus venosus and foramen ovale. This example of dynamic physiology is essential to understand as it changes drastically in the setting of congenital heart disease, and CMR equips us with a way to study and quantify those changes.

Oxygen Content and Delivery

Previous studies have demonstrated steady brain oxygenation during fetal hypoxia and hyperoxia.[10] A variation in streaming may explain this continuous oxygen

Table 2. Comparing Obstetric Ultrasonography, Fetal Echocardiography, and Fetal Cardiac Magnetic Resonance

	Screening obstetric ultrasonography	Fetal echocardiography	Fetal cardiac magnetic resonance
Indications	All pregnancies	Concern on screening ultrasound, suspected fetal anomalies*, maternal risk factors†, in vitro fertilization	Research protocol, center-specific protocols
Optimal timing	18–22 weeks' gestation	Second trimester	Third trimester
Strengths‡	Availability, low cost	Images all fetal cardiac anatomy, high spatial and temporal resolution, dedicated scan	Large field of view, very high spatial resolution structures in any plane, estimates blood flow, venous and arterial oxygen content
Limitations	Includes only 4-chamber view and outflow tracts. Oligohydramnios, maternal obesity, multiple gestations can make imaging difficult.[34] Requires skilled personnel.	Requires consultation with pediatric cardiology. Oligohydramnios, maternal obesity, multiple gestations can make imaging difficult. Small structures difficult to visualize. Requires skilled personnel.	Low availability currently. Requires reliable cardiac gating strategy, motion correction algorithms to compensate for maternal respiratory artifact and gross fetal movement.

*Extracardiac abnormalities, chromosomal abnormalities, arrhythmias, hydrops, increased first-trimester nuchal translucency, multiple gestation, suspicion of twin-to-twin transfusion syndrome.
†Maternal family history of congenital heart disease, metabolic disorder.
‡Lack of ionizing radiation.

delivery to the developing fetal brain in the setting of stress. Fetuses with left-sided CHD did not vary foramen ovale flow well compared with a control population.[9] In left-sided CHD, the ductus arteriosus supplies a significant proportion of cerebral blood flow via retrograde flow in the aortic arch. In fact, this is the main supply of cerebral blood flow in fetuses with hypoplastic left heart syndrome.

The oxygen content of ascending aortic blood and thus cerebral blood supply are likely to correlate well to oxygen delivery by the placenta. Infants with left-sided CHD may need more cerebral vasoreactivity to achieve adequate cerebral oxygenation in the setting of variations in placental oxygen delivery. Other studies have measured reduced middle cerebral artery pulsatility in fetuses with CHD. One theory of explanation is cerebral vasodilation as an adaptive response to longstanding hypoxia. To investigate a relationship between fetal hemodynamics, in utero cerebral oxygenation, and brain growth in CHD, investigators enrolled 30 fetuses with CHD and 30 controls in a CMR study.[11] Phase contrast MRI and T2 mapping were conducted at mean gestational age of 36 weeks. The equation used to calculate oxygen saturation, established by Wright et al was $1/T2 = T/T2_0 + K\ [1-\text{oxygen saturation } (SaO_2)/100\%]^2$, where $T2_0$ is the T2 of fully oxygenated blood for a given hemoglobin concentration and constant K depends on magnetic field strength and refocusing interval of T2.[35] Average hemoglobin concentrations based on gestational age were used. The subjects were divided into 4 groups based on CHD diagnosis: single ventricle, biventricular, transposition of great arteries, and tetralogy of Fallot. The MR sequences allowed the researchers to calculate fetal oxygen delivery [oxygen delivery = (UV flow)×(UVO_2 content)] and consumption [VO_2 = (UV flow)×(UV–umbilical artery O_2 content)]. Due to the small size of umbilical arteries, the O_2 content was estimated based on T2 measurement in their direct supply, the descending aorta. To calculate fetal cerebral oxygen delivery and VO_2, SVC flow and oxygen content were used as a surrogate for small vessels draining the brain because cerebral blood flow accounts for most SVC drainage. The aortic arch was used as a surrogate for cerebral blood supply.

Fetuses with CHD demonstrated a 6% reduction in UV SaO_2 and coupled with lower UV flow, there is a 17% reduction in oxygen delivery to the growing fetus. There was no correlation between fetal VO_2 and fetal cerebral VO_2 or between combined ventricular output and SVC flow. Umbilical venous flow correlated with combined ventricular output. The differential in oxygen saturation between the ascending aorta and main pulmonary artery was 7% in controls and dropped to 2% in the setting of CHD. Fetuses with CHD had a 10% reduction in SaO_2 of cerebral blood supply and a 15% reduction in cerebral oxygen delivery compared with controls.[11] There was a 32% reduction in cerebral oxygen consumption in CHD. When the CHD subgroups were examined, this cerebral oxygen consumption reduction was seen in all except for single ventricle. There was a significant correlation between ascending aorta SaO_2 and fetal cerebral VO_2 but not between either of these and brain volume.[11] Investigators found a 13% reduction in brain volume in fetuses with CHD compared with controls.[11]

Calculations derived from this imaging study gave valuable insight into the intrauterine hemodynamics and brain growth of developing fetuses affected and unaffected by CHD. Overall, these results may be consistent with a theory of reduced fetal cerebral

oxygen consumption in CHD as a sequela of chronic hypoxia. This opposes the brain-sparing physiology seen in acute fetal hypoxia, such as with preeclampsia. Another possible explanation is that fetal cerebral oxygen consumption is independent of oxygen delivery in the setting of CHD. In other words, normalizing oxygen delivery to the brain may not result in increased extraction, use, or subsequent growth in a fetus with CHD. This raises the concern that a fetus with CHD has a developing brain that is less metabolically active than one unaffected by CHD.

Cerebral Blood Flow and Growth

Intuitively, one approach to management of decreased cerebral oxygen delivery and consumption in fetuses with CHD would be a trial of maternal hyperoxia, and this has been explored as a potential therapy to augment ventricular growth in fetuses with CHD. In a maternal hyperoxia study, 17 controls and 20 fetuses with CHD underwent MRI and hyperoxia was induced to achieve fraction of inspired oxygen 70% for 10 min. Before hyperoxygenation, umbilical venous SaO_2 was lower in fetuses with CHD compared with controls, but the difference was not significant. This may be reflective of abnormal placental function in pregnancies complicated by CHD. After hyperoxygenation, fetuses with CHD had a 19% increase in UV T2 (correlated with SaO_2), whereas controls had no significant change. Pulmonary blood flow approximately doubled in both groups. With no change in UV flow, fetuses with CHD had a predictable increase in oxygen delivery and pulmonary vasodilation in the setting of maternal hyperoxia. The ductus arteriosus flow was higher in the CHD group at baseline and was significantly reduced during maternal hyperoxia. There was no change in ductus arteriosus flow in the controls.[12] The researchers' conclusions support maternal hyperoxia as a potential treatment to promote lung and brain maturation and growth in the setting of CHD. This study did not directly investigate the effect of maternal hyperoxia on fetal cerebral oxygen delivery.

In another related area, MRI has been validated to measure hematocrit in fetal anemia. It is less invasive than the gold standard, fetal blood sampling. Using ungated T1 and T2 mapping sequences in the short axis of the intrahepatic UV using modified Look–Locker inversion and T2 preparation pulse sequences, the group published an equation to calculate hematocrit.[36] The mean absolute difference between the MRI estimated and laboratory hematocrit was 6%±5% with a correlation of 0.77 (P<0.001).[13]

Fetal CMR Influence on Postnatal Management

Fetal CMR is a comprehensive process and should be utilized selectively, considering the time and resources required. Considering the fact that the expense of the MR imaging is high, along with the experience of maternal discomfort and the burden of undergoing MR late in pregnancy, our field has a need to define which cases along with when and how prenatal CMR findings significantly affect prenatal counseling, postnatal management, and potentially improve outcomes.

In cases where the diagnosis was unclear on echo, most referrals for CMR were for suspected extracardiac vascular abnormalities especially involving the aortic arch and pulmonary vessels, which are historically difficult to diagnose on ultrasound. Single-shot fast spin-echo T2 weighted images visualized extracardiac vascular anatomical structures well since they move less during the cardiac cycle. In some instances, high-risk coarctation was identified on CMR and confirmed postnatally. In other cases, CMR revealed a low suspicion of coarctation, and no postnatal intervention was required. Large tortuous solitary bilateral pulmonary veins were identified in 1 fetus with hypoplastic left heart syndrome. In several cases, cardiac rhabdomyomas were well visualized on CMR.[14] CMR, especially with development in motion correction and gating techniques, has the potential as a clinically important adjunct to echocardiography in CHD.

A case study illustrated how using iterative golden-angle radial sparse parallel (iGRASP) MRI changed postnatal management in the case of an unbalanced common atrioventricular canal with limited fetal echocardiographic image quality and poor visualization of the aortic arch. CMR confirmed and revealed an unbalanced common atrioventricular canal, no ventricular septal defect, and arch hypoplasia.[15] A study was designed to assess if and how prenatal CMR after an inconclusive echo changed patient management. In this study, there were 4 main categories prompting referral to CMR: (1) to determine aortic arch anatomy; (2) to measure atrioventricular valve annulus diameter and evaluate ventricular size, function, morphology for assessment of univentricular versus biventricular outcome; (3) to assess signs of restrictive atrial septum including pulmonary lymphangiectasia in hypoplastic left heart syndrome and suspected restrictive or intact atrial septum for risk stratification and delivery planning; and (4) to provide information for parental counseling regarding diagnosis, postnatal outcome, possible mode of surgery, and postnatal care. The authors found that fetal CMR added diagnostic information in 80% of those imaged for aortic arch anatomy concerns. More so, fetal CMR visualized intracardiac anatomy and ventricular function, allowing outcome assessment, in 87% of patients. The addition of CMR affected patient management or parental counseling in 84% of cases in this study.[16]

In a study including 1573 pregnant people who underwent CMR as an adjunct to technically inadequate

fetal echocardiograms, a CMR was done at 22 to 36 (mean 24.5) weeks of gestational age.[17] The vast majority were confirmed to have normal cardiovascular structures postnatally. CMR identified 99.2% of these as such but interpreted 10 cases (0.8%) incorrectly as CHD (including 5 ventricular septal defect, 3 coarctation of aorta, and 2 pericardial effusion). Fetal CMR correctly diagnosed 56.3% of postnatally confirmed cases of CHD.[17] It should be noted that it is widely accepted that postnatal patent ductus arteriosus and secundum atrial septal defect are nearly impossible to diagnose to reliably diagnose prenatally and were included in the incorrectly diagnosed category. Fetal CMR diagnoses of transposition of great arteries, pulmonary atresia/intact ventricular septum, and hypoplastic left heart syndrome, lesions most commonly requiring surgical treatment in the neonatal period, were diagnosed correctly in most cases by CMR. The investigators concluded that CMR should not be used as a first-line fetal heart imaging tool; however, it could correctly identify critical CHD.

Extracardiac manifestations are common in CHD and can significantly affect postnatal management. Airway compression can occur in the case of an absent pulmonary valve and is amenable to assessment on CMR. Airway imaging with 2-dimensional (2D) MRI could help stratify postnatal risk of airway compression as the aberrant origin of left subclavian or double aortic arch can cause tracheoesophageal compression.[18]

Coarctation of the aorta has strong evidence for improved outcomes when the diagnosis is made prenatally. Fifty-one pregnant women whose fetuses had suspected coarctation of the aorta after fetal echocardiography were referred for fetal CMR using metric optimized gating between 26 and 38 weeks of gestation. A higher risk of postnatal coarctation was associated with reduced ascending aortic flow, increased angle between aortic isthmus and ductus arteriosus, increased distance between posterior walls of aortic isthmus and descending aorta, and increased distal arch index. This study had a predictive accuracy greater than 99% at advanced gestation and in the setting of already suspected coarctation on echocardiography. The same center previously attempted to generate a predictive model from echocardiography alone and found 63% of cases were correctly classified.[27]

Coarctation of the aorta and total anomalous pulmonary venous return are very strong candidates for CMR. These 2 fetal CHD diagnoses have historically poor prenatal detection rates with fetal echocardiography, have markedly improved prognosis with prenatal diagnosis, and involve extracardiac structures (aortic arch and pulmonary veins, respectively) that are less vulnerable than intracardiac structures to challenges with cardiac gating. Future studies are needed to assess our diagnostic accuracy with technological advances in CMR imaging.

NEW FETAL CMR IMAGING TECHNIQUES AND ADVANCEMENT

To date, some of the technical factors limiting fetal CMR have centered around the general maternal–fetal environment and include (1) gross fetal movements, (2) maternal respiratory motion artifacts, (3) the need for a reliable cardiac gating strategy, and (4) challenges related to late pregnancy CMR, such as the dielectric effect. Several approaches and tools have been developed to address these challenges.

Motion correction algorithms and techniques have been developed to overcome the motion artifacts inherent to imaging a fetus and pregnant mother (1 and 2). The more commonly used CMR pulse sequences are summarized in Table 3. All anatomic CMR methods rely on synchronization of the MR signal to the quiescent cardiac phase.[20] In other words, either prospective or retrospective cardiac gating is required (3), sometimes using MR-compatible hardware devices such as those listed in Table 4. With these tools, researchers have been able to study previously difficult-to-visualize fetal structures and connections, hemodynamics, oxygenation patterns, and brain growth. Fetal CMR is most successful in late gestation when the fetus is larger and produces less motion artifact.

A summary of CMR pulse sequence classes (techniques) and their pathophysiologic targets is provided in Table 3. Cine CMR is one class of imaging pulse sequences that provide cardiac phase-resolved images for assessment of cardiac function and morphology. Real-time phase contrast MRI involves a tradeoff between spatial resolution and scan time that has significant limitations in the fetal population. A form of cardiac gating must be established to overcome these challenges. Data acquisition is divided over several cardiac cycles and then gated in a way that each image is centered on a desired cardiac phase, creating a reconstruction of the time series of images. This is cine imaging.[21,37]

Phase contrast-MRI methods are widely used in adults to quantify blood flow measurements of the heart. Applications to the fetal cardiovascular system has been limited to the sheep fetus and pregnant rhesus macaques; imaging was performed under anesthesia to prevent movement, which can otherwise severely compromise phase contrast-MRI imaging quality. The fetus is amenable to balanced steady-state free precession acquisitions because the uterus and fetal lungs are fluid filled. This, along with low flow rates, mitigates banding and flow-related artifacts.

Table 3. Overview of CMR Imaging Modalities and Their Potential to Assess Pathophysiologic Targets

CMR method	Description of technique	Pathophysiologic targets*	Limitations
CMR techniques			
Cine CMR	Images acquired at multiple time points throughout cardiac cycle to capture motion	Ventricular volumes, ejection fraction[7]	Gross fetal movement and maternal breathing artifact
2D phase contrast (PC)	Velocity mapping that relies on differential phase in flowing blood compared with static tissues	Time-resolved volume flow rates,[37] valve regurgitation, shunt volume[7]	Movement artifact. Reliant on accuracy velocity encoding at time of imaging.
4D flow PC	Entire 3D volume flow encoded and reconstructed with motion correction and cardiac gating[22]	Volumetric imaging: intricate vasculature, complex connections and shunts visualized in any 2D plane desired in postprocessing.[22] Blood flow through vasculature, cardiac chambers, any other regions of interest.	Peak velocity measurements less than those found in 2D PC-MRI in term fetuses.[22] Low spatial resolution, limited temporal resolution relative to fetal structure size and heart rate.
Reconstruction algorithms			
2D MRI (single shot fast spin echo) + slice-volume registration motion correction algorithm	Initial 3D thorax reconstruction created from 2D image stack with least movement artifact. Additional 2D stacks then automatically processed using a motion-correction algorithm to optimize the 3D reconstruction.[18]	3D structures generated with high resolution[18]	Smaller volumes measured compared with corresponding echocardiograms[18]
Motion compensated cine MRI	Motion correction algorithm applied	High-quality images. Short acquisition time.	Identified fewer anatomic features compared with echo.[8] Hard to assess ventriculoarterial connections and thus diagnose outlet tract abnormalities.[8] Limited by gross fetal movement.
Cine MRI + iterative golden-angle radial sparse parallel	Parallel imaging (k-space data acquired by multiple receiver coils at once) and compressed sensing (undersamples k-space) to accelerate image acquisition[20]	Suppresses image artifacts. Very short acquisition time. Self-gated.	Cardiac self-gating signal difficult to extract.[20] When inaccurate, introduces artifact in reconstruction. Long reconstruction times.
Doppler ultrasound gated MR + phasrresnet, phasrGAN super-resolution cine image enhancement	Artificial intelligence-aided reconstruction techniques. Superresolution neural networks trained on fetal cine CMR low- and high-resolution images acquired using generalized autocalibrating partial parallel acquisition.[23]	Short acquisition time; 33% undersampling method with superresolution enhancement produced high image quality.	Potential to introduce anatomical or motional abnormalities

CMR indicates cardiac magnetic resonance; MRI, magnetic resonance imaging; PC, phase contrast; 2D, 2-dimensional; 3D, 3-dimensional; and 4D, 4-dimensional.

*All can quantify tissue and blood oxygenation by taking advantage of opposing properties of oxy- and deoxy-hemoglobin.

Motion Correction Techniques

In a large fetal CMR study, 85 pregnancies affected by CHD underwent T2 single-shot fast spin-echo sequences to produce stacks of 2D images.[18] The image stack containing the least movement artifact was used to generate an initial 3-dimensional (3D) thorax reconstruction and the additional stacks were then automatically processed using a motion-correction algorithm to optimize the 3D reconstruction. The reconstructions were assessed for the ability to visualize structural areas of interest including the systemic venous return, pulmonary artery supply, pulmonary venous return, and aortic and ductal arch anatomy. All 4 anatomical regions were identified in 53% of 2D data sets and 97% of 3D reconstructions. There was moderate agreement between the mean measurements of the same structures on echocardiography but evidence to suggests a systemic bias toward smaller values from MRI.

In another study, motion-compensated cine MRI was performed and evaluated in 25 pregnancies affected by fetal CHD and compared with standard of care echocardiography. Free-breathing CMR image acquisition was limited to 5 minutes as a part of a 1-hour complete fetal study. Images were reconstructed with maternal respiration and fetal movement suppression. The CMR interpretation was limited by inadequate coverage of fetal cardiac anatomy and noncontiguous slices because of gross fetal movement. Reviewers were able to identify fewer (7.1 versus 7.8 out of 9) major fetal cardiac anatomic features on CMR compared with an echocardiogram, but the difference is not statistically significant if subjects with gross fetal

Table 4. Cardiac Gating Strategies

Image acquisition and gating method	Gating strategy description	Advantages and use	Limitations
Real-time Imaging	None. Images acquired fast enough to eliminate motion artifact.[37]	No gating needed. Short imaging time.	Limited spatial and temporal resolution and signal to noise ratio[37]
Nontriggered acquisition	None. Image acquired across several cardiac cycles.[37]	No gating needed	Loss of dynamic information.[37] Need for reconstruction.
Self-gating	Imaging mode acquires k-space segments while self-gating mode samples k-space centerline repeatedly to capture cardiac motion. Gating signal extracted from MR data. Imaging sorted retrospectively.[38]	Uses intrinsic MR signal to identify cardiac motion and synchronizing imaging events. Can be done prospectively or retrospectively. No hardware required.[38]	Long reconstruction time. Arrhythmias would complicate.
Retrospective cardiac gating	Continuously acquires data over entire R-R interval, using HR monitor to trigger moving between segments. Data then interpolated to set of cardiac phases.[37]	Acquired images synchronized to cardiac cycle	Requires every segment to be sampled at every cardiac phase. Fetal HR unknown, monitor often unavailable.[37] Oversampling. Arrhythmias would complicate.
Phase contrast-MR imaging metric optimized gating	Postprocessing, retrospective cardiac gating. Synthetically gated and oversampled data collected. Images reconstructed using varied hypothetical triggers until metric is optimized. Employs image metrics to detect misgating artifact.[25]	Does not require HR information.[37] Flow volume measurements reproducible.[25]	Cannot fully correct data when images acquired during widely varied heart rates or arrhythmias.[37]
Balanced steady state free precession+DUS	DUS used to determine HR in real time, allowing cardiac gating during image acquisition	Real-time fetal HR determination. Can synchronize data acquisition with varying fetal cardiac cycle. Overall imaging quality and cardiac diagnostic quality assessed as high.[26]	Require DUS probe (expensive) and training

DUS indicates Doppler ultrasound; HR, heart rate; and MR, magnetic resonance.

movement are excluded. These findings suggest that a fetal cine CMR protocol that focuses on a specific clinical question and includes repeat measurements and improved slice coverage could accurately assess clinically significant ventriculoarterial connections and pulmonary artery branches.

In the area of 4-dimensional cardiac imaging, which provides dynamic information about cardiac function and blood flow, investigators created a framework to generate fetal motion-corrected 4-dimensional flow volumes to depict temporally dynamic 3D velocity vector fields of blood in the heart and great vessels.[22] With these reconstructed volumes, complicated fetal cardiac structures and connections can be reviewed in any desired 2D plane. The measured blood flows were lower than other MRI techniques by 26% in the ascending aorta and 61% in the ductus arteriosus.[22]

Cine MRI with tiny golden angle radial sampling and iGRASP were compared with metric optimized gating (MOG) and real-time imaging.[20] The team noted that the cardiac self-gating signal extraction, on which gating and thus image reconstruction solely depends, was most challenging. Images produced in this study were analyzed for overall image, cardiac diagnostic, and extracardiac diagnostic quality. The iGRASP and MOG cine method rendered images scored similarly, but with a higher trend for iGRASP images' overall image quality, cardiac diagnostic quality, and extracardiac diagnostic quality. The real-time images had lower scores.[20] Delineating was notably more difficult and time consuming to perform in MOG and real-time cine images in comparison to iGRASP.

Superresolution cine image enhancement was applied using phasrresnet and phasrGAN to Doppler ultrasound (DUS) gated fetal CMR to decrease acquisition time while maintaining high image quality. The 2 networks were trained and tested on 2 types of fetal CMR data sets: (1) synthesized low-resolution fetal cine MR images based on acquired fetal cine cardiac MR fully sampled high-resolution images, and (2) images acquired with low and high resolution from the same fetus. The images were acquired using generalized autocalibrating partial parallel acquisition.[23] Standard acquisition times are 9 seconds for a typical fetal heart rate of 140 bpm. Therefore, for low-phase resolution image slice scan times were 2.25 s (25%), 3 s (33%), and 4.5 s (50%). The total scan time ranged from 15 to 60 min. For the 25% phase-encoding resolution, all the enhancement methods showed significantly lower image quality compared with standard. For the 33%

resolution, 3 times faster than standard image acquisition, the phasrGAN and phasrresnet applied image sets had standard qualitative imaging scores. Using the 33% undersampling with superresolution networks has the potential to generate high-quality fetal cine MR images when fetal motion otherwise limits quality, such as early on in pregnancy, and reduces scan time. In the 50% phase-encoding resolution, there was no statistically significant difference in image quality between standard clinical acquisition and superresolution enhancement. No unexpected pathology was found in any of the image enhancements; furthermore, all pathology existing in standard clinical acquisitions was also present in the enhanced image sets.[23]

Cardiac Gating Strategies

The need for cardiac gating is not unique to CMR. In echocardiography, a retrospective cardiac gating strategy is applied to volume sonographic acquisitions by plotting pixel intensity changes over time, reflective of the heart's periodic mechanical activity and thus cardiac cycle, and assigning each acquired image to its proper position in the cardiac cycle.[39] This approach is used in spatiotemporal image correlation, which is an automatic way to produce 3D images of the fetal heart throughout the cardiac cycle.[40]

Cardiac gating can be prospective or retrospective. These strategies must be dynamic due to fetal variation in heart rate and R-R interval length. In prospective cardiac gating, the scanner starts at the beginning of each cardiac cycle and acquires a predetermined number of measurements. It waits for a specific trigger signal (eg, R wave) before imaging the next cycle. Then, the measurements are input into specific elements of k-space matrices that are transformed to images corresponding to consistent points in the cardiac cycle. In retrospective cardiac gating, data acquisition is continuous, and the data are rearranged according to their temporal correspondence to the ECG signal that is recorded simultaneously. Oversampling is required to ensure that every segment of k-space is acquired at every cardiac phase.[21] The resulting image series fully covers the cardiac cycle while slightly sacrificing temporal resolution.[37]

Fetal CMR requires a form of gating to acquire a reliable, clinically accurate set of imaging in a short time frame (ideally less than 30 minutes of imaging time). Because the fetal cardiac cycle is only 330 to 540 ms, only 5 to 7 frames can be collected per heart beat versus 30 plus frames per adult cardiac cycle.[22] In the absence of traditional ECG detection available in postnatal CMR, technological innovation is needed. Several options have been explored including real-time imaging, no trigger, self-gating, metric optimized gating, and use of an MR compatible ultrasonography probe.[29]

Alternatively, real-time imaging does not require a gating signal because image acquisition is fast enough to eliminate motion artifacts. The tradeoff is compromised spatial and temporal resolution, not acceptable for diagnostic fetal CMR. Nontriggered acquisitions rely on the principle that a particular area will be sampled evenly across several cardiac cycles such that a mean flow can be assigned.[29]

Self-gating uses intrinsic MRI signal to detect cardiac motion and synchronize imaging. Self-gating techniques require scan time to develop the cardiac motion self-gating signal. This can be done prospectively at the beginning of the scan, which is more technically challenging but efficient, or retrospectively after acquisition, which requires oversampling and longer acquisition time. A self-gating signal produced accurate cardiac triggers and corresponded well to ECG triggers with low temporal variability. The image quality of self-gated cine images was equivalent to ECG-gated image quality. The prospective self-gating technique detected 100% of the 85 cardiac triggers and successfully switched scan modes in real time.[38] Self-gating sequencing techniques have a reliable trigger detection and produce solid cardiac image quality in the absence of gross motion.

Metric optimized gating is a retrospective gating technique that uses modeled heart rates to overcome traditional cardiac trigger requirement. Without a cardiac gating signal, each segment is acquired continuously for a period longer than a cycle in the expected fetal heart rate. This results in oversampled data that are grouped by cardiac phase and then retrospectively reconstructed using hypothetical cardiac triggers across the normal range of fetal heart rates. This process is repeated with adjusted heart rate model parameters to optimize the image metric and finalize a time-series of reconstructed images with the least entropy.[21,24] The MOG trigger times were precise compared with ECG triggers and using a 1.5 T MRI with multichannel abdominal coils and steady-state free precession sequences, the team was able to capture 15 to 30 heartbeats in the fetal scans. Fetal image quality was high enough to allow for an assessment of cardiac function.[25]

MOG is the first fetal CMR gating technique that produces high-quality clinically useful images without the need to reprogram the MRI scanner during imaging. However, it may produce misgating artifact that can cause image ghosting or loss of vessel pulsatility. Misgating could be systematic, resulting from a discrepancy between modeled and actual heart rate, or random, resulting from short-term variation in heart rate that is unaccounted for in the model. Investigators sought metrics to detect misgating artifact and found that time entropy (entropy evaluated in time on a voxel by vowel basis and summed spatially,

providing a surrogate measure of pulsatility) best satisfied the criteria. This relies on the assumption that the best reconstruction produces the most pulsatile waveform.

Finally, the last gating technique to discuss is using DUS to provide a time-averaged measure of fetal heart rate at regular intervals.[29] Building images over multiple cardiac cycles optimizes temporospatial resolution. In the first study to use external fetal cardiac gating in humans, 15 fetuses gestational ages 30 to 39 weeks were imaged across 3 centers. Cardiac signals from CMR compatible external DUS device, Northh Medical GmbH (Hamburg, Germany), were used to retrospectively gate balanced steady-state free precession cine imaging in 4 chamber and short-axis views during maternal breath holding.[26] The images were evaluated for overall image quality and cardiac diagnostic quality on a scale of 1 to 4. The image quality was high and in an agreement between both observers: 3.6±0.6.[26] Fetal cardiac structures were reliably identified. Clear differentiation between myocardium and lumen was seen, indicating high gating quality. The myocardial border sharpness was quantified by measuring endocardial blurring. Results demonstrated a reliable assessment of volumetric data.

Another study compared an MR compatible DUS device to a traditional ECG trigger in 5 healthy adult patients. The signals generated by the DUS and ECG correlated. There was a time delay of 394±9 ms for DUS behind ECG. Cardiac MRI obtained using both DUS and ECG triggers was compared. The DUS trigger-generated images had comparable image quality when endocardial border sharpness was assessed. There was no significant difference between left ventricle volume and ejection fraction between DUS and ECG trigger-generated images.[41]

With hopeful advances in DUS gating in CMR, one will want to validate DUS gated CMR blood flow quantification against those determined by the previously discussed standard, MOG techniques. Metric optimized gating is heavily dependent on postprocessing for image reconstruction, so the studies are inherently limited by a lack of real-time image quality control. DUS gating has the potential to overcome this in addition to eliminating a lot of the postprocessing reconstruction time. In a study designed to validate DUS gated CMR against MOG, fetal blood flow was measured in the descending aorta and UV in 19 fetuses. The descending aortic flow was 726 mL/min by DUS and 708 mL/min by MOG. The umbilical venous flow was 366 mL/min by DUS and 404 mL/min by MOG. Repeatability was high. Investigators recommend choosing a region of interest close to vessel size or slightly larger. This study validated vessel flow quantification by DUS gated CMR.[27]

CONCLUSION

The fetal heart is a very small and dynamic structure in a large field of view. The complexity and significant morbidity and mortality associated with CHD, combined with the frequent need for urgent postnatal management and interventions, render accurate prenatal diagnostic imaging critical. Particularly for cardiac lesions with low detection rates with conventional fetal cardiac imaging,[34] fetal CMR has a vital role as a complementary diagnostic tool to echocardiography.

Despite its diagnostic potential, fetal CMR has been underdeveloped and underused due to several technical limitations, including artifact from maternal respiration and gross fetal movements limiting image quality, and the high and variable fetal heart rate and maternal ECG interference posing challenges for cardiac gating. Technological advances to overcome these challenges including motion correction, metric optimized gating, and DUS for cardiac gating have permitted unique investigations into in utero hemodynamics, oxygenation, and growth. These innovations equip us with a customizable tool kit to learn more about congenital heart disease in the prenatal arena.

CMR remains far from the standard of care in evaluating the fetal heart, in part because of its limited availability, and in part due to the expertise, time, and resources required to perform it correctly. Much remains to be learned regarding clinical utility, technological advancement, and influence on postnatal management and outcomes. The precise patient population that will benefit from CMR imaging as an adjunct to fetal echocardiography is still being refined. We believe, with some ongoing fine-tuning, that fetal CMR could be used to accurately diagnose a number of complex fetal CHD lesions including coarctation of the aorta, abnormalities in the pulmonary veins, heterotaxy syndrome configurations, and other forms of complex CHD. The goal, of course, remains to work toward improving the overall morbidity and mortality for infants born with CHD.

ARTICLE INFORMATION

Affiliations

Division of Neonatology, Department of Pediatrics, UCLA Mattel Children's Hospital, Los Angeles, CA (A.D., M.G.); Diagnostic Cardiovascular Imaging Laboratory, Department of Radiological Sciences, David Geffen School of Medicine, UCLA, Los Angeles, CA (K.-L.N., A.E.P., J.P.F.); Division of Cardiology, David Geffen School of Medicine at UCLA, VA Greater Los Angeles Healthcare System, Los Angeles, CA (K.-L.N., J.P.F.); Department of Radiological Sciences, David Geffen School of Medicine, UCLA, Los Angeles, CA (K.-L.N., C.T.W., A.E.P., J.P.F.); Division of Pediatric Cardiology, Department of Pediatrics, David Geffen School of Medicine, UCLA Mattel Children's Hospital, Los Angeles, CA (M.S., G.M.S.); Division of Cardiac Surgery, Department of Surgery (G.S.V.A.) and Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology (Y.A.), David Geffen School of Medicine, UCLA, Los Angeles, CA and Molecular Biology Institute, University of California, Los Angeles, CA (Y.A.).

Sources of Funding

Y.A. is supported by National Institutes of Health K12 HD000849 by the Eunice Kennedy Shriver National Institute of Child Health & Human Development and American College of Obstetricians and Gynecologists, as part of the Reproductive Scientist Development Program and the Burroughs Wellcome Fund. K.L.N. is supported by grant funding from the National Institutes of Health (R01HL148182, R01HL127153) and the Veterans Health Administration (I01CX001901, I01CX002208).

Disclosures

Y.A. has served as a consultant to Mirvie. The remaining authors have no disclosures to report.

REFERENCES

1. Oster ME, Lee KA, Honein MA, Riehle-Colarusso T, Shin M, Correa A. Temporal trends in survival among infants with critical congenital heart defects. *Pediatrics*. 2013;131:e1502–e1508. doi: 10.1542/peds.2012-3435
2. Schneider PD, Groner A. Understanding the limitations of fetal cardiac imaging. *NeoReviews*. 2018;19:e134–e142. doi: 10.1542/neo.19-3-e134
3. Cloete E, Bloomfield FH, Sadler L, de Laat MWM, Finucane AK, Gentles TL. Antenatal detection of treatable critical congenital heart disease is associated with lower morbidity and mortality. *J Pediatr*. 2019;204:66–70. doi: 10.1016/j.jpeds.2018.08.056
4. Scott M, Neal AE. Congenital heart disease. *Prim Care*. 2021;48:351–366. doi: 10.1016/j.pop.2021.04.005
5. Quartermain MD, Pasquali SK, Hill KD, Goldberg DJ, Huhta JC, Jacobs JP, Jacobs ML, Kim S, Ungerleider RM. Variation in prenatal diagnosis of congenital heart disease in infants. *Pediatrics*. 2015;136:e378–e385. doi: 10.1542/peds.2014-3783
6. Donofrio MT, Moon-Grady AJ, Hornberger LK, Copel JA, Sklansky MS, Abuhamad A, Cuneo BF, Huhta JC, Jonas RA, Kirshnan A, et al. Diagnosis and treatment of fetal cardiac disease. *Circulation*. 2014;129:2183–2242. doi: 10.1161/01.cir.0000437597.44550.5d
7. Sun L, Marini D, Saini B, Schrauben E, Macgowan CK, Seed M. Understanding fetal hemodynamics using cardiovascular magnetic resonance imaging. *Fetal Diagn Ther*. 2020;47:354–362. doi: 10.1159/000505091
8. Roy CW, Marini D, Lloyd DFA, Mawad W, Yoo SJ, Schrauben EM, Jaeggi E, Seed M, Macgowan CK. Preliminary experience using motion compensated CINE magnetic resonance imaging to visualise fetal congenital heart disease. *Circ Cardiovasc Imaging*. 2018;11:e007745. doi: 10.1161/CIRCIMAGING.118.007745
9. Al Nafisi B, van Amerom JF, Forsey J, Jaeggi E, Grosse-Wothmann L, Yoo SJ, MacGowan CK, Seed M. Fetal circulation in left-sided congenital heart disease measured by cardiovascular magnetic resonance: a case–control study. *J Cardiovasc Magn Reson*. 2013;15:65. doi: 10.1186/1532-429X-15-65
10. Sørensen A, Peters D, Simonsen C, Pedersen M, Stausbol-Gron B, Christiansen OB, Lingman G, Uldbjerg N. Changes in human fetal oxygenation during maternal hyperoxia as estimated by BOLD MRI. *Prenat Diagn*. 2013;33:141–145. doi: 10.1002/pd.4025
11. Sun L, Macgowan CK, Sled JG, Yoo SJ, Manlhiot C, Porayette P, Grosse-Wortmann L, Jaeggi E, McCrindle BW, Kingdom J, et al. Reduced fetal cerebral oxygen consumption is associated with smaller brain size in fetuses with congenital heart disease. *Circulation*. 2015;131:1313–1323. doi: 10.1161/CIRCULATIONAHA.114.013051
12. Porayette P, Madathil S, Sun L, Jaeggi E, Grosse-Wortmann L, Yoo SJ, Hikey E, Miller SP, Macgowan CK, Seed M. MRI reveals hemodynamic changes with acute maternal hyperoxygenation in human fetuses with and without congenital heart disease. *Prenat Diagn*. 2016;36:274–281. doi: 10.1002/pd.4762
13. Xu J, Duan AQ, Marini D, Lim JM, Keunen J, Portnoy S, Sled JG, McCrindle BW, Kingdom J, Macgowan CK, et al. The utility of MRI for measuring hematocrit in fetal anemia. *Am J Obstet Gynecol*. 2020;222:81.e1–81.e13. doi: 10.1016/j.ajog.2019.07.016
14. Lloyd DFA, van Amerom JFP, Pushparajah K, Simpson JM, Zidere V, Miller O, Sharland G, Allsop J, Fox M, Lohezic M, et al. An exploration of the potential utility of fetal cardiovascular MRI as an adjunct to fetal echocardiography. *Prenat Diagn*. 2016;36:916–925. doi: 10.1002/pd.4912
15. 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;39:231–235. doi: 10.1111/cpf.12566
16. Ryd D, Fricke K, Bhat M, Arheden H, Liuba P, Hedström E. Utility of fetal cardiovascular magnetic resonance for prenatal diagnosis of complex congenital heart defects. *JAMA Netw Open*. 2021;4:e213538. doi: 10.1001/jamanetworkopen.2021.3538
17. 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;10:12373. doi: 10.1038/s41598-020-69375-3
18. Lloyd DFA, Pushparajah K, Simpson JM, van Ameron JFP, van Poppel MPM, Schulz A, Kainz B, Deprez M, Lohezic M, Allsop J, 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;393:1619–1627. doi: 10.1016/S0140-6736(18)32490-5
19. Lloyd DFA, van Poppel MPM, Pushparajah K, Vigneswaran TV, Zidere V, Steinweg J, van Ameron JFP, Roberts TA, Schulz A, Charakida M, et al. Analysis of 3-dimensional arch anatomy, vascular flow, and postnatal outcome in cases of suspected coarctation of the aorta using fetal cardiac magnetic resonance imaging. *Circ Cardiovasc Imaging*. 2021;14:e012411. doi: 10.1161/CIRCIMAGING.121.012411
20. Haris K, Hedström E, Bidhult S, Testud F, Maglaveras N, Heiberg E, Hansson SR, Arheden H, Aletras A. Self-gated fetal cardiac MRI with tiny golden angle iGRASP: a feasibility study. *J Magn Reson Imaging*. 2017;46:207–217. doi: 10.1002/jmri.25599
21. Jansz MS, Seed M, van Amerom JFP, Wong D, Grosse-Worthmann L, Yoo SJ, Macgowan CK. Metric optimized gating for fetal cardiac MRI: metric optimized gating for fetal cardiac MRI. *Magn Reson Med*. 2010;64:1304–1314. doi: 10.1002/mrm.22542
22. Roberts TA, van Amerom JFP, Uus A, Lloyd DFA, van Poppel MPM, Price AN, Tournier JD, Mohanadass CA, Jackson LH, Malik SJ, et al. Fetal whole heart blood flow imaging using 4D cine MRI. *Nat Commun*. 2020;11:4992. doi: 10.1038/s41467-020-18790-1
23. Berggren K, Ryd D, Heiberg E, Aletras AH, Hedström E. Super-resolution cine image enhancement for fetal cardiac magnetic resonance imaging. *J Magn Reson Imaging*. 2022;56:223–231. doi: 10.1002/jmri.27956
24. Seed M, van Amerom J FP, Yoo SJ, Nafisi BA, Grosse-Wortmann L, Jaeggi E, Jansz MS, Macgowan CK. 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;14:79. doi: 10.1186/1532-429X-14-79
25. Roy CW, Seed M, van Amerom JFP, Al Nafisi BA, Grosse-Wortmann L, Yoo SJ, Macgowan CK. Dynamic imaging of the fetal heart using metric optimized gating. *Magn Reson Med*. 2013;70:1598–1607. doi: 10.1002/mrm.24614
26. Kording F, Yamamura J, de Sousa MT, Ruprecht C, Hedstrom E, Aletras AH, Grant PE, Powell AJ, Fehrs K, Adam G, et al. Dynamic fetal cardiovascular magnetic resonance imaging using Doppler ultrasound gating. *J Cardiovasc Magn Reson*. 2018;20:17. doi: 10.1186/s12968-018-0440-4
27. Ryd D, Sun L, Steding-Ehrenborg K, Bidhult S, Kording F, Ruprecht C, Macgowan CK, Seed M, Aletras AH, Arheden H, 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;21:74. doi: 10.1186/s12968-019-0586-8
28. De Groote K, Vanhie E, Roets E, Ramaekers P, De Wilde H, Panzer J, Vandekerckhove K, Bove T, Francois K, Van Herck K, et al. Outcome after prenatal and postnatal diagnosis of complex congenital heart defects and the influence of genetic anomalies. *Prenat Diagn*. 2017;37:983–991. doi: 10.1002/pd.5117
29. Morton SU, Quiat D, Seidman JG, Seidman CE. Genomic frontiers in congenital heart disease. *Nat Rev Cardiol*. 2022;19:26–42. doi: 10.1038/s41569-021-00587-4
30. Chang CS, Hong SY, Kim SY, Kim YM, Sung JH, Choi SJ, Oh SY, Roh CR, Song J, Huh J, et al. Prevalence of associated extracardiac anomalies in prenatally diagnosed congenital heart diseases. *PLoS One*. 2021;16:e0248894. doi: 10.1371/journal.pone.0248894
31. Dovjak GO, Zalewski T, Seidl-Mlczoch E, Ulm PA, Berger-Kulemann V, Weber M, Prayer D, Kasprian GJ, Ulm B. Abnormal extracardiac

development in fetuses with congenital heart disease. *J Am Coll Cardiol*. 2021;78:2312–2322. doi: 10.1016/j.jacc.2021.09.1358
32. Rabbat MG, Kwong RY, Heitner JF, Young AA, Shanbhag SM, Petersen SE, Selvanayagam JB, Berry C, Nagel E, Heydari B, et al. The future of cardiac magnetic resonance clinical trials. *JACC Cardiovasc Imaging*. 2022;15:2127–2138. doi: 10.1016/j.jcmg.2021.07.029
33. Barison A, Baritussio A, Cipriani A, De Lazzari M, Aquaro GD, Guaricci AI, Pica S, Pontone G, Todiere G, Indolfi C, et al. Cardiovascular magnetic resonance: what clinicians should know about safety and contraindications. *Int J Cardiol*. 2021;331:322–328. doi: 10.1016/j.ijcard.2021.02.003
34. Sklansky M, Afshar Y, Anton T, DeVore GR, Platt L, Satou G. Guidance for fetal cardiac imaging in patients with degraded acoustic windows. *Ultrasound Obstet Gynecol*. 2022;59:709–712. doi: 10.1002/uog.24872
35. Wright GA, Hu BS, Macovski A. 1991 I.I. Rabi Award. Estimating oxygen saturation of blood in vivo with MR imaging at 1.5 T. *J Magn Reson Imaging JMRI*. 1991;1:275–283. doi: 10.1002/jmri.1880010303
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;78:2352–2359. doi: 10.1002/mrm.26599
37. Jansz M. Metric optimized gating for fetal cardiac MRI. Dissertation. University of Toronto; 2010. Accessed August 10, 2022. https://tspace.library.utoronto.ca/bitstream/1807/25634/1/Jansz_Michael_S_201011_MSc_thesis.pdf
38. Han F, Rapacchi S, Hu P. Prospective cardiac motion self-gating. *Quant Imaging Med Surg*. 2017;7:215–226. doi: 10.21037/qims.2017.03.02
39. Nelson TR, Pretorius DH, Sklansky M, Hagen-Ansert S. Three-dimensional echocardiographic evaluation of fetal heart anatomy and function: acquisition, analysis, and display. *J Ultrasound Med*. 1996;15:1–9. doi: 10.7863/jum.1996.15.1.1
40. Viñals F, Poblete P, Giuliano A. Spatio-temporal image correlation (STIC): a new tool for the prenatal screening of congenital heart defects. *Ultrasound Obstet Gynecol*. 2003;22:388–394. doi: 10.1002/uog.883
41. Kording F, Yamamura J, Much C, Adam G, Schoennagel B, Wedegartner U, Ueberle F. Evaluation of an MR compatible Doppler-ultrasound device as a new trigger method in cardiac MRI: a quantitative comparison to ECG. *Biomed Tech (Berl)*. 2013;58:1–2. Accessed September 7, 2013. https://www.degruyter.com/document/doi/10.1515/bmt-2013-4267/html#Vancouver