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Pregnancy and Cardiovascular Disease (N Scott, Section Editor)

Prenatal Detection of Congenital Heart Disease: the Past, Present, and Future

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Abstract

Purpose of review Prenatal diagnosis of congenital heart disease (CHD) is continuously evolving with each passing decade. Early efforts in fetal cardiology focused on identifying CHD in mid-gestation and understanding of fetal circulation in pathologic conditions. Improving prenatal detection rates for CHD remains an ongoing challenge and increasingly the field of fetal cardiology is moving to not only diagnosing CHD prenatally but also assessing the impact of prenatal diagnosis of CHD outcomes. Future directions include earlier diagnosis of fetal CHD, improved diagnostic rates, widespread sonographer education, and a better understanding of antenatal factors that impact outcomes. Our goal in this review is to describe the past, present, and future of prenatal diagnosis of CHD.
Recent findings There has been a steady improvement in the prenatal diagnosis rate for CHD; however, there remains a significant variation between countries and within the USA. Prenatal diagnosis of CHD allows for counseling and delivery planning in those fetuses with critical CHD, thereby providing parents with resources and important tools while dealing with a challenging situation of carrying a child with heart disease and helping them with important decisions for their family and their future. There are several specific conditions which continue to pose a challenge from a diagnostic standpoint as they may appear mild at the time of initial diagnosis and may be missed but progress through the pregnancy and lead to significant CHD in the neonatal period.
Summary In summary, continued efforts aimed at collaborative research and education are needed in order to be able to improve CHD detection rates. We need to cautiously assess lesions that appear minor in mid-gestation but have the potential to progress in late gestation. Earlier detection of CHD by means of a transvaginal or a first-trimester fetal echocardiogram may further help families with delivery planning and decision-making.

Introduction: Overview of prenatal diagnosis of CHD

Prenatal echocardiography allows for detection of congenital heart disease (CHD) in the fetus. The benefits of prenatal diagnosis of CHD in the fetus have been established and include the opportunity to counsel the family prior to the child's birth as well as coordination and planning of delivery at a tertiary care hospital prepared to manage CHD. There is mixed evidence on the degree to which prenatal diagnosis of CHD improves perinatal outcomes. There is some evidence indicating improvement in perinatal morbidity and possibly better neurologic outcomes with a prenatal diagnosis of select conditions; however, data on the impact on survival is conflicting [1–4]. There is also increasing interest in the epigenetics of congenital heart disease and the assessment of prenatal risk factors, both genetic and environmental, that may contribute to CHD as well as impact its outcomes.

Despite the advances made in prenatal detection of CHD, there is considerable variability in the rate of prenatal detection within the USA and around the world, even amongst nations with advanced health care capabilities and higher resource availability. The largest study to date evaluating prenatal detection rates looked at 31,374 CHD patients from 91 Society of Thoracic Surgeons (STS) Database–participating centers across the USA from 2006 to 2012 [5••]. Prenatal diagnosis rate improved over the study time period, but there was significant variation in rates of prenatal diagnosis between states (range 11.8–53.4%, $p < 0.0001$). Additionally, there was wide variation in prenatal detection rate between CHD diagnoses, ranging from 67% for hypoplastic left heart syndrome (HLHS) to 28% for total anomalous pulmonary venous connection [5••].

An earlier study evaluated data from 20 registries of congenital malformations in 12 European countries and showed an overall detection rate of 25%, again with variable rates based on regions with lower detection rates in Eastern European countries compared to Western European countries [6]. However, more recently, a large cohort study of more than 1900 fetuses from the Netherlands showed a higher detection rate of ~ 60% with nearly universal detection for HLHS (98%), compared to an earlier Dutch study reporting HLHS detection rates at 20–25%. They attributed this improvement as the effect of a national screening program [7].

A more recent international retrospective cohort study assessed prenatal diagnosis and prevalence of critical CHD from 15 institutions spanning 12 countries in Europe, Asia, North America, and South America and found that detection rates of critical CHD varied widely with the detection rate ranging from 13% in Slovak Republic to 87% in France [8].

Recent advancements

Over the last decade, the American Heart Association (AHA), American Institute of Ultrasound in Medicine (AIUM), and International Society of Ultrasound in Obstetrics and Gynecology have put forth guidelines for the diagnosis and treatment of fetal cardiac disease that have provided indications for fetal echocardiogram (Table 1) and have recommended fetal cardiac screening views extend beyond the 4-chamber view (4CV) [9••, 10, 11]. With implementation of these recommendations, there has been a consistent improvement in CHD screening by obstetricians and maternal-fetal medicine (MFM) specialists, specifically with regard to the outflow tract view and the 3-vessel view (3VV). Addition of outflow tracts and 3VV evaluation to the standard four-chamber view (4CV) increases sensitivity for detection of critical CHD to as high as 90% [9••]. The 4CV can theoretically detect > 50% of serious cardiac defects. However, it may not identify conotruncal lesions such as D-looped transposition of the great arteries (D-TGA), truncus arteriosus, and double outlet right ventricle (DORV) (Fig. 1). While the additional views of the fetal heart have been recommended as part of routine obstetric ultrasound [10, 11], challenges

Table 1. Indications for fetal echocardiogram

Fetal factors
- Suspected cardiac structural anomaly
- Suspected cardiac functional abnormality
- Persistent fetal tachycardia (>180 bpm) or bradycardia (<120 bpm)
- Suspected heart block
- Frequent irregular cardiac rhythm
- Nuchal translucency of 3.5 mm or greater or at or above the 99th percentile for gestational age
- Major extracardiac fetal anomaly
- Evidence of hydrops fetalis or effusions
- Chromosomal abnormality by cell-free fetal DNA or invasive genetic testing
- Monochorionic twinning
- Systemic venous anomaly (persistent right umbilical vein, absent ductus venosus, or left superior vena cava)
- May be considered for nuchal translucency measurement between 3 and 3.4 mm
Maternal factors:
- Pregestational diabetes
- Early (first or second trimester) gestational diabetes
- In vitro fertilization, including intracytoplasmic sperm injection
- Phenylketonuria
- Autoimmune disease with anti-SSA antibodies with or without a prior affected fetus
- First-degree relatives of a fetus with CHD
- Rubella infection
- First- or second-degree relative with disease of Mendelian inheritance and a history of childhood cardiac manifestations
- May be considered for selected teratogen exposure including lithium, carbamazepine, paroxetine, ACE inhibitors, NSAIDs, and vitamin A/isotretinoin
The following are considered "possible indications" for a fetal echocardiogram with limited data that exist to support its utility but are commonly reasons for referral such as:
- Obesity (BMI ≥ 30 kg/m^2)
- SSRI exposure other than paroxetine
- Noncardiac markers for aneuploidies in the absence of karyotype information
- Abnormal maternal serum analyses such as alpha-fetoprotein level
- Isolated single umbilical artery

remain with technical skills and expertise required for obtaining and interpreting these views [12].

The 3VV has been demonstrated as a clinically useful supplemental to the 4CV for screening of CHD as it allows visualization of major abnormalities with the outflows such as arch anomalies, pulmonary artery hypoplasia, or atresia, and is easier to obtain for the sonographer (Fig. 2). The 3VV has been recommended as a part of the NHS Fetal Anomaly Screening Program (FASP) since 2015. A recent study showed a sixfold increase in referrals for a fetal echo due to

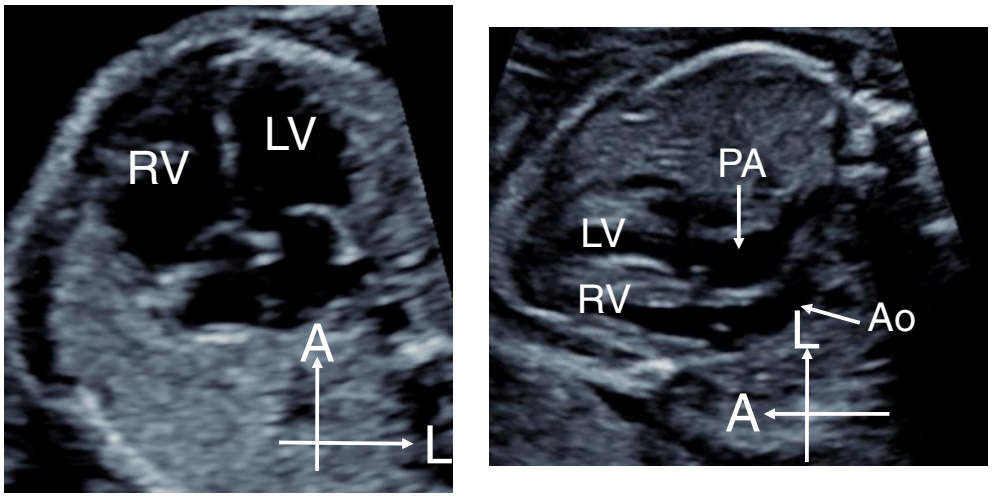

Fig. 1. Fetal D-loop transposition of the great arteries. Panel **a**, normal 4-chamber view. Panel **b**, the diagnosis is clear from outflow tract view showing parallel course of the aorta (Ao) arising anteriorly right ventricle (RV) and pulmonary artery (PA) posteriorly from the left ventricle (LV).

an abnormal 3-vessel view in response to the new recommendations [13]. With the advancement of ultrasound technique, increased recognition of minor variations and anomalies such as a left superior vena cava (LSVC), right aortic arch (RAA), aberrant subclavian arteries, and isolated aortic or pulmonary dilation has occurred.

Areas for improvement

Despite the advances described above, prenatal diagnosis of CHD continues to pose a challenge with room for improvement in lesions not visible in the 4CV

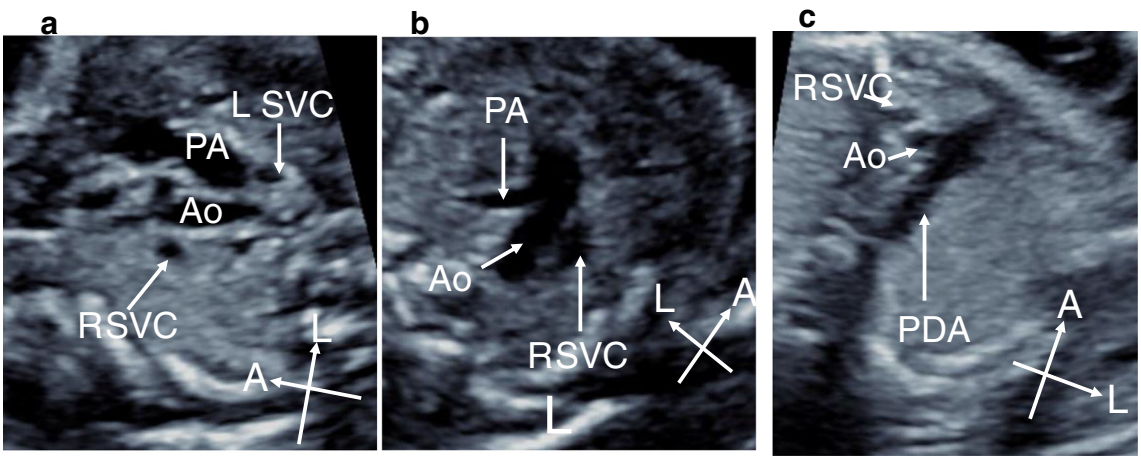

Fig. 2. Examples of abnormalities detected using the 3-vessel view. Panel **a**, left superior vena cava resulting in 4 visible vessels in this view. Panel **b**, hypoplastic transverse aorta raising concern for postnatal aortic coarctation. Panel **c**, truncus arteriosus in which aorta and pulmonary arteries arise from a common root and only 2 vessels in this view. L SVC, left superior vena cava; PA, pulmonary artery; Ao, aorta; R SVC, right superior vena cava; PDA, patent ductus arteriosus; A, anterior; L, left.

and those that may be subtly abnormal or even normal at the time of mid-gestation screening but progress through mid- and late gestation such as isolated aortic stenosis (AS) and pulmonary stenosis (PS). A study evaluating the natural history of neonates with critical AS found that only 10/117 (9%) neonates with critical AS were diagnosed prenatally and detection rate did not improve over time [14]. This persistent, abysmally low detection rate is likely related to the evolving nature of fetal AS. In many cases of fetal AS, the 4CV is fairly normal in mid-gestation but the findings progress through gestation with worsening LV function, LV dilation, endocardial fibroelastosis, and in some cases retrograde aortic arch flow. Detection of mid-gestation fetal AS can be subtle, particularly in cases with preserved left ventricular function, but incorporation of Doppler flow velocity measurement across the aortic valve and careful assessment for thickened or dysplastic aortic valve leaflets, a dilated aorta, and endocardial fibroelastosis should allow identification of mid-gestation fetal AS (Fig. 3).

Similar to AS, isolated PS is also a difficult diagnosis to make in utero given its progressive nature. In a recent study of 91 fetuses with postnatal diagnosis of critical PS, the prenatal detection rate was only 37% [14]. Features associated with this diagnosis include thickened or dysplastic pulmonary valve leaflets, a dilated main pulmonary artery, increased Doppler velocity across the right ventricular outflow tract or pulmonary valve, and pulmonary regurgitation (Fig. 4) [14, 15]. In more severe cases, there may be bidirectional or reversal of flow across the ductus arteriosus. Additional findings that should warrant consideration of the diagnosis of fetal PS include right atrial dilation, right ventricular hypertrophy, and tricuspid regurgitation [16]. In a study of the natural history of PS in 23 fetuses, diagnosed at 14–17 weeks' gestation, there was a diverse spectrum of outcomes. At their initial scan, 8 fetuses were noted to have an isolated finding of high flow velocity across the pulmonary valve and 12 fetuses demonstrated aliasing across the pulmonary valve. Of the 12, outcomes were as follows: 2 were normal, 8 had mild to moderate pulmonary stenosis postnatally, and 2 developed right ventricular hypoplasia and pulmonary atresia at their 19–20 weeks' scan [15].

In both fetal AS and PS, it is important to underscore the importance of Doppler interrogation of the outflow tracts in addition to 2D visualization, as this may not be routinely performed in a routine obstetric scan, and can result in a missed or delayed diagnosis, with potentially adverse perinatal outcomes. Other findings such as ventricular hypertrophy, atrial dilation, thickened valve leaflets, and ductal and foramen flow direction are helpful but typically require a higher level of expertise (Figs. 3 and 4).

Dilemmas of prenatal CHD diagnosis

The ability of fetal echocardiography to diagnosis select CHD remains limited and controversial. Prenatal diagnosis of coarctation of the aorta (CoA) remains difficult, despite multiple studies attempting to predict the development of ductal-dependent CoA. A number of scoring systems aimed at developing a successful mechanism of prediction have been proposed [17–20]. A primary limitation of the current models and clinical practice is a high rate of false positives (i.e., prenatal concern for CoA with no CoA postnatally once the patent ductus arteriosus has closed), reported to be as high as 25–30% in mid-gestation [21], and even as high

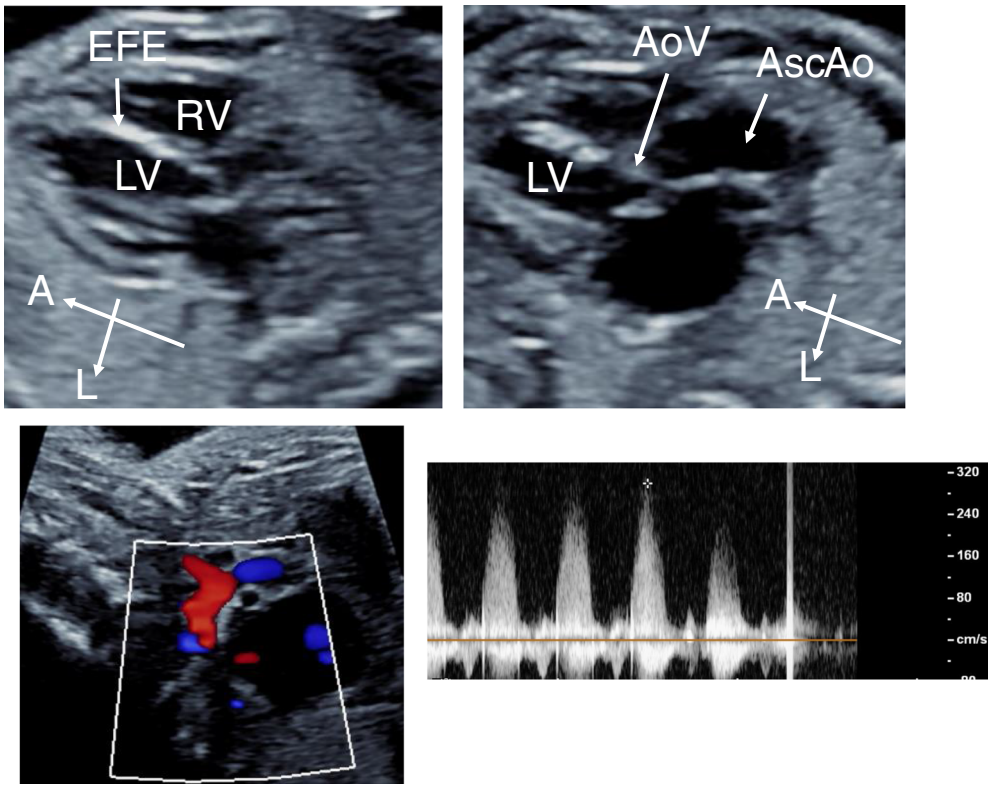

Fig. 3. Characteristic findings in severe fetal aortic stenosis. Panel **a**, 4-chamber view showing normal-sized left ventricle with evidence of endocardial fibroelastosis involving the ventricular septum. Panel **b**, thickened aortic valve leaflets and dilated ascending aorta. Panel **c**, retrograde flow in the aortic arch. Panel **d**, Doppler velocity measured across the aortic valve showing elevated flow velocity at ~ 3 m/s. RV, right ventricle; LV, left ventricle; EFE, endocardial fibroelastosis; A, anterior; L, left; Aov, aortic valve; Asc Ao, ascending aorta.

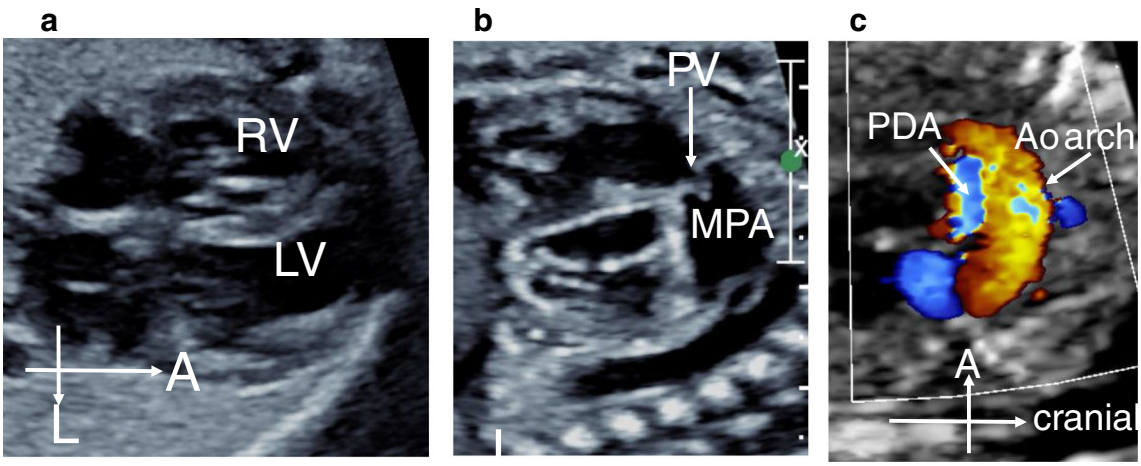

Fig. 4. Characteristic findings in pulmonary atresia/intact ventricular septum. Panel **a**, 4-chamber view showing right ventricular hypertrophy. Panel **b**, thickened pulmonary valve leaflets that do not open and dilated main pulmonary artery. Panel **c**, retrograde flow in patent ductus arteriosus. RV, right ventricle; LV, left ventricle; A, anterior; L, left; PV, pulmonary valve; MPA, main pulmonary artery; PDA, patent ductus arteriosus.

as 60–80% in late gestation [18, 22]. This can result in prolonged hospitalization for observation with resultant parental anxiety, and at times subjecting a neonate to a neonatal intensive care unit stay, unnecessary exposure to prostaglandin, and delayed oral feeding as well as increased high resource utilization. On the other hand, missed diagnosis of CoA can result in the neonate developing compromised systemic perfusion, cardiogenic shock, and associated ventricular dysfunction [23].

A systematic review and meta-analysis looking at the risk factors for CoA on prenatal ultrasound showed that the mitral valve, aortic valve, and aortic isthmus (Ao) diameter were significantly lower in fetuses with CoA compared to normal, and the tricuspid and pulmonary valve diameter *z*-score was significantly higher in CoA fetuses. When comparing various ratios, the right ventricle/left ventricle (RV/LV) and pulmonary artery/ascending aorta (PA/AAo) diameter ratios were higher and the Ao-to-duct diameter was lower in fetuses who developed CoA. This study also found that a persistent LSVC, presence of a ventricular septal defect, and/or bicuspid aortic valve were not associated with an increased risk whereas the presence of a coarctation shelf was more common in fetuses with CoA. However, a different meta-analysis reported that CoA was associated with an isolated LSVC in 21% cases [24]. A hypoplastic aortic arch was independently associated with the occurrence of CoA with a sensitivity of 90% and specificity of 87%. The presence of a coarctation shelf, which can be difficult to detect and a subjective finding, had high specificity of ~ 98% but low sensitivity [25].

In general, the sensitivity of fetal diagnosis of CoA varies from 50 to 70% [21]. The changes that occur from fetal to postnatal circulation may preclude a higher prenatal diagnostic accuracy. However, the factors mentioned provide red flags that should trigger delivery planning and postnatal observation in fetuses with possible CoA. In cases of possible prenatal CoA, a postnatal "coarctation watch" that includes assessment of upper and lower extremity pulses for a delay or diminished pulsations, and a blood pressure gradient between the right arm and legs, along with serial echocardiograms to evaluate the aortic arch appearance and gradient as well as the abdominal aortic Doppler flow profile, is warranted.

Future of prenatal CHD diagnosis

Moving forward, continued education of our maternal-fetal medicine and obstetric colleagues as well as sonographers is needed in order to improve diagnostic accuracy and capabilities. The barriers to earlier fetal diagnosis of CHD continue to be pushed, with first-trimester echocardiography (performed between 12 and 16 weeks) and transvaginal ultrasound gaining traction for earlier diagnosis of CHD, particularly related to the implementation of first-trimester nuchal translucency screening and early serum screening for aneuploidy risk [26, 27]. A study of late first-trimester fetal echocardiography revealed that complete visualization of the 4-chamber view and great arteries could be achieved in ~ 77% of cases when performed by operators with varying levels of experience [28]. A meta-analysis evaluating early CHD detection at ≤ 14 weeks showed detection rates of ~ 53% [29]. More recently, fetal echocardiography has been performed as early as 8 weeks using transabdominal and transvaginal ultrasound with the availability of high-frequency transabdominal and transvaginal ultrasound probes. In a study aimed at evaluating the efficacy of early fetal echocardiograms in 261 fetuses, a 4-chambered heart could be identified in 52%, 80%, and 98% by the eighth, tenth, and eleventh

week respectively. Both outflow tracts could also be imaged from 11 to 13 weeks and both the arches were seen in > 80% using color Doppler in the 11th week. They concluded that the ideal timing of a complete early fetal echocardiogram, excluding pulmonary vein assessment, appears to be after 11 weeks' gestation [30].

Factors affecting early detection include operator skills and limitations of the equipment. The biggest advantage of earlier diagnosis is the time and opportunity that it provides to families for decision-making, which can be more limited when diagnosis is made in mid-gestation. However, the pitfalls of earlier diagnosis should be recognized as well, such as conditions which are not evident until later in pregnancy (cardiac tumors, and cardiomyopathies, or those that progress through pregnancy) [26]. We anticipate that earlier fetal echocardiograms will be performed more routinely in the future in high-risk groups where it may be beneficial and where the objectives of the scan are clearly outlined.

Lastly, with artificial intelligence (AI) and deep learning seeping into most other aspects of life, the use of AI in the detection of fetal cardiac abnormalities is developing. An ongoing study is evaluating deep learning using an ensemble model to identify recommended cardiac views, distinguish between normal hearts and complex CHD, and the use of segmentation models to calculate standard fetal cardiac measurements. The early results of this new technology have been encouraging excellent recognition of lesions such as hypoplastic left heart syndrome and tetralogy of Fallot [31].

Conclusion

In conclusion, significant progress was made in the field of fetal echocardiography and prenatal detection of CHD as a result of the combined efforts of the obstetricians, maternal-fetal medicine specialists, pediatric cardiologists, and sonographers. However, there remains room for considerable improvement with continued focus on education and implementation of best practice guidelines especially in areas with inadequate resources, in order to reduce the numbers of missed diagnoses. Vigilance is needed for detection of forms of CHD that appear minor in mid-gestation but have the potential to progress and cause adverse consequences if not adequately detected. There are also exciting developments to look forward to in the future with the hope of achieving success in earlier detection and the utility of AI in fetal CHD.

Compliance with Ethical Standards

Conflict of Interest

Priyanka Asrani declares that she has no conflict of interest. Kevin Friedman declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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