REVIEW

EDUCATIONAL SERIES IN CONGENITAL HEART DISEASE
Prenatal diagnosis of congenital heart disease

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Abstract

This review article will guide the reader through the background of prenatal screening for congenital heart disease. The reader will be given insight into the normal screening views, common abnormalities, risk stratification of lesions and also recent advances in prenatal cardiology.

Key Words
▸ congenital heart disease
▸ prenatal diagnosis
▸ fetal cardiology
▸ echocardiography

Introduction

Cardiac abnormalities occur with an estimated incidence of approximately 5–6 per 1000 live-born infants and are the most common group of congenital malformations (1, 2, 3, 4). Most affected children will be born to mothers with no identifiable risk factors for congenital heart disease (CHD). Data from the mid-to-late 20th century published by the World Health Organisation indicated that heart defects accounted for approximately 40% of infant deaths attributable to congenital abnormalities (5). Congenital cardiac surgery has provided a 'revolution' in the treatment and management of patients with CHD, and the introduction of deep hypothermic arrest in the 1970s meant that primary repair of congenital cardiac defects became a reality. Prior to this, intervention had been mainly palliative, for example the Blalock Tausig Shunt introduced in 1945. Since then, there has been a sustained improvement in surgical outcomes, currently surgical 30-day and 1-year survival in the United Kingdom for the arterial switch procedure for isolated transposition of the great arteries was 100% and 96.7% respectively (2013–2014 data) https://nicor4.nicor.org.uk/. This is in comparison to the natural history of transposition of the great arteries, where without intervention, survival at

1 month and 1 year of life was recorded at 48.4% and 10.7% respectively (6).

The majority of fetuses affected by CHD do not exhibit signs of heart failure *in utero* as nutrition and oxygen are provided to the fetus by the placental circulation. As the lungs are not needed for oxygenation, blood is deviated from the lungs via two fetal shunts: the foramen ovale and arterial duct (Fig. 1). In most cases it is only after birth and following transition from the fetal to postnatal circulation with closure of these fetal shunts, that the symptoms of major CHD become evident. Any critical obstruction to the left side of the heart will lead to systemic hypo-perfusion and acidosis in the presence of a duct dependent systemic circulation, for example, hypoplastic left heart syndrome (HLHS), critical aortic stenosis and coarctation of the aorta. Likewise, any critical obstruction to the right side of the heart will lead to significant cyanosis, a duct dependent pulmonary circulation, for example pulmonary atresia. Closure or restriction of the foramen ovale can lead to severe cyanosis and collapse in the context of transposition of the great arteries (TGA), where the systemic and pulmonary circulations work in parallel and mixing of oxygenated and deoxygenated
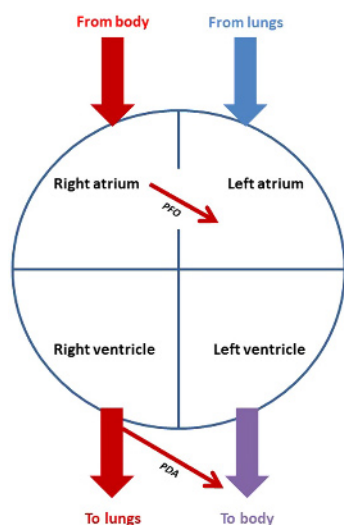
Figure 1
Schematic of the fetal circulation. PDA, patent ductus arteriosus; PFO, patent foramen ovale.

blood at the foramen ovale level is vital for survival. Major CHD is defined as pathology which requires intervention within the first year of life and includes many other forms of cardiac anomalies to those described above. Septation defects, for example large ventricular septal defects (VSDs) or atrioventricular septal defects (AVSDs), result in symptoms of breathlessness and failure to thrive following the physiological drop in pulmonary vascular resistance and increased pulmonary blood flow that occurs during the first few weeks of life.

Population screening for CHD clearly fulfils screening criteria in regions where cardiac surgery and cardiac catheter intervention is available (7, 8). CHD is an important health problem, with known natural history and accepted treatments and as discussed, CHD can be detected *in utero*, at a latent stage, with a suitable and accepted screening test in the form of antenatal ultrasound.

The use of ultrasound in screening for CHD

Prenatal cardiac screening was introduced in the mid-1980s when the four-chamber view of the heart was incorporated into the routine obstetric scan between 18 and 22 weeks gestation (9). Since that time, screening programmes have developed incorporating views to assess the outflow tracts and more recently blood vessels in the upper mediastinum (10). A landmark study by Yagel *et al.* proposed examination of the fetal heart by five transverse views, which are currently used for cardiac screening.

Other views used in transthoracic echocardiography can be obtained, for example, parasternal short, long axis and sagittal arch views, but take more practice and are mainly reserved for assessment by those trained specifically in fetal cardiology. Despite this, most cardiac anomalies can be diagnosed using the five transverse views proposed by Yagel and are the cornerstone of fetal echocardiography (10).

Historically, only the four-chamber view of the heart was assessed, however, addition of the outflow tracts enables detection of major cardiac anomalies that have a normal four-chamber view, for example tetralogy of Fallot and TGA. This extension of the screening views has led to significant improvement in antenatal detection rates. A UK study by Bull *et al.* over a 3-year period (1993–1995), identified an average national detection rate of 25% (11); this study only included CHD detected during pregnancy which required cardiac intervention within the 1st year of the child's life. In comparison, following the introduction of the outflow tract views by the National Fetal Anomaly Screening Program (FASP) the detection rate of CHD was as high as 45% (12). Despite this improvement, both studies highlight a significant variation in detection rates within regions of the United Kingdom. Gardiner *et al.* demonstrated that local 'champions' improve the likelihood of detection and confirms that sonographer training is critical for improving detection rates (13, 14). In 2015, the three-vessel and tracheal (3VT) view was added to the UK screening protocol in a bid to increase detection of major CHD, including coarctation of the aorta (12, 15).

Prenatal screening for CHD has shown improvement; however, there are limitations in the form of raised maternal BMI, placental position, liquor volume, fetal position and the presence of multiple fetuses. In addition, secundum atrial septal defects and patent ductus arteriosus are vital structures within the fetal circulation and their closure cannot be predicted by fetal echocardiography. Finally, there are lesions that remain a diagnostic challenge even in the hands of an experienced fetal echocardiographer: total anomalous pulmonary venous drainage (TAPVD); coarctation of the aorta (CoA) and progressive valvar abnormalities.

Echocardiographic views for the diagnosis of CHD

Fetal echocardiography is not for the impatient and with both time and patience diagnostic data can usually be
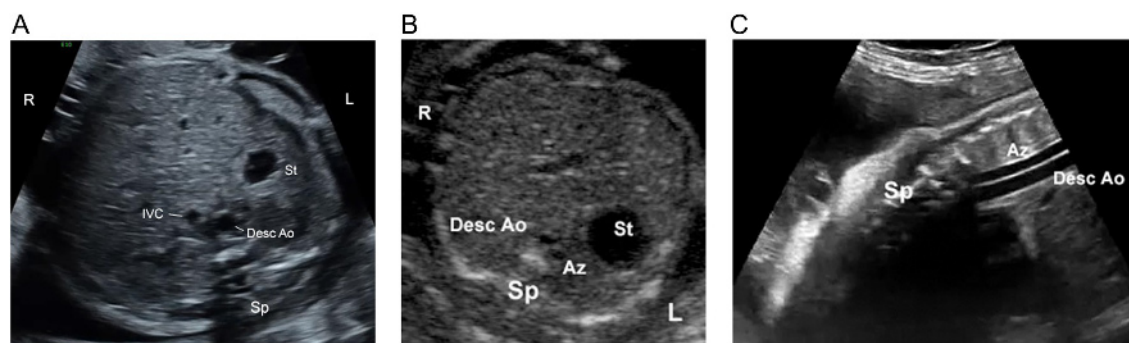
Figure 2
(A) Normal cardiac situs. (B) Situs view of left atrial isomerism with the azygos vein lying posterior and on the same side as the aorta. (C) Sagittal view of the azygous vein in parallel to the spine and descending aorta. Az, azygous; Desc Ao, descending aorta; IVC, inferior vena cava; Sp, spine; St, stomach.

obtained. The highest resolution probe should be used to clarify anatomical detail, which can be problematic in the presence of an elevated maternal BMI or in late gestation when lower frequency probes with better penetration are required to visualise the heart. Image optimisation is essential with appropriate alteration in sector width, focus position and zoom. Fetal movements, particularly in early gestation, can add to the challenge. In the United Kingdom, assessment of the fetal heart is incorporated into the FASP, which is offered to all pregnant women between 18 and 22 weeks of gestation. The five key views include cardiac situs; four-chamber view; left ventricular outflow tract view; right ventricular outflow tract view/3 vessel view (3VV) and the three-vessel and tracheal view (3VT) (9). In the hands of an experienced fetal echocardiographer, the five key views are interrogated with the addition of more advanced screening techniques. These techniques and views include PW Doppler and colour Doppler assessment of the AV valves; aortic and pulmonary valves; pulmonary and systemic venous connections; rhythm and rate assessment by M-mode and Doppler techniques and 2D and colour assessment of the ductal and aortic arch in the longitudinal plane.

Cardiac situs

Before assessing the heart it is essential to determine which is the right and left side of the fetus. This may take practice as the fetus can lie in any position within the maternal abdomen: cephalic; breech; transverse and in early gestation may be constantly moving. In a transverse plane of the fetal abdomen, assessment of the great vessels and position of the stomach are used to determine the atrial arrangement. In normal atrial arrangement, the fetal stomach and aorta lie to the left, with the inferior vena cava (IVC) anterior and to the right (Fig. 2A) (Video 1).

If the configuration is reversed, we assume mirror-imaged atrial arrangement (situs inversus). In the presence of right atrial isomerism, the IVC and aorta usually lie on the same side of the spine, which can be difficult to detect prenatally. Right atrial isomerism is often associated with more complex intra-cardiac abnormalities (16). In the presence of left atrial isomerism, the IVC is interrupted and continues as the azygous vein, passing posterior to the aorta, behind the heart and draining superiorly to the superior vena cava (SVC) (Fig. 2B and C). Many fetuses with an abnormal cardiac situs view have abnormal intracardiac anatomy; however, in the presence of left atrial isomerism (LAI), there may be isolated azygous continuation of the IVC to SVC, which does not require cardiac intervention. Fetuses with LAI are at risk of conduction defects and should be monitored for the development of bradycardia and complete heart block, which significantly alters the pre and postnatal prognosis (17, 18).

Video 1

Normal cardiac situs. View Video 1 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0027/video-1.

Four-chamber view of the heart

A single rib should be visualised around the fetal thorax to ensure that the transverse cut is 'on axis'. In the normal fetus, the apex of the heart lies to the left and should be deviated approximately 40–45° to an imaginary line between the fetal spine and sternum (Fig. 3). Abnormal fetal heart position may indicate an extra-cardiac anomaly, for example congenital diaphragmatic hernia or a hypoplastic lung, deviating the heart towards one side of the chest (19, 20). In addition, deviation of the cardiac axis towards the left of the thorax should raise suspicion of an intracardiac problem, for example a conotruncal
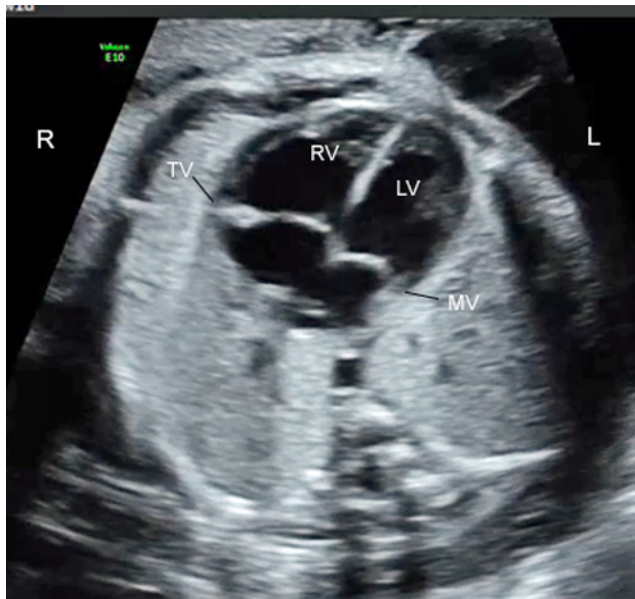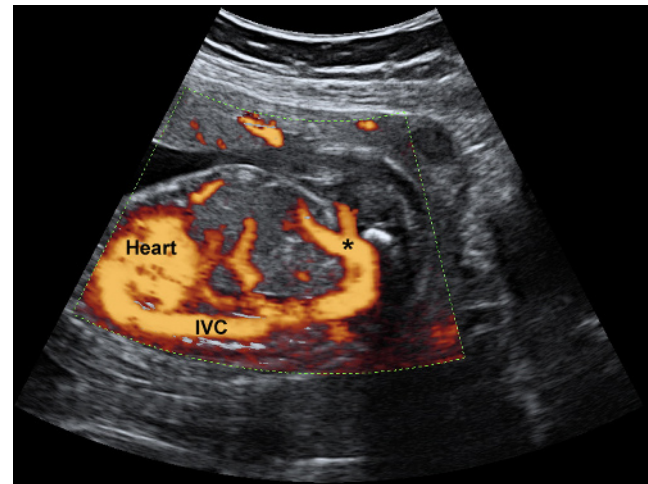
Figure 3
Balanced four-chamber view. LV, left ventricle; MV, mitral valve; RV, right ventricle; Sp, spine; TV, tricuspid valve.

Figure 4
Sagittal view of an absent ductus venosus; the umbilical vein is draining directly into the iliac veins and the inferior vena cava is significantly dilated. IVC, inferior vena cava; *, umbilical vein.

abnormality: Tetralogy of Fallot or common arterial trunk (21). Due to the nature of the fetal circulation, the presence of a severe abnormality on one side of the heart will be compensated for by the other and therefore prenatal heart failure is rare. Critical heart failure in the fetus presents as hydrops, defined as fluid accumulation in two or more fetal compartments: pleura; abdomen; skin; pericardium +/− excess amniotic fluid. In this situation, the fetus should be assessed for evidence of impaired cardiac function; an intracardiac abnormality or an extra-cardiac abnormality for example, fetal anaemia or an AV malformation.

Cardiomegaly, when the heart encompasses greater than a third of the fetal thorax, can also be a sign of heart failure. A fetus with an absent ductus venosus, where the umbilical vein drains directly into the iliac veins or directly into the heart, is a rare but important anomaly of the fetal circulation. Normally the ductus venosus controls the amount of blood flow to the heart from the umbilical veins and absence of this structure can result in right heart volume over-load and lead to heart failure (22, 23) (Fig. 4). In the scenario of an absent ductus venosus, early delivery, thereby removing the fetal circulation, cures the heart failure but is at the cost of prematurity. Another cause of prenatal heart failure and hydrops is the presence of fetal Ebstein's malformation of the tricuspid valve and tricuspid valve dysplasia. In severe cases the right atrium is hugely dilated due to severe tricuspid valve regurgitation. The presence of pulmonary regurgitation, forming a circular shunt, is poorly tolerated both pre and postnatally (24, 25).

The size of the left and right-sided chambers should be balanced, and a moderator band is seen in the right ventricle, with 'off-setting' of the atrioventricular valves (Video 2). Off-setting describes the position of the tricuspid and mitral valves; the tricuspid valve lies slightly closer to the apex of the heart than the mitral valve. Lack of off-setting of the AV valves can indicate an AVSD. Detection of an AVSD in a fetus, raises the suspicion of chromosomal anomalies in up to 80%, in particular trisomy 21, but also lethal syndromes such as trisomy 18 and 13 (26, 27). The ventricular septum should be intact, therefore interrogating the septum at least 30 degrees from the ultrasound beam prevents 'drop-out' that may masquerade as a VSD. In the fetal circulation, VSDs can be challenging to detect on colour flow Doppler as the left and right heart pressures are almost equal. Figure 5 illustrates a fetus with an AVSD, there is loss of off-setting of the atrioventricular valve and a globular appearance of the heart.

Video 2
Normal four-chamber view, balanced ventricles, normal AV valve offset. View Video 2 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0027/video-2.

A discrepancy in length and width dimensions of the right and left ventricles is known as ventricular disproportion. Significant disproportion between the
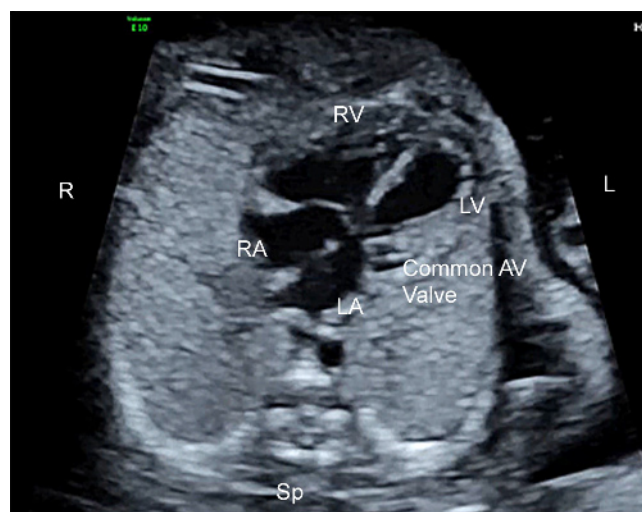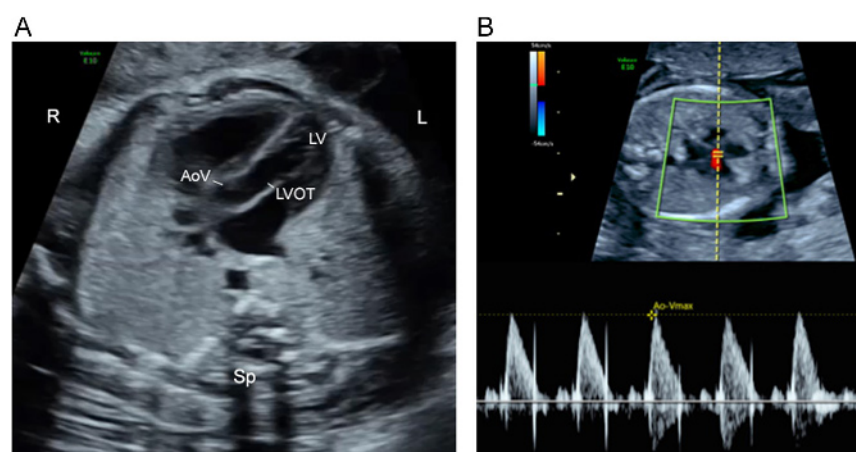
Figure 5
Four-chamber view of an atrioventricular septal defect (AVSD). There is a primum atrial septal and ventricular septal defect, with loss of 'off-setting' of the AV valve, indicating a common atrioventricular junction. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; Sp, spine.

right and left sides of the heart is readily detected at the second trimester scan and accounts for the high antenatal detection of fetuses with functionally univentricular circulations (28, 29, 30). However, ventricular disproportion is often more subtle and serial scans are needed throughout pregnancy to assess the development of the heart structures. In this scenario, particular attention should be paid to ensure the pulmonary veins are not draining anomalously and that the aortic arch is not hypoplastic or diminutive towards the isthmus, suggesting a coarctation/arch hypoplasia. When assessing disproportion it is always important to consider the gestation, as the optimal time for assessment of the fetal heart is usually between 18 and 28 of weeks gestation and

right heart dominance is a normal physiological feature in the third trimester. Therefore, assessment of the heart in the latter stages of pregnancy is more challenging, with the additional effect of relatively limited echocardiographic windows.

Left ventricular outflow tract view

As the echocardiographer sweeps cranially from the transverse plane of the four-chamber view, the left ventricular outflow tract (LVOT) is delineated. The LVOT arises from the centre of the fetal heart continuing as the ascending aorta and sweeping towards the right shoulder of the fetus (Fig. 6A) (Video 3). The aortic valve leaflets should be seen to move freely without evidence of dysplasia. The use of colour flow Doppler and pulsed-wave (PW) Doppler across the aortic valve identifies colour flow aliasing or an increased Doppler velocity, which may represent progressive valvar stenosis (31) (Fig. 6B). Careful valvar examination should be undertaken in certain circumstances: the presence of a family history of valvular abnormalities; the recipient twin affected by twin-to-twin transfusion syndrome where pulmonary valve obstruction may occur and in the presence of more complex intracardiac abnormalities (32, 33). A repeat fetal echo in the third trimester may be warranted in these conditions to identify evidence of a progressive valve lesion. Although the aforementioned techniques may be applied, valvar lesions remain challenging to detect at the mid-trimester screening scan and can progress insidiously throughout gestation. Even in the presence of a developing critical aortic stenosis, the four-chamber view at the mid-gestation screening scan may be relatively normal and thus the lesion remains undetected (34).

Figure 6
(A) Left ventricular outflow tract. Continuity of the ventricular septum and the aortic valve. (B) Aortic valve Doppler. AoV, aortic valve; LV, left ventricle; LVOT, left ventricular outflow tract; Sp, spine; Vmax, maximum velocity.

Video 3

Normal LVOT view. View Video 3 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0027/video-3.

When assessing the LVOT, the ventricular septum should be visualised in continuity with the LVOT and aortic valve; creating a continuous line from the apex of the fetal heart to the ascending aorta. Lack of continuity of the septum and LVOT indicates the presence of an outlet VSD and increases the detection of many conotruncal abnormalities, for example, tetralogy of Fallot; common arterial trunk or pulmonary atresia/VSD (Fig. 7A and B). Recognising outlet VSD's is a particular pitfall in fetal cardiology due to frequent 'drop-out' in this region of the ventricular septum and highlights the importance of interrogating the septum at least 30 degrees from the ultrasound beam. Within the subsets of the conotruncal abnormalities, there is marked heterogeneity, therefore, not only detection of the lesion, but identification of the fine anatomical details and associated extra-cardiac abnormalities is essential when providing accurate prenatal parental counselling. For example, tetralogy of Fallot is a heterogenous lesion encompassing mild right outflow tract obstruction to pulmonary atresia. In the severest spectrum of pulmonary atresia/VSD, there may be absence of intra-pericardial pulmonary arteries, and the pulmonary blood supply arises from major aorto pulmonary collateral arteries (MAPCAs). This severe morphology alters the prenatal parental counselling and the surgical course in the postnatal period.

Right ventricular outflow tract view

As the transducer is tilted cranially, the right ventricular outflow tract (RVOT) arises anteriorly from the fetal heart, continuing straight back towards the spine as the arterial duct (Fig. 8A). Normally the right pulmonary artery (RPA) is seen to arise from the main pulmonary artery (MPA)

extending into the lung parenchyma. Rarely both branch PAs are viewed simultaneously. Akin to the aortic valve, the pulmonary valve leaflets should be seen to move freely with normal colour flow and PW Doppler imaging (Fig. 8B). It is essential that the RVOT and LVOT are not visualised in the same transducer plane or in 'parallel' (Fig. 9), either in the transverse or the sagittal views, as this may represent TGA. Identification is important as evidence has shown that prenatal detection of TGA reduces preoperative morbidity and mortality (35).

Three-vessel view and three-vessel tracheal view

As the echocardiographer tilts the transducer cranially in the transverse plane, the vessels lying in the upper mediastinum are identified, traditionally described as the three-vessel view (3VV) (10). In the normal fetal heart, the vessels in order from left to right are PA, aorta and SVC (Video 4) (Fig. 10A). The MPA, continuing back towards the spine as the arterial duct, is visualised in longitudinal section, to the right the aorta and SVC are visualised in cross section. The arterial duct and aorta are of relative size with slight reduction in calibre to the SVC. To increase identification of CHD, the 3VV is examined carefully for the number of vessels present: two, three or four and also for evidence of size discrepancy and finally the order of the vessels (Fig. 10B, C and D). Two vessels may represent TGA; four vessels may represent bilateral SVCs. Any abnormality in the 3VV should trigger the fetal echocardiographer to retrace their steps to the four-chamber view; LVOT and RVOT to ensure an associated abnormality has not been overlooked.

Video 4

Normal 3VT. MPA continuing directly back to the spine as the arterial duct. Aorta and SVC in cross section and of equal dimensions. View Video 4 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0027/video-4.
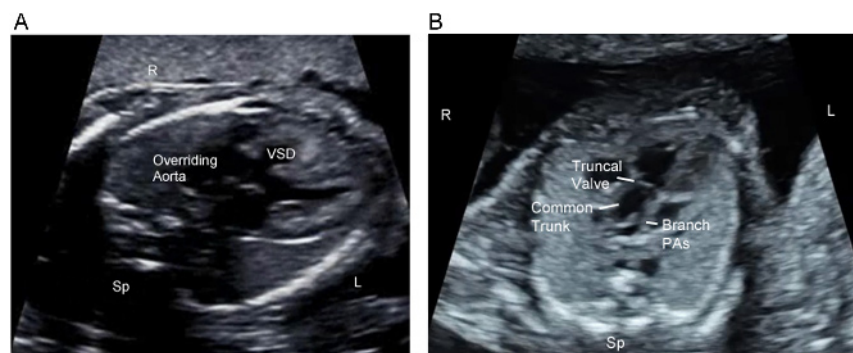
Figure 7
Lack of continuity of the septum and LVOT indicates the presence of an outlet VSD in the presence of (A) tetralogy of Fallot (B). Common arterial trunk, with the pulmonary arteries arising from the trunk. PAs, pulmonary arteries; Sp, spine; VSD, ventricular septal defect.
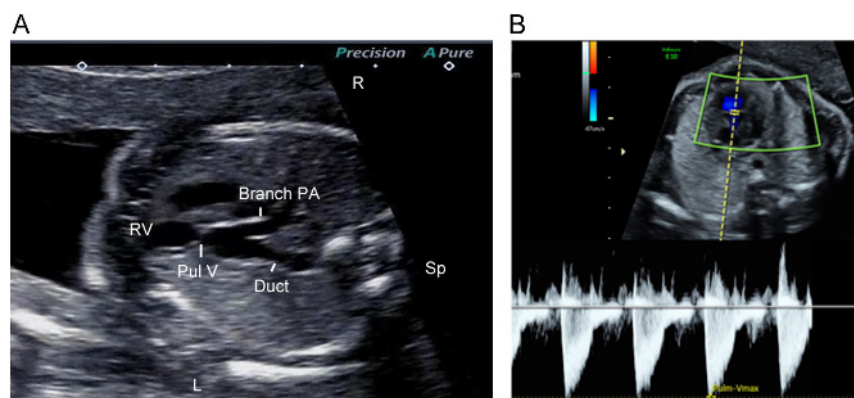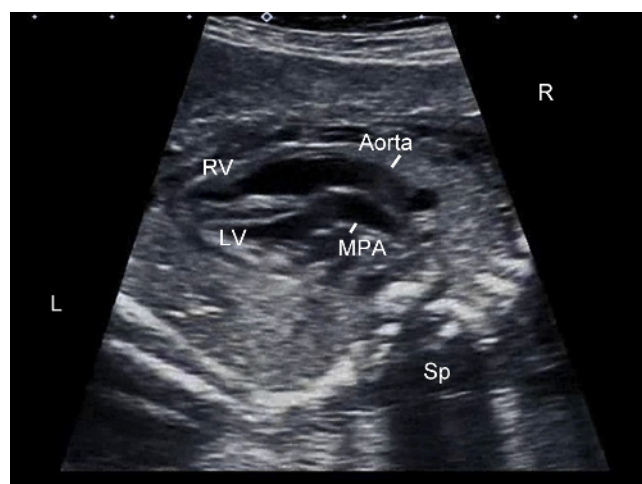
Figure 8
(A) Right ventricular outflow tract, continuing towards the spine as the arterial duct. (B) Normal pulmonary valve Doppler. PA, pulmonary artery; PulV, pulmonary valve; RV, right ventricle; Sp, spine; Vmax, maximum velocity.

Moving cranially from the 3VV, the three-vessel tracheal view (3VT) is visualised. This view incorporates the transverse aortic arch, the aortic isthmus and the arterial duct (12, 32, 36, 37). The aortic isthmus is defined as the segment of the aortic arch distal to the left subclavian artery and proximal to the insertion of the arterial duct (Video 5). Examination of the 3VT allows for assessment of the dimensions of the transverse aortic arch in the longitudinal plane but also the course of the aortic arch or the arch 'sidedness', left or right, in relation to the fetal trachea. In the normal fetal heart, the transverse aortic arch is seen in the longitudinal plane, passing to the left of the trachea, meeting the arterial duct at the isthmus, forming a classic 'V' shape of a left aortic arch (LAA) (Fig. 11A and B). A right aortic arch (RAA) is formed embryonically from abnormal regression of the primordial paired aortic arches (Video 6). The RAA is detected by prenatal echocardiography as the arterial duct on the left and the aortic arch passing to the right of the trachea and creating a 'U' shape in the upper mediastinum (38) (Fig. 11C). Prevalence in the 'low-risk' population is estimated between 0.05 and 0.1% and in some case series as high as 0.35% (39, 40, 41). A RAA can readily be detected when examining the 3VT during the mid-trimester screening scan, occurring as an isolated finding; as a variant of normal or in association with congenital anomalies: intracardiac, extra-cardiac and chromosomal abnormalities. As detection increases the significance and management of an isolated RAA remains controversial. The presence of a right arch with a right arterial duct does not constitute a vascular ring, and may go undetected prenatally. Detection of a RAA warrants referral to fetal cardiology for detailed assessment to exclude an intra-cardiac abnormality, for example, Tetralogy of Fallot or heterotaxy syndromes (12). Chromosomal abnormalities, most commonly 22q.11.2 deletion (Di George syndrome), are associated with a RAA and have been reported as high as 15–40% in some published series (42, 43, 44). Thus, evidence of an intra-cardiac abnormality; extra-cardiac abnormality; double aortic arch or a RAA with an aberrant left subclavian artery warrants parental counselling and discussion regarding the option of invasive prenatal testing to exclude a chromosomal abnormality. Conversely, in the absence of extra-cardiac or intracardiac abnormalities 22q.11.2 deletion is reported in only 0–4% of cases (42, 45). Therefore, in the presence of an isolated RAA, the risk of invasive testing may outweigh the incidence of a chromosomal abnormality (46).

Figure 9
Aortic arch and pulmonary artery arising in parallel from the ventricular mass indicating transposition of the great arteries. LV, left ventricle; MPA, main pulmonary artery; RV, right ventricle; Sp, spine.

Video 5
Normal 3VT. Left aortic arch forming a classic V shape. View Video 5 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0027/video-5.
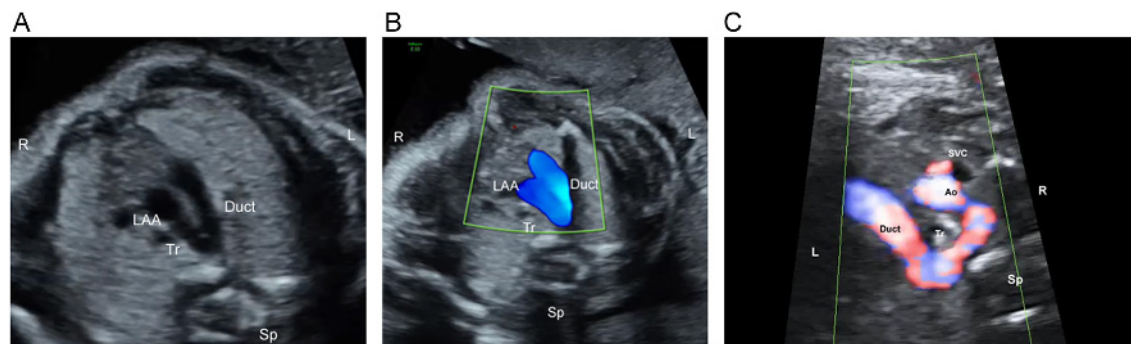
Figure 10
(A) Normal 3VV in the upper mediastinum. (B) Abnormal 3VV in the presence of transposition of the great arteries, only two vessels seen in the upper mediastinum. (C) Abnormal 3VV view illustrating bilateral SVCs with a persistent left sided superior vena cava (LSVC). Ao, aortic arch; DA, ductus arteriosus; LSVC, left superior vena cava; MPA, main pulmonary artery; PA, pulmonary artery; Sp, spine; SVC, superior vena cava; Tr, trachea.

Video 6
Right aortic arch, classic 'U' shape. View Video 6 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0027/video-6.

In addition to the arch sidedness, the 3VT has improved the prenatal detection of vascular rings due to abnormal branching patterns of the aortic arch (40, 47, 48, 49). RAA with a left arterial ductal ligament and an left aberrant subclavian artery has been reported in around 12–25% of patients presenting with a vascular ring (50). Vascular rings are a heterogenous group of congenital anomalies caused by several morphological mechanisms that can result in oesophageal, or more commonly, symptoms of tracheobronchial compression (51, 52). Greater than 60% of children referred for vascular ring surgery present with significant stridor; however, recent evidence may suggest that asymptomatic compression can occur during the first two years of life when the delicate cartilaginous rings of the airway are developing (51, 53). Although associated

morbidity and mortality following surgical resection of a vascular ring is low (54), some children have persistent symptoms of airway compression postoperatively (52), thus hypothesising that this may be related to a delay in repair and irreversible damage to the airways. A recent report identified that 91% of asymptomatic patients known to have a prenatal RAA and vascular ring had evidence of airway compression evident on postnatal bronchoscopy (53). In these circumstances surgical repair of the vascular ring was undertaken to relieve compression of the delicate, developing cartilaginous rings in a bid to prevent potential long term airway and GI sequelae (53). This is a highly controversial subject and due to the paucity of evidence and varying management strategies, a population-based study assessing outcome of children with prenatal diagnosis of isolated RAA would help us understand the significance of this finding *in utero*. Currently, the largest series is a systematic review and meta-analysis of prenatal detection of the RAA that identified that 25% of infants demonstrated symptoms

Figure 11
(A) 3VT view. Left aortic arch, both arches pass to the left of the trachea to form a classic 'V' shape. (B) Colour flow Doppler of a left aortic arch, antegrade flow (blue) in both vessels. (C) Colour flow Doppler of an isolated right aortic arch, the aortic arch passes to the right of the trachea and the ductal arch to the left, forming a classic 'U' shape. LAA, left aortic arch; Sp, spine; SVC, superior vena cava; Tr, trachea.

of airway compression or oesophageal symptoms, 17% of which required surgical intervention (55).

Less controversial is the management of vascular rings in the form of double aortic arches which can be successfully identified in the prenatal population. A double aortic arch is formed when the bilateral fourth embryonic aortic arches and dorsal aortic roots fail to regress (49). The right arch is dominant in 70%, therefore identification of a RAA during the second trimester scan warrants a repeat echocardiogram later in gestation to exclude aberrant subclavian vessels or a diminutive, but patent left arch (49, 56). Postnatally, identification of a double arch can be more challenging as the arterial duct transitions to its ligamentum form, with no antegrade flow, providing a diagnostic challenge even by cross sectional imaging (49). Rarely a double aortic arch can present as airway obstruction in the fetus, so called 'congenital high airways obstruction syndrome'. The appearance of bright lungs during the sonographic scan may indicate obstruction of the airway as a result of intrinsic airway defects or in the case of a double aortic arch, external airway compression (57).

Effect of prenatal diagnosis on outcome and risk stratification

Congenital heart defects remain the commonest of congenital anomalies and sadly without prenatal diagnosis some children die before assessment at a tertiary cardiac centre (58). With increasing centralisation of paediatric cardiac services and geographical challenges it is essential to provide risk stratification for all prenatally detected cardiac lesions. Each lesion encompasses a heterogenous subset, therefore, risk stratification includes timing of delivery; location of delivery; neonatal management plan and attendance of appropriate clinicians at or within the first few hours of delivery (59). Prenatal diagnosis of a congenital cardiac lesion allows engagement with the multidisciplinary team so optimal management can be planned. Input from fetal and maternal medicine specialists, midwives, cardiac nurse specialists, neonatologists and geneticists is beneficial. Identification of additional extra-cardiac and genetic abnormalities is also crucial and can often determine the final outcome.

Prenatal detection of certain cardiac lesions, for example AVSD, has not shown to alter morbidity or mortality in the neonatal period, but due to the association

of extra-cardiac and chromosomal abnormalities detection allows for complete and informative prenatal counselling. As previously mentioned many subsets of the cardiac lesions are heterogenous, for example tetralogy of Fallot can range from well-developed branch pulmonary arteries (PAs) to complete absence of intra-pericardial PAs, in the form of pulmonary atresia/VSD and MAPCAs. The surgical management is markedly different and parents must be counselled as accurately as possible to allow them to make informed decisions. Risk stratification of tetralogy of Fallot is not only important in predicting the immediate and long term medical management but discussing known chromosomal abnormalities, in particular 22q11.2 deletion. The implications of detecting 22q.11.2 deletion include a wide spectrum of enhanced learning needs, immune dysfunction, hypocalcaemia and in the longer term psychiatric comorbidities (60).

In the context of critical CHD, identifying neonates in whom immediate cardiac intervention will be required at the time of delivery or within the first 24 h of life, is essential to reduce morbidity and mortality (61, 62, 63). Lesions that are deemed to be a form of critical CHD include: duct dependent lesions; obstructed TAPVD; HLHS or TGA with restrictive atrial septum and some cases of congenital complete heart block. The use of intravenous prostaglandin can delay the need for intervention in most, but not all, duct dependent lesions.

The strongest evidence for prenatal detection of CHD in reducing postnatal morbidity and mortality is most evident in TGA. Prenatal detection of TGA has been shown to reduce the incidence of preoperative metabolic acidosis; reduce the length of inpatient hospital admission and the incidence of acute neurological injury (35) (Video 7). Although a neonate with a prenatal diagnosis of TGA can be commenced early on prostaglandin to maintain ductal patency or undergo a balloon atrial septostomy (BAS) to increased mixing at the level of the atrial septum, despite this appropriate and timely intervention a mortality rate of 4% is reported as a result of significant pulmonary hypertension (64). In a bid to predict the likelihood of requiring an urgent balloon atrial septostomy (BAS), studies have assessed ductal flow; the anatomy of the atrial septum – including flow, degree of hypermobility or atrial aneurysm, but all have shown limited predictive value. However, more recent work by Vigneswaran *et al.*, assessing the ratio of the foramen ovale (FO) length: total septal length (TSL), identified that neonates with a FO:TSL >0.5 are unlikely to require an urgent BAS (65).

Video 7

Transposition of the great arteries. Pulmonary artery arising posteriorly from the LV, aorta from the RV anteriorly. Only two vessels seen in the upper mediastinum. View Video 7 at http://movie-usa. glencoesoftware.com/video/10.1530/ERP-18-0027/video-7.

Conversely, some studies have suggested that prenatal diagnosis of HLHS, a duct dependent lesion, does not impact upon the surgical mortality (66, 67, 68, 69). However, patients with a postnatal diagnosis, that sadly died before reaching a tertiary cardiac centre, were not included in the datasets. In addition more complex and severe abnormalities are often detected in the prenatal population, resulting in parents opting not to continue the pregnancy or the pregnancy resulting in an intrauterine death. However, it has been reported that if women with a prenatal diagnosis of HLHS are delivered within or close to a cardiac centre, mortality rates are lower than after a postnatal diagnosis and delivery in a geographical remote location (30). In addition a cohort of infants with HLHS will have a restrictive atrial septum and require urgent decompression of the left atrium or immediate placement upon cardiopulmonary bypass in the delivery suite (Fig. 12A and B) (Videos 8 and 9). Predicting atrial restriction allows for prenatal discussion and planning, ensuring the most appropriate and experienced personnel are present at delivery. Prenatally, pulmonary venous Doppler waveforms are assessed in a bid to demonstrate evidence of severe atrial restriction. Absent diastolic forward flow, a 'to fro' pattern in the pulmonary venous waveform; or ratio of the velocity time integrals of antegrade pulmonary venous flow against retrograde flow from the left atrium, 3:1 being the upper limit of normal, are indicators of prenatal restriction (70, 71). Although immediate intervention provides a short term solution for left atrial restriction, there is increasing evidence that prolonged exposure to left atrial hypertension in fetal life results in irreversible damage to the pulmonary microvasculature, evident on fetal MRI, so called nutmeg lung (72). In the longer term these microvasculature changes limit the success of the Fontan circulation.

Video 8

Mitral and aortic atresia of hypoplastic left heart syndrome. View Video 8 at http://movie-usa. glencoesoftware.com/video/10.1530/ERP-18-0027/video-8.

Video 9

Retrograde filling of the aortic arch (red) and antegrade filling of the ductal arch (blue) in HLHS. View Video 9 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0027/video-9.

Historically, prenatal detection of CoA is a diagnostic challenge due to the nature of the fetal circulation in the presence of the arterial duct, and remains an antenatal suspicion with postnatal confirmation (73, 74, 75). Assessment of the distal aortic arch in the 3VT is undertaken in a bid to increase prenatal detection. Suspicion of coarctation may be raised in the presence of ventricular disproportion, great artery disproportion, or a calibre change at the isthmus visible on the 3VT or sagittal views (76, 77) (Fig. 13A and B). In the presence of cardiac disproportion other cardiac and extra-cardiac differential diagnoses must also be considered, for example: TAPVD; or a persistent left superior vena cava (LSVC). Certainly marked ventricular or great artery disproportion in the second trimester scan will increase the rate of detection; however, in later pregnancy it can be difficult to diagnose as right ventricular dominance is a normal feature of the third trimester scan (73). Failing to recognise CoA can have implications for morbidity and mortality, as this is a duct
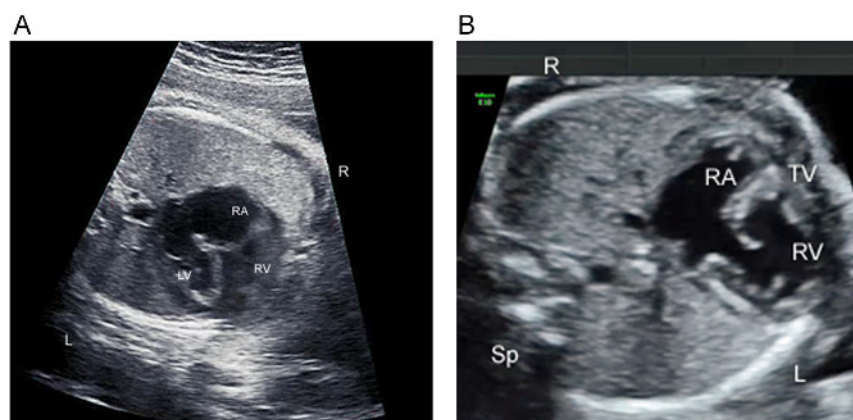
Figure 12
(A) Four-chamber view of the heart, an echogenic left ventricle in the context of HLHS. (B) HLHS, dominant right heart structures with no discernible mitral valve or left ventricle. LV, left ventricle; RA, right atrium; RV, right ventricle; TV, tricuspid valve.
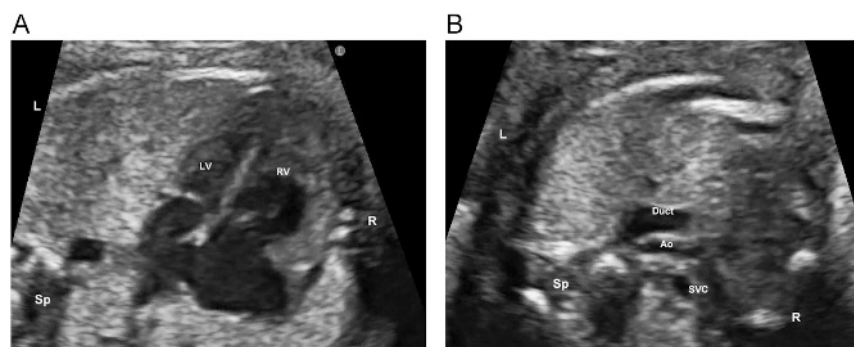
Figure 13
(A) Ventricular disproportion in the 4 chamber view. (B) 3VT view illustrating aortic arch hypoplasia and likely coarctation of the aorta. Ao, aorta; LV, left ventricle; RV, right ventricle; Sp, spine, SVC, superior vena cava.

dependent lesion and comes under the guise of critical CHD (61, 78). If there is a prenatal suspicion the infant should be closely observed in the special care baby unit as the arterial duct closes ensuring no cardiovascular compromise occurs and in the presence of a confirmed coarctation, prostaglandin E is commenced to maintain ductal patency until surgical repair is performed. There is further evidence to suggest that all infants with a prenatal suspicion of CoA should be monitored in the outpatient setting during the first year of life to ensure a delayed CoA does not develop (79). However, more recent studies have attempted to use non-traditional adjuncts to improve diagnosis in the form of myocardial deformation and fetal MRI (80, 81). Utilising deformation techniques, the left ventricular (LV) global systolic longitudinal strain and diastolic and systolic strain rate were shown to be reduced in fetuses with CoA, compared to gestational matched controls (80).

Prenatal diagnosis and neurodevelopmental outcomes

Historically prenatal counselling has focused on surgical outcomes and associated abnormalities that impact upon the short and medium term outcomes. However, as more children with CHD are surviving into adulthood increasing focus has been placed upon long term neuro developmental outcomes and as such are frequently discussed during prenatal counselling sessions. It is increasingly evident that the neurodevelopment prognosis for children with CHD is multifactorial and accumulative from fetal life to adulthood. These factors include: genetic and epigenetic factors, which account for around 30% of the neurodevelopmental outcomes in CHD (82); fetal haemodynamics and fetal circulation; gestational age at delivery; complexity of CHD; exposure to cardiopulmonary bypass; parent child relationships; and parental perception of their child's illness (83). At term, the brain of an infant with CHD is known to be

developmentally immature and smaller when compared to a term baby unaffected by CHD (84, 85). Prolonged exposure of the fetal brain to abnormal haemodynamics results in abnormal maturation and white matter injury more akin to a preterm infant. Therefore timing of delivery is critical, particularly if the already fragile neonatal brain is subsequently exposed to the rigours of cardiopulmonary bypass (84, 86, 87, 88, 89). A 'brain sparing' phenomenon has been observed in fetuses with placental insufficiency, shown by a reduction in the middle cerebral artery pulsatility index. This 'brain sparing' effect has also been witnessed in fetuses with CHD, but despite this potentially protective phenomenon some infants with CHD demonstrate impaired brain growth and development secondary to lower cerebral oxygenation and lower nutritional content of the cerebral blood (90, 91). Long term follow up studies have demonstrated that children with CHD have a lower than average outcome in several neurodevelopmental domains: executive function; psychomotor; literacy; numeracy and processing (92, 93, 94). Conversely McCusker et al. found no statistical difference in verbal reasoning scores or general IQ. Positively, children with CHD have been shown to have increased resilience; however, maternal perceptions of the severity of the child's condition has a greater influence on psychological outcomes than the medical personnel's perception of the severity of the disease (83, 95, 96). Thus there are pre-set factors, but also variables in which early intervention has the potential to positively improve the long term neurodevelopmental outcome of children with CHD (92, 83).

Emerging technologies

First-trimester cardiac screening

As previously discussed CHD is usually identified between 18 and 22 weeks during the second trimester screening ultrasound scan. First-trimester screening ultrasound

scans are performed in early pregnancy to confirm the fetal heartbeat; identify multiple pregnancies; estimate date of delivery and aid screening for chromosomal anomalies. Nuchal translucency (NT) is the ultrasound appearance of the fluid filled space at the back of the fetal neck and is measured between 11–13 weeks and 6 days. First-trimester NT screening is utilised to increase identification of fetuses at risk of genetic abnormalities, in particular at high risk of trisomy 21 (97). Subsequently an additional association with fetal CHD was recognised and observed to be independent of fetal karyotype (98). Initial data suggested that the majority of CHD would be detected by using the 99th percentile of NT as a threshold for triggering the need for a detailed fetal echocardiogram (99). This would clearly have significant resource implications due to the number of fetuses that would be included in this group. In view of pressure on resources, other screening markers have been proposed to refine the detection of CHD in early pregnancy, these include the presence of tricuspid valve regurgitation, and absent or reversal of the a-wave flow in the ductus venosus (100, 101). Studies have demonstrated that altered ductus venosus flow pattern may infer a threefold increase in the incidence of CHD in chromosomally normal fetuses (102).

Technological advances have improved the ability to detect CHD earlier in gestation, either by the transabdominal or transvaginal approach. First-trimester screening is technically challenging due to multiple fetal movements and reduced image resolution. Due to the progressive nature of certain CHD lesions, the four-chamber and outflow tract views may appear relatively normal in early gestation, but in the presence of a progressive obstructive lesion the growth and development of the cardiac structures will be severely affected (103, 104, 105, 106). In many developed countries, first-trimester fetal echocardiography has been reserved for assessing women considered 'high risk' of having a baby with CHD. Even in the presence of a normal first-trimester scan, most units will re-evaluate the fetal heart in the second trimester. In some regions of the world first-trimester fetal echocardiography is used for population screening of CHD. Jicinska *et al*. analysed the impact of first-trimester screening on the spectrum of CHD detected later in pregnancy, and on the outcome of fetuses and children born alive with CHD (107). First-trimester screening had a significant impact on the spectrum of CHD and on the outcomes of pregnancies with CHD diagnosed in the second trimester. Early detection of severe forms of CHD and significant comorbidities resulted in an increased rate of termination of pregnancy during the first trimester.

The most recent and significant advance in prenatal screening has been the introduction of non-invasive prenatal testing (NIPT) (108). This involves detection of fetal DNA in a maternal blood sample and is a highly sensitive and specific test for Down syndrome and the lethal chromosomal syndromes trisomy 13 and 18 (109). In the UK the economic argument for first-trimester screening is based on the early detection of important chromosomal problems, to date screening has involved assessing the NT by ultrasound thereby increasing detection of fetuses at risk of CHD. Therefore, the introduction of NIPT has implications on the early detection of CHD if replacing NT screening scans.

Fetal cardiac intervention

Fetal echocardiography enables detection of cardiac lesions prenatally, but can any benefit be gained from fetal intervention for CHD? The first report of fetal therapy for a cardiac abnormality was an attempt to pace a hydropic baby with congenital complete heart block (110). One of the most successful forms of fetal cardiac intervention is transplacental pharmacological treatment of fetal tachyarrhythmia (111, 112). Supraventricular re-entry tachycardia, atrial flutter and, very rarely, ventricular tachycardia can occur in the fetus and if incessant result in fetal hydrops and subsequent in utero demise. The mainstay of diagnosis of a fetal arrhythmia is by auscultation and ultrasound as fetal ECG/magnetography (fMCG) are mainly research techniques (113). M-mode and Doppler techniques demonstrate fetal atrial and ventricular rates and conduction patterns (Fig. 14). The mother is administered an anti-arrhythmic medication which passes across the placenta to the fetal circulation. Due to the high circulating blood volume in pregnant women, relatively high doses are required to cardiovert the fetal heart rhythm. Due to paucity of data and absence of randomised controlled trials, various combinations of maternal therapy are administered, these include: digoxin; flecainide; sotalol and amiodarone (114). There is a potential for maternal side-effects, therefore, blood levels and maternal ECGs should be monitored regularly. The aim of therapy is to either cardiovert the fetus to sinus rhythm, or rate control the fetal heart and prolong the pregnancy until the fetus reaches a viable gestation for delivery with postnatal cardioversion (111).

Fetal bradyarrhythmia in the form of congenital complete heart block (CCHB) can be secondary to structural heart disease, for example, LAI or discordant AV connections, or in the presence of maternal auto
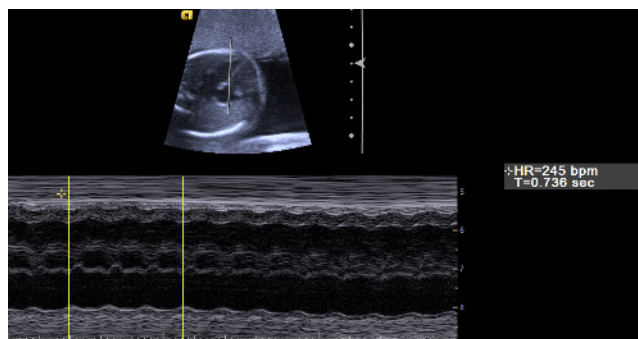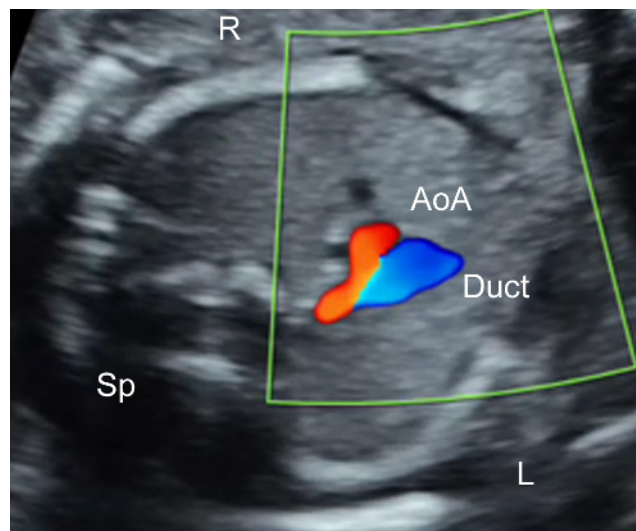
Figure 14
Fetus with supraventricular tachycardia, m-mode demonstrates 1:1 conduction with fetal heart rate of 240 bpm.

antibodies to Ro/SSA and La/SSB antibodies of susceptible fetuses (Fig. 15). In around 3% of antibody positive women, a complex autoimmune process takes place in which auto antibodies cross the placenta, damaging the fetal conduction system and cause fetal CCHB (115). Medical therapy has included prophylactic treatment with transplacental steroids, IV immunoglobulins (IVIG), hydroxycholoroquine, azathioprine, and B cell depletion in a bid to prevent damage to the fetal conduction system and thus preventing progression or development of heart block. Once CCHB has developed there is little evidence for maternal therapy, although in the presence of fetal hydrops maternal steroids may be effective (115, 116). It has been suggested that mother's with particularly high levels of anti-Ro/SSA antibodies (50–>100 U/mL) may be at increased risk of developing CCHB and should be monitored with regular fetal echocardiograms and PW Doppler assessment of the 'PR interval', known as

Figure 15
M-Mode image of congenital complete heart block, bradycardiac with complete AV dissociation.

Figure 16
Colour flow Doppler image of the great arteries in the presence of HLHS. Blue, antegrade flow in the arterial duct; red, retrograde filling of the diminutive aortic arch. AoA, aortic arch; Sp, spine.

the atrioventricular contraction time interval (AVCTI) (117, 118, 119, 120).

Fetal intervention has also been attempted for structural heart lesions. Critical aortic stenosis diagnosed in the second trimester can progress to HLHS by term (28). The rational for fetal intervention is that relieving the obstruction to the LV outflow will promote growth of the left heart structures, although technically feasible it is not clear whether intervention alters the natural history of the disease. Scoring systems, based on ultrasound findings, have been developed to predict which fetuses presenting with critical aortic stenosis at the mid-trimester scan, will progress to HLHS. Risk factors for progression include: left to right flow at the level of the atrial septum; evidence of LV dysfunction; retrograde filling of the transverse aortic arch, bidirectional flow in the pulmonary veins and a monophasic mitral valve inflow Doppler (121) (Fig. 16). Further scoring systems, in the form of the threshold scoring system, are employed to predict those who may benefit from fetal intervention, preventing progression to HLHS by term and increasing the likelihood of a biventricular repair in childhood (122, 123). Under ultrasound guidance, a needle is passed percutaneously through the maternal uterus directed towards the fetal aortic valve, followed by a coronary balloon being inflated across the valve. Freud *et al.* presented the postnatal outcomes of 100 patients undergoing fetal aortic valvuloplasty, of which 43% (*n* = 38) of all live-born patients were managed with a biventricular circulation (124). However, Gardiner *et al.* have recently challenged the scoring systems used to

identify cases of evolving HLHS showing that a substantial proportion of fetuses meeting the criteria for emerging HLHS had sustained a biventricular circulation without fetal intervention (125). Although a biventricular repair may be achieved in a highly selected population with fetal critical aortic stenosis, many survivors have evidence of persistent diastolic dysfunction; pulmonary hypertension and right heart failure in teenage years (126, 127, 128). Similar intervention in the form of prenatal pulmonary valvuloplasty in the presence of critical pulmonary stenosis has also been performed in selected centres (129). In the presence of a restrictive septum in the context of both TGA and HLHS, in utero balloon septostomy and stenting has been described (130, 131). However, stenting in the context of HLHS seems to have little impact on ultimate survival. Conversely in the context of TGA, a recent case report has suggested in high risk cases that an *in utero* septostomy may reduce the need for an emergent BAS in the immediate neonatal period, followed by a successful biventricular repair (132).

Fetal cardiac MRI

2D fetal echocardiography remains an excellent screening tool due to its accuracy, widespread availability and acceptability to patients, but still has limitations in identifying certain congenital cardiac defects, in particular TAPVD; CoA and complex vascular rings with potential for compression of the surrounding airways. MRI was incorporated into the assessment of the cardiovascular system from as early as the 1980s. More recently the emergence of fetal cardiac MRI has been developed as an adjunct to two dimensional (2D) echocardiography. Unlike fetal echocardiography, fetal MRI is not limited by fetal lie; volume of liquor or an increased maternal BMI, as suboptimal ultrasound visualisation of the fetal cardiac structures has been reported as high as 50% in obese pregnant women (133). Akin to prenatal echocardiography, fetal MRI has been shown to have an excellent safety record (134). The main disadvantage of fetal MRI is availability and utility as a screening tool, thus at present fetal MRI is an adjunct in tertiary cardiac centres and in research settings. The most common referral reason or indication for fetal MRI is examination of the extra-cardiac vasculature (81). Gaur *et al.* used cardiac MRI as an adjunct to assess the aetiology of fetal malposition. Fetal MRI demonstrated a 30% increase in structural information, particular beneficial in the classification of heterotaxy/isomerism and where there was a combination of lung and cardiac pathology. In this

series, some patients diagnosed with abnormal cardiac position had an additional lung pathology not detected by fetal echo or ultrasound. The addition of fetal MRI defined the type of heterotaxy, which in turn provided more accurate prenatal counselling and postnatal management plans (20).

MRI delineates the cardiac anatomy but its accuracy is limited by fetal movements and increased fetal heart rate. Recent technical advances have been made to reduce the impact of fetal and maternal motion and improve the quality of image acquisition. The use of phased contrast MRI with metric optimised gating has been used to successfully assess fetal blood flow during the third trimester (135). Motion corrected slice volume MRI techniques have been employed in diagnostic challenges and increasingly fetal MRI has been used to create 3D models of the fetal heart (81). This has proven a particularly useful adjunct in the detection of vascular rings and prediction of suspected CoA. There is increasing evidence that fetal MRI has utility in the presence of aortic arch abnormalities; cardiac tumours; diverticuli; pulmonary vasculature and vascular rings (81). Finally the use of real-time virtual sonography, or 'fusion imaging', has been employed, where ultrasound images and MRI images are displayed synchronously. Preliminary data examining fetal CNS abnormalities has proven useful in combining the strengths of both modalities to improve diagnostic accuracy (134, 135).

Speckle tracking of the fetal heart

Advanced 2D echo techniques assessing fetal cardiac function have been employed, these include tissue Doppler imaging, and deformation imaging in the form of velocity vector imaging and speckle tracking of the fetal myocardium. Speckle tracking is a technique utilised in the assessment of fetal myocardial velocity and deformation, regionally and globally (136). This is a process through which unique speckle 'kernels' are identified during the cardiac cycle (137). Deformation imaging is feasible in the clinical setting due to the rapid acquisition and non-reliance on angle of insonation, but problems arise with the lower frame rates produced compared to tissue Doppler methods (138). Miranda *et al.* compared the patterns of fetal myocardial deformation in prenatal coarctation compared to gestational age matched controls and demonstrated a reduction in LV systolic longitudinal strain; lower systolic and diastolic strain rate in the coarctation cohort. The presence of abnormal deformation provides early insight into the explanation

for ventricular disproportion in some of these fetuses (80). More recent studies have examined the feasibility of rotational mechanics in the form of torsion and twist assessment of the fetal myocardium. The net LV twist is defined as the absolute apex-to-base difference in LV rotation, and torsion which is the base-to-apex gradient in angle rotation (139). In the normal fetal heart, basal rotation, longitudinal strain, and strain rate show minimal variation with gestational age (GA) and estimated fetal weight (EFW), but other parameters related to rotation, twist and torsion are affected by GA and EFW. Abnormal deformation is known to occur in the fetal heart in the presence of CHD but also in the presence of abnormal loading conditions, for example twin to twin transfusion syndrome (140).

Telemedicine and the role of 3/4D echocardiography

Telemedicine has been utilised in both the prenatal and postnatal setting and is particularly advantageous if the referring centre is geographically remote from the tertiary cardiac centre. In addition, a telemedicine diagnosis provides socioeconomic benefits and a reduction in travelling times over significant distances where parents require extra time away from work to incorporate travel time (141, 142). High spatial and temporal resolution images are required to ensure good-quality images are transmitted for expert review, and fetal lie and maternal BMI continue to challenge image acquisition. Referring centres have demonstrated accurate confirmation of normality in around 80% of referred cases. However, clearly demonstrating the LVOT, and in particular, continuity of the ventricular septum, remains the most challenging view for referring centres (143). Some referring centres have examined the utility of transmitting 3D datasets via telemedicine to the tertiary cardiac centre for assessment. 3D acquisition provides sequential imaging but has the disadvantage in its inability to assess myocardial function and associated functional abnormalities. Other modalities in the form of spatiotemporal image correlation (STIC) 3D and 4D, have also been used to examine the fetal heart via a telemedicine link. STIC has the advantage of allowing a general obstetrician to obtain images of the fetal heart, which can be stored offline and assessed by a fetal cardiologist. Unfortunately, the accuracy of STIC can be reduced due to the differences in acquisition and inter observer variability, and fetal movements also make acquisition challenging (144). Although it is possible to confirm normality, accurately diagnosing CHD via telemedicine brings to light other important aspects of a

fetal cardiology service: the provision of accurate diagnostic information; detailed parental counselling and ongoing parental support. Counselling via this modality has been shown to be acceptable to both the referring clinicians and parents/families and the lack of personal contact with a fetal cardiologist does not appear to be detrimental to the families (142, 145). It is important to ensure that referring clinicians retain a high level of skill to accurately demonstrate diagnostic images, thus, there are obvious benefits in providing additional teaching and support (141, 142). Supporting the referring teams is important but challenges arise in providing 'real-time' support of a telemedicine service, particularly if a large number of referral centres are linked to the tertiary centre (146).

In summary, ultrasound plays a vital role in the prenatal diagnosis of CHD, with ongoing progress in the development of newer echocardiographic techniques and other imaging technologies which may improve accuracy of diagnosis. A fetal cardiology service not only ensures accurate prenatal diagnosis of CHD with risk stratification, but a neonatal management plan to reduce morbidity and mortality, while working within the prenatal multidisciplinary team to provide a complete assessment of the fetus. It is essential to support an appropriate environment through which parents receive bespoke counselling and are able to make informed decisions and prepare for the short- and longer-term outcomes of caring for a child with CHD.

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