Seminars in Fetal & Neonatal Medicine 18 (2013) 251–260

Contents lists available at SciVerse ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Fetal heart defects: Potential and pitfalls of first-trimester detection

Asma Khalil [a], Kypros H. Nicolaides [a,b,*]

[a] Department of Fetal Medicine, St George's Hospital, University of London, UK
[b] Department of Fetal Medicine, King's College Hospital, London, UK

Keywords:
Congenital heart defects
Ductus venosus
Echocardiography
Fetal
First trimester
Nuchal translucency
Tricuspid regurgitation

SUMMARY

Congenital heart defects (CHDs) are the leading cause of infant mortality due to birth defects. In the last 15 years, with the shift in screening for aneuploidies to the first trimester, extensive research has concentrated on early screening and detection of CHDs. Early detailed assessment of the fetal heart requires a high level of expertise in early anomaly scanning and fetal echocardiography. However, the detection of major CHDs at 11–13 weeks is influenced by their association with easily detectable markers, such as the nuchal translucency, ductus venosus blood flow and tricuspid regurgitation, and a policy decision as to the objectives of this scan and the allocation of resources necessary to achieve them. The use of transvaginal ultrasound and newer techniques are likely to improve the detection rate. However, the limitations of fetal echocardiography in the first trimester must be borne in mind, and follow-up at mid-gestational echocardiography is prudent in some cases.

1. Introduction

Congenital heart defects (CHDs) account for one-third of all congenital anomalies and are the leading cause of infant mortality due to birth defects.[1] They are commonly associated with fetal aneuploidy and genetic syndromes. In the last 30 years extensive studies have reported the prenatal diagnosis of cardiac defects during the second trimester of pregnancy.[2] However, in the last 15 years, with the shift in screening for aneuploidies to the first trimester, extensive research has concentrated on early screening and detection of CHDs.[3–8] Although the primary aims of the early ultrasound scan, which takes place at 11–13 weeks of gestation, are dating of the pregnancy, detection of multiple pregnancies and screening for aneuploidies there is increasing emphasis on the early detection of major defects. The advantages of early detection of major fetal defects include the possibility of scheduling additional assessment well before the limits for legal termination, the option for an earlier and safer pregnancy termination, and, in cases with a normal scan, earlier reassurance that a major defect is unlikely to be present.[9,10]

This article reviews the detection of major cardiac defects during the first trimester of pregnancy including description of the markers which could help identify the high-risk group requiring specialist fetal echocardiography and the techniques which could improve the detection of these defects.

2. Detection rate of congenital cardiac defects in the first trimester

The results of screening studies providing data on the prevalence of cardiac abnormalities and the proportion detected in the first-trimester scan are summarised in Table 1.[3–8,11–30] In most of these studies, all abnormalities were classified by the authors as being major. Most studies included only euploid fetuses but four included fetuses with aneuploidies. The combined data on specific groups of cardiac abnormalities and their early detection in euploid fetuses from 14 studies that provided such details are presented in Table 2. The early detection rate for the most common cardiac abnormalities varied from around 51% for hypoplastic left heart to 16% for coarctation of the aorta, 18% for tetralogy of Fallot and transposition of the great arteries.[3–8,11–28]

The largest study, involving 44 859 singleton pregnancies undergoing a first-trimester ultrasound scan as part of routine screening for aneuploidies, reported that the detection rate of major CHDs was 34%.[3] The study reported that this scan led to the diagnosis of around half of the cases of double outlet right ventricle, hypoplastic left heart and transposition of the great arteries, around one-third of the cases of atrio-ventricular septal defect, coarctation of the aorta, tetralogy of Fallot and pulmonary atresia,

* Corresponding author. Address: Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, Denmark Hill, London SE5 9RS, UK. Tel.: +44 (0) 203 2998256; fax: +44 (0) 207 7339534.
E-mail address: kypros@fetalmedicine.com (K.H. Nicolaides).

1744-165X/$ – see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.siny.2013.05.004

Table 1
Screening studies reporting on the effectiveness of the first-trimester scan in the diagnosis of major fetal cardiac abnormalities.

Study	Total	Scan route	GA (weeks)	Minor defects excluded	Prevalence	Aneuploidies	Early detection	Increased NT	
								Cut-off	Prevalence
Hernádi and Töröcsik[11]	3991	TA, TV	11–14	2	1 (0.02%)	–	–	–	Not stated
D'Ottavio et al.[4]	4078	TV	13–14	2	12 (0.29%)	–	3 (25.0%)	–	Not stated
Bilardo et al.[13]	1690	TA, TV	10–14	–	4 (0.23%)	–	–	3.0 mm	2 (50.0%)
Hafner et al.[14]	4233	TA	10–14	5	14 (0.33%)	–	1 (7.1%)	2.5 mm	4 (28.6%)
Hyett et al.[12]	29 154	TA	10–14	7	43 (0.15%)	–	1 (2.3%)	95th centile	25 (58.1%)
Schwarzler et al.[19]	4523	TA	10–14	2	9 (0.20%)	–	–	2.5 mm	1 (11.1%)
Mavrides et al.[17,a]	7339	TA	10–14	2	24 (0.33%)	–	4 (16.7%)	2.5 mm	4 (16.7%)
Michailidis and Economides[18]	6650	TA, TV	10–14	2	9 (0.14%)	–	2 (22.2%)	95th centile	2 (22.2%)
Orvos et al.[20]	4309	TV	10–13	7	32 (0.74%)	–	–	3.0 mm	16 (53.3%)[b]
Taipale et al.[5]	4789	TV	10–16[c]	7	18 (0.38%)	–	1 (5.6%)	3.0 mm	4 (22.2%)
Chen et al.[6]	1609	TA, TV	12–14	5	7 (0.44%)	4 (57.1%)	4 (57.1%)	–	Not stated
Bahado-Singh et al.[21]	8167	TA	10–14	15	6 (0.07%)	–	–	2.5 mm	3 (50.0%)
Bruns et al.[22]	3664	?	11–14	11	9 (0.25%)	–	–	95th centile	2 (22.2%)
Becker and Wegner[23]	3094	TA, TV	11–14	–	11 (0.36%)	–	6 (54.5%)	2.5 mm	6 (54.5%)
Cedergren and Selbing[7]	2708	TA	11–14	6	3 (0.11%)	–	–	–	Not stated
Dane et al.[16]	1290	TA	11–14	–	1 (0.08%)	–	–	–	Not stated
Westin et al.[24,d]	16 260	TA	12–14	–	29 (0.18%)	–	–	3.0 mm	2 (6.9%)
Muller et al.[25]	4144	TA	10–14	–	13 (0.31%)	–	–	99th centile	2 (15.4%)
Chen et al.[15]	7642	TA	10–14	13	19 (0.25%)	10 (52.6%)	7 (36.8%)	–	Not stated
Oztekin et al.[26]	1805	TA	11–14	1	2 (0.11%)	–	–	95th centile	0 (0.0%)
Hildebrand et al.[27]	21 189	?	11–14	–	62 (0.29%)	–	0	–	Not stated
Syngelaki et al.[3]	44 859	TA, TV[e]	11–13	–	106 (0.24%)	–	36 (34%)	95th centile	30 (28.3%)
Volpe et al.[8]	4445	TA, TV	11–14	11	28 (0.63%)	10 (35.7%)	23 (82.1%)	95th centile	14 (50%)
Grande et al.[28]	13 723	TA, TV	11–14	80	44 (0.32%)	312 (2.2%)	25 (56.8%)	97.5th centile	16 (36.4%)

GA, gestational age; TA, transabdominal; TV, transvaginal; NT, nuchal translucency., In some of the studies, the authors included minor defects (atrial or ventricular septal defect) and functional abnormalities (tricuspid or aortic regurgitation) and in this analysis we have excluded these abnormalities.
Adapted from Syngelaki et al.[11]
[a] Includes the data published by Carvalho et al.[29] (not shown) and 25% of data of Schwarzler et al.[19]
[b] NT available in 30 of the 32 fetuses with cardiac defects.
[c] 10% of the population were above 14 weeks.
[d] Includes all data published by Westin et al.[30]
[e] TA mainly, only TV if inadequate views.

but none of the cases of ventricular septal defect, Ebstein anomaly, aortic or pulmonary stenosis, tricuspid atresia or cardiac tumours.[3]

A recent review of the published series with more than 1000 cases from 1993 to 2008, which included data from 36 237 pregnancies generated by eight centres, suggests that the overall detection rate of major congenital anomalies at 11–13 weeks is 29% (95% confidence interval: 25–33).[27] The pooled detection rate of cardiac defects was 17% (10–25%). The authors suggested that the detection rate could be improved if the ultrasound assessment at the first trimester follows well-delineated protocols.[31]

3. Approach to ultrasound examination of the heart in the first trimester

The basic principles are the same as ultrasound examination of the heart in the second or third trimester but colour flow mapping

Table 2
Studies providing details on the early diagnosis of specific cardiac abnormalities in euploid fetuses.

Cardiac abnormality	Screening study[a]														Total
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Coarctation of the aorta		0/1		0/3		0/1		0/1	2/5	0/2	0/8	4/15	0/1		6/37 (16.2%)
Tetralogy of Fallot		1/2	0/1	0/2		0/1	0/1		0/3	0/2	0/9	3/10	2/3		6/34 (17.6%)
Hypoplastic left heart		1/2	0/2	1/3				0/1	1/2	1/3	0/6	5/10	2/2	10/10	21/41 (51.2%)
Transposition of the great arteries				0/2	0/1			0/3	0/3	0/1	0/8	2/5	2/2	2/8	6/33 (18.2%)
Atrioventricular septal defect		0/3		0/7							0/2	3/9	8/9	4/5	15/35 (42.9%)
Pulmonary stenosis			0/1	0/1		0/1		0/1	0/4		0/1	0/5	1/1		1/15 (6.7%)
Aortic stenosis		1/3							0/2			0/1	2/3		3/9 (33.3%)
Tricuspid atresia	0/1								0/2			1/1	1/1		2/5 (40.0%)
Ebstein's anomaly								0/1			0/2	0/5			0/8 (0.0%)
Double outlet right ventricle					0/2							4/7			4/9 (44.4%)
Anomalous pulmonary venous return		0/1									0/1				0/2 (0.0%)
Mitral atresia											0/1		1/1		1/2 (50.0%)
Interrupted aortic arch											0/1		1/1		1/2 (50.0%)
Pulmonary atresia											0/1	1/3			1/4 (25.0%)
Double inlet left ventricle									0/1						0/1 (0.0%)
Common truncus arteriosus											0/1				0/1 (0.0%)
Ventricular septal defect	1/2			0/7	1/1	0/4		0/8	0/1	0/2	0/7	0/16	5/8		7/56 (12.5%)
Total	1/3	3/12	0/4	1/25	1/4	0/7	0/1	0/15	3/23	1/10	0/48	23/87	25/32	16/23	74/294 (25.1%)

Adapted from Syngelaki et al.[11]
[a] 1, Hernandi and Torocsic[11]; 2, D'Ottavio et al.[4]; 3, Bilardo et al.[13]; 4, Taipale et al.[5]; 5, Chen et al.[6]; 6, Cedergren and Selbing[7]; 7, Dane et al.[16]; 8, Chen et al.[15]; 9, Mavrides et al.[17]; 10, Michailidis and Economides[18]; 11, Hyett et al.[12]; 12, Syngelaki et al.[3]; 13, Volpe et al.[8]; 14, Grande et al.[28].

has a more important role in the first trimester. A systematic approach should be used which includes assessment of the fetal position and orientation, examination of the four-chamber view to assess heart size, position, chamber sizes and the crux, assessment of the tricuspid valve and slow sweep upwards towards the head from the four-chamber plane in order to identify the great arteries (Figs. 1 and 2).[32]

3.1. Assessment of the fetal position and orientation

The position of the abdominal aorta and inferior vena cava at the level of the diaphragm may be clear enough to determine the atrial situs. The stomach and cardiac apex can always be identified.

3.2. Examination of the four-chamber view

This should be assessed in both apical and transverse views. Colour flow mapping should delineate the flow into both ventricles and gives an indication of the ventricular size.

3.3. Assessment of the tricuspid valve

The presence or absence of tricuspid regurgitation (TR) is determined by pulsed-wave Doppler during fetal quiescence. The presence of TR is best detected by colour flow mapping. If TR is seen on colour, a sample volume of 2.0–3.0 mm is positioned above the tricuspid valve in an apical four-chamber view such that the angle to the direction of flow is $<20^{\circ}$. The colour Doppler will demonstrate the direction of the regurgitation jet, which may vary its direction within the right atrium. Tricuspid regurgitation is diagnosed if it was found during at least half of the systole and with a velocity of >80 cm/s, since aortic or pulmonary arterial blood flow at this gestation can produce a maximum velocity of 50 cm/s (Fig. 3). Examples of CHD associated with tricuspid regurgitation are atrioventricular septal defect, Ebstein's anomaly, and pulmonary atresia with intact ventricular septum.

3.4. Slow sweep upwards towards the head from the four-chamber plane

The left outflow appears first in the heart with concordant ventriculo arterial connections and continues as the aorta, initially directed towards the right shoulder. At a slightly higher level, the pulmonary artery arises anteriorly from the right ventricle and passes almost directly posteriorly, in continuity with the arterial duct. Slightly higher still, the aortic arch is seen close to the right side of the arterial duct as the two converge to meet the descending aorta. Colour flow mapping is useful in delineating the great arteries.

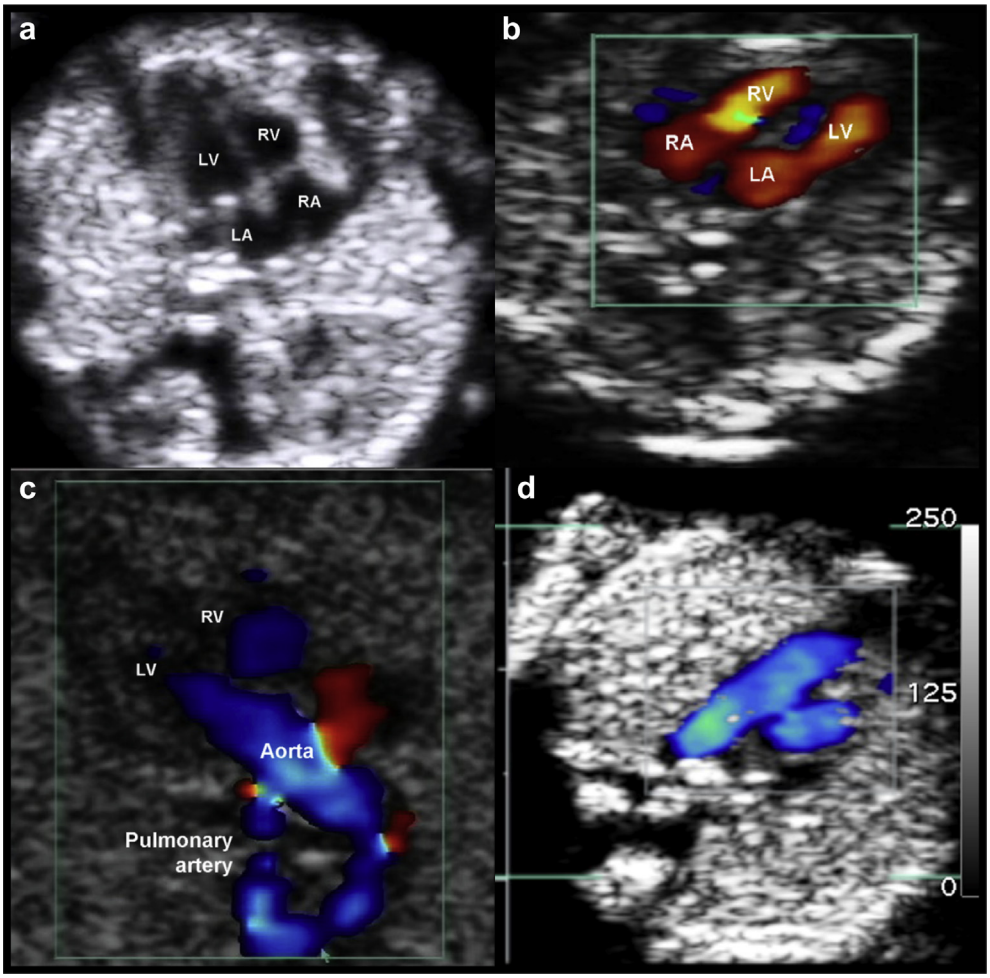

Fig. 1. (a) Ultrasound image at 12 weeks demonstrating a normal four-chamber view with equal ventricles and normal offsetting of the atrio-ventricular valves. (b) Colour Doppler demonstrating a normal four-chamber view with forward flow and equal filling of both ventricles. (c) Colour Doppler demonstrating crossing of the aorta and the pulmonary artery (X sign). (d) Colour Doppler demonstrating forward flow and equal size of the aortic arch and the ductus arteriosus at their confluence (V sign). LV, left ventricle; RV, right ventricle; LA, left atrium; RA, right atrium. Adapted from Persico et al.[35]

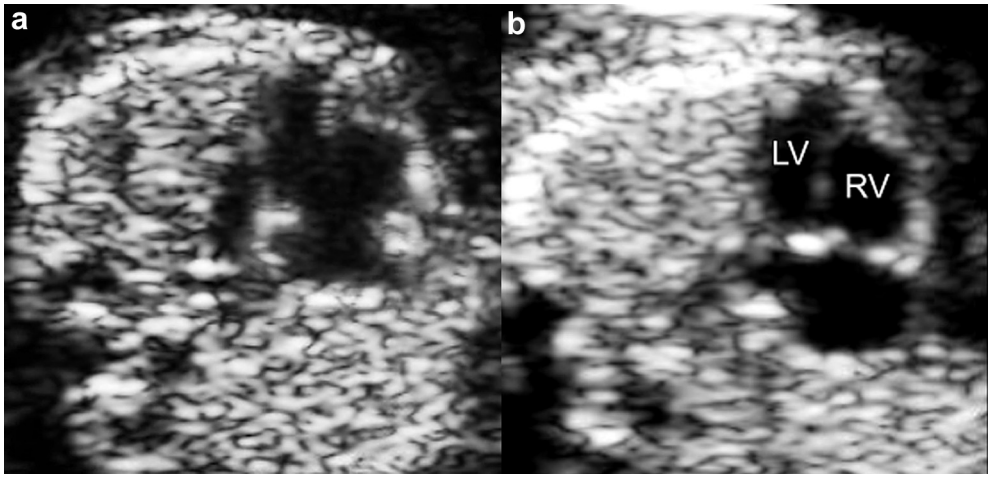

Fig. 2. (a) Ultrasound image at 12 weeks showing the absence of atrio-ventricular valves offsetting in a case of atrio-ventricular septal defect. (b) Ultrasound image at 12 weeks showing disproportion. LV, left ventricle; RV, right ventricle. Adapted from Persico et al.[35]

Failure to visualise the two great arteries should raise the suspicion of a cardiac abnormality. Identification of a single blood vessel may be associated with a diagnosis of a common arterial trunk, aortic atresia or severe coarctation, pulmonary atresia with intact ventricular septum or tetralogy of Fallot. If the normal 'crossover' relationship between the aorta and pulmonary artery is not seen, transposition of the great arteries should be excluded.

4. Improvement in first-trimester imaging of the fetal heart

Increasingly, a combination of transabdominal and transvaginal sonography using high-frequency transducers (4–8 and 5–9 MHz, respectively) is used for detailed assessment of the fetal heart in the first trimester. Two strategies have been proposed; the first uses the transvaginal approach only when transabdominal cardiac views are suboptimal, and the second uses both transabdominal and transvaginal accesses as a routine, as it is felt that they provide complementary information.

Factors affecting the ability to detect fetal heart defects at 11–13 weeks can be divided into operator-dependent skills and equipment limitations. The necessary operator skills include good scanning technique in the detailed first-trimester assessment, competence in transvaginal scanning, a high level of expertise in fetal echocardiography, and technical efficiency in image optimization. The ultrasound machine used for assessment of the fetal heart in the first trimester should include a wide spectrum of modern image enhancers, such as high harmonics, low compounding and high levels of speckle reduction algorithm. Harmonic imaging improves spatial resolution to enable visualization of smaller objects, and contrast resolution to demonstrate fine

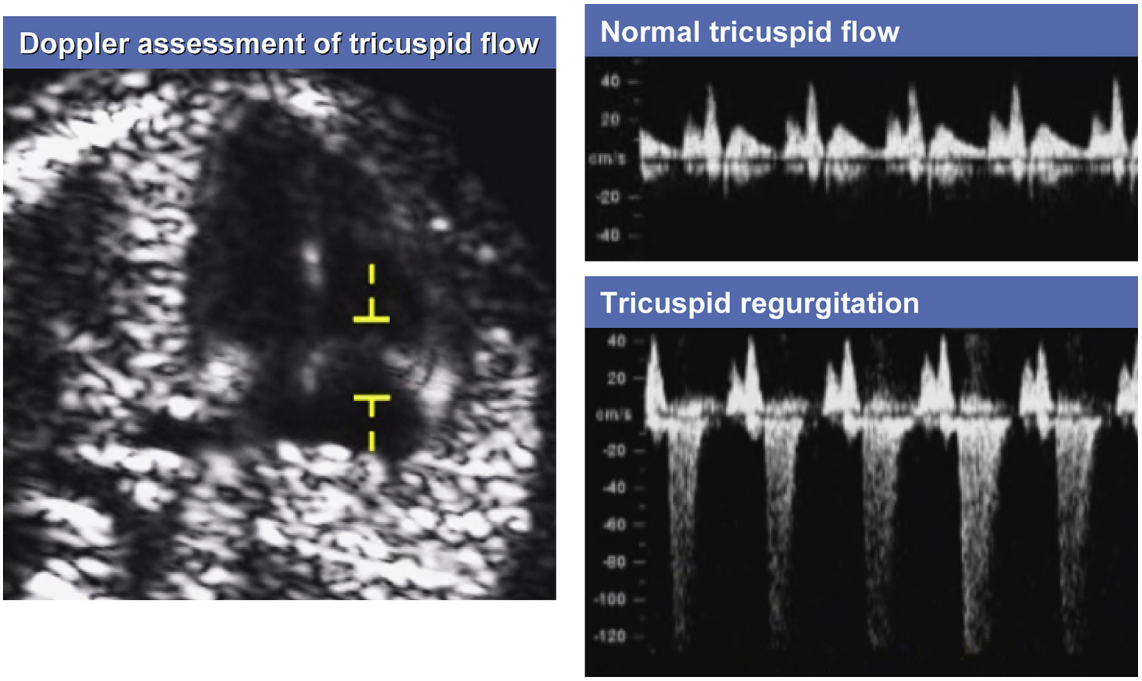

Fig. 3. An apical four-chamber view of the heart at 12 weeks of gestation, with the pulsed wave Doppler positioned across the tricuspid valve. Tricuspid regurgitation is diagnosed if it is found during at least half of the systole and with a velocity of >80 cm/s.

differences in greyscale. Compounding enhances contrast resolution and allows for better tissue differentiation. von Kaisenberg et al.[33] have shown that good reproducibility and improved cardiac imaging in the first trimester could be achieved using the combination of harmonics and compounding. Speckle reduction algorithm results in imaging based on speckle suppression, edge enhancement and feature preservation. Dynamic range control and rejection control should be optimised for the particular patient to produce better contrast imaging.

In the first trimester the fetal heart is only 6–10 mm across. It is therefore essential to utilise the maximum available high-definition zoom box which creates a field of up to 24 mm × 29 mm in the axial view. This maximises spatial and temporal resolution. Lombardi et al.[34] demonstrated that high-quality first-trimester cardiac views could be obtained using linear probes with frequencies of 6 and 15 MHz. In a prospective study, transabdominal fetal heart examination was performed by a well-trained obstetrician using a 9 MHz linear transducer (9L, Acuson Sequoia 512, Imagegate, Siemens, Erlangen, Germany) at 11–13 weeks of gestation and successfully identified 93.1% of the 58 major cardiac defects.[35]

Recent studies have reported that the use of spatio-temporal image correlation (STIC) in the first trimester is feasible and is likely to improve the detection of CHD in expert hands.[36–38] STIC combines the advantages of volume imaging with the application of fetal echocardiography, where all of the basic cardiac views can be assessed along with secondary views in motion in multiple viewing planes. However, the angle of acquisition needs to be set according to the size of the heart, and the time of capture should be as short as possible.

5. Pitfalls in first-trimester imaging of the fetal heart

Some cardiac abnormalities are not evident until later in pregnancy, such as cardiac tumours, complete heart block and cardiomyopathies.[32] Some forms of CHD, such as aortic and pulmonary stenosis, can progress into more severe malformations with advancing gestation, so may not have been obvious at 11–13 weeks. These cardiac abnormalities often go undetected, even at the routine anomaly scan in the second trimester.

Adequate examination of the fetal heart may be hampered by technical difficulties such as image resolution, limited clarity in relation to the size of the structures being examined and fetal movements. The precise gestation of the first-trimester scan is important. Early detailed examination of the fetal heart is technically more difficult at 11 compared to 13 weeks of gestation. The overall success rate in the assessment of the fetal heart has been reported to be 45% at 11 weeks and 90% at 13 weeks.[39] Similarly, successful examination of the four-chamber view, great arteries and three-vessel view was reported in 20% of cases at 11 weeks increasing to 92% at 13 weeks.[40] Another study reported successful examination of the four-chamber view, great arteries, ascending aorta and ductus arteriosus in 43%, 56% and 62% of cases at 11, 12 and 13 weeks, respectively.[41]

6. First-trimester markers of congenital cardiac defects

Measures to improve the detection of cardiac abnormalities include the appropriate training of sonographers, extra time allocated to the scan and inclusion of detailed examination of the heart in the protocol. However, effective diagnosis ultimately depends on the examination being carried out by an expert in fetal echocardiography, as demonstrated by the experience with the second-trimester scan in the last 30 years. Therefore the major challenge in routine scanning is to identify easily recognizable markers of the high-risk group that can then be referred to the expert. The sonographic markers that have been investigated in their relation to CHDs are increased nuchal translucency (NT), abnormal flow in the ductus venosus (DV) and tricuspid regurgitation (TR).

6.1. Increased nuchal translucency

Increased NT was first shown to be strongly associated with the risk of CHD in a screening study involving 29 154 singleton pregnancies with chromosomally normal fetuses at 10–14 weeks of gestation.[12] The study included 50 cases with major CHD and reported that increased NT above the 95th centile could achieve a detection rate of 56%. The prevalence of CHD increased with increasing NT thickness (3% and 20% in cases with NT 3.5–4.4 mm and ≥5.5 mm respectively). In this study increased NT was observed with all types of CHD, but there was a stronger association with left-sided abnormalities, such as hypoplastic left heart and coarctation of the aorta.[12]

The observation of increased NT in fetuses with CHD is not fully explained. Proposed mechanisms include narrowing of the aortic isthmus accompanied by narrowing of the aortic valve and ascending aorta, leading to diversion of more blood to the head and neck, heart failure due to the potential strain that the abnormalities impose on cardiac function at a stage of pregnancy when a high proportion of cardiac output is normally diverted to the head and neck.[42] The latter theory was supported by the finding of increased cardiac mRNA expression of atrial natriuretic peptide and brain natriuretic peptide in fetuses with increased NT.[43] However, in another study, which included 83 fetuses with CHD, Simpson and Sharland[44] performed a retrospective quantitative analysis of cardiac size and left ventricular ejection fraction in fetuses with ventricular septal defects or hypoplastic left heart syndrome. The authors demonstrated that all measurements of cardiothoracic ratio and left ventricular ejection fraction were within the normal range and there was no significant difference between fetuses with increased and those with normal NT.

Recent studies have confirmed the findings reported in the earlier study by Hyett et al.[12] A study of 6921 fetuses reported that the prevalence of CHD increases with the degree of thickening of the NT (Fig. 4). The prevalence of CHD was about 0.5% in fetuses with NT < median; 1% for NT between median and 95th percentile, 2% for NT between 95th and 99th percentiles and increased to 3.5%,

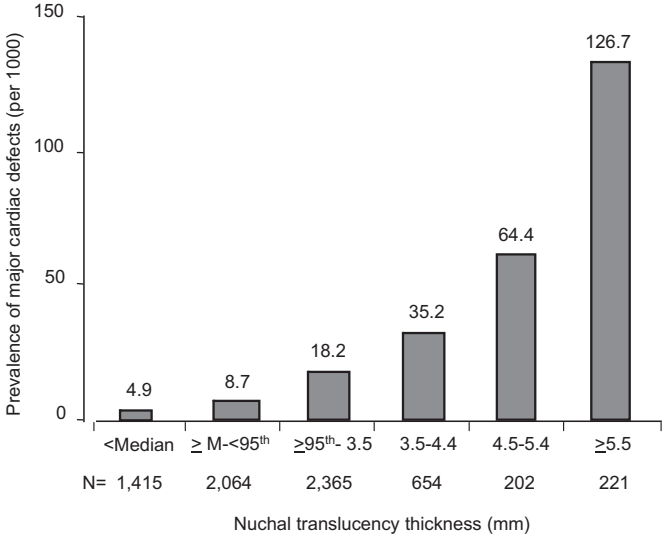

Fig. 4. Nuchal translucency thickness distribution in fetuses with normal karyotype and cardiac defects. M, median; 95th, 95th centile. Adapted from Atzei et al.[45]

6.5% and 12.5% for NT of 3.5–4.4 mm, 4.535.4 mm, and ≥5.5 mm, respectively. The study also reported that there was no obvious difference in the distribution of NT in the different types of cardiac defects.[45] In the study by Syngelaki et al.[3] involving 44 859 singleton pregnancies including 85 with major CHDs, the incidence of increased NT was 35.3% in the cases with CHD. The NT was increased in 64.3% of the 28 fetuses with cardiac abnormalities diagnosed at 11–13 weeks compared with 15.4% of the 78 diagnosed in the second trimester or postnatally. Table 1 shows the data on NT screening performance in the studies reporting on the effectiveness of the first-trimester scan in the diagnosis of major CHD.

A pooled analysis of data from major fetal echocardiography centres concluded that finding NT ≥3.5 mm may lead to an earlier diagnosis of all major types of CHDs.[46] Earlier studies have demonstrated a significant association between increased NT and left heart lesions and septal defects.[12,21] However, the multicentre study, based on 637 CHDs, did not replicate this finding.[46] In a meta-analysis, involving 58 492 pregnancies which aimed to assess the screening performance of NT for major CHD, the detection rate was poor (31% for a false-positive rate of 1%).[47] However, the studies varied in their definition of what constituted increased NT (Table 1).

The NT cut-off recommended to use for referral for specialist fetal echocardiography varies according to the local set-up and facilities, in particular the access to specialist fetal echocardiography service. In the study by Atzei et al.[45] we have demonstrated that the prevalence of major CHD in fetuses with NT above the 99th centile (>30 per 1000) is substantially higher than in patients with a family history of cardiac defects and diabetes mellitus (about 20 per 1000), which are commonly used as indications for fetal echocardiography.

Fetal NT >3.5 mm is found in about 1% of pregnancies. The risk of major chromosomal abnormalities in such fetuses is very high and increases from about 20% for NT of 4.0 mm to 33% for NT of 5.0 mm and 60% for NT of ≥5.5 mm.[48] Consequently, our proposed management would be first to offer the parents the option of fetal karyotyping by chorionic villus sampling. The prevalence of major fetal defects or fetal death in the chromosomally normal group increases with NT thickness from about 10% for NT of 4.0 mm to 20% for NT of 5.0 mm and 50% for NT of ≥5.5 mm.[18,49] The next step would be to carry out a detailed scan, including fetal echocardiography at 14–16 weeks of gestation in the fetuses with normal karyotype with increased NT.[45]

In fetuses with NT between the 95th and 99th centiles, the prevalence of cardiac defects is about 2%, which is similar to that found in patients with a family history of cardiac defects and diabetes mellitus. The extent to which specialist fetal echocardiography should be offered to these pregnancies, which constitute about 4% of the total population, depends on the availability of such services.

6.2. Abnormal ductus venosus blood flow

Abnormal DV flow was initially reported in the second and third trimesters in association with cardiac dysfunction associated with structural heart defects, post-tachycardia cardiomyopathy and end-stage fetal hypoxia or increased right ventricular afterload.[50,51] In hearts with markedly impaired diastolic function, atrial contraction occurs against increased impedance to forward flow, resulting in a transient flow reversal in the ductus venosus, which constitutes the negative a-wave. However, DV flow reversal beyond the first trimester has been noted mainly in situations where there were other manifestations of cardiac dysfunction, such as fetal hydrops.

In the assessment of ductus venosus a right ventral mid-sagittal view of the fetal trunk is obtained and colour flow mapping is used to demonstrate the umbilical vein, ductus venosus and fetal heart. A small pulsed Doppler sample (0.5–1.0 mm) is used to avoid contamination from the adjacent veins and it is placed in the yellowish aliasing area which is the portion immediately above the umbilical sinus. The insonation angle should be <30°, the filter should be set at a low frequency (50–70 Hz) to allow visualization of the whole waveform and the sweep speed should be high (2–3 cm/s) so that the waveforms are widely spread. Impedance to flow is assessed by measuring the pulsatility index or by qualitative classification of the a-wave into positive, negative or reversed (Fig. 5).

The first study reporting on the association between abnormal DV flow and CHDs in the first trimester demonstrated reversed or

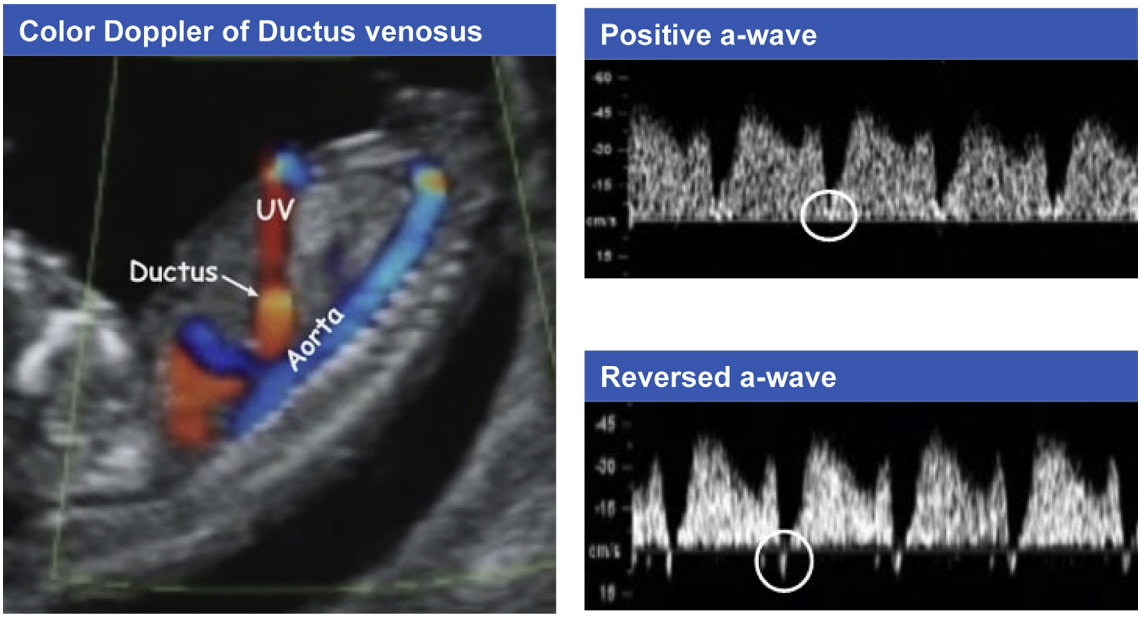

Fig. 5. Mid-sagittal view of the fetal trunk demonstrating, with colour flow mapping, the umbilical vein, ductus venosus and fetal heart and ductus venosus flow velocity waveforms showing a positive waveform and reversed a-wave.

absent flow during atrial contraction in 10 of 140 euploid fetuses.[52] Major CHDs were present in six of the 10 with abnormal DV flow but in none of the 134 with normal flow.[52] In a meta-analysis including seven studies (n = 50 354) regardless of the NT status, nine studies (n = 2908) with increased NT and seven studies (n = 47 610) with normal NT, the summary sensitivity and specificity of abnormal DV flow in the detection of CHDs were 50% and 93%, 83% and 80%, and 19% and 96% respectively.[53] The corresponding positive likelihood ratio of the test was 8.1, 4.35 and 4.97 and the negative likelihood ratio was 0.52, 0.20 and 0.8, respectively.

Maiz et al.[54] have studied the additive effect of DV velocimetry and reported that the risk of CHD, based on NT measurement, was three-fold higher or two-fold lower depending on the presence of reverse or positive a-wave, respectively (Fig. 6). A recent study assessed the best method of combining NT and DV Doppler in the detection of major CHD in euploid fetuses.[55] The study included 37 fetuses with a major CHD and 12 799 unaffected pregnancies. The authors demonstrated different detection rates depending on the cut-offs of NT or DV PI used (Table 3).[55]

The mechanism of abnormal DV flow in fetuses with CHD is not clear. Similar to increased NT, the proposed theories include cardiac dysfunction. It was proposed that DV reversed flow corresponds to similar abnormalities described in inferior caval vein blood flow. However, the normal inferior caval vein blood flow is reversed, corresponding to atrial contraction, and abnormality will be manifest as a quantitative rather than a qualitative change. By contrast, in DV forward flow throughout the cardiac cycle is normal and any flow reversal is abnormal. Obstructive right heart defects have been reported to be more frequently associated with abnormal DV flow and normal NT, suggesting that the pathophysiology of the reversed a-wave could be attributed to a right heart overload and diastolic dysfunction.[56–58]

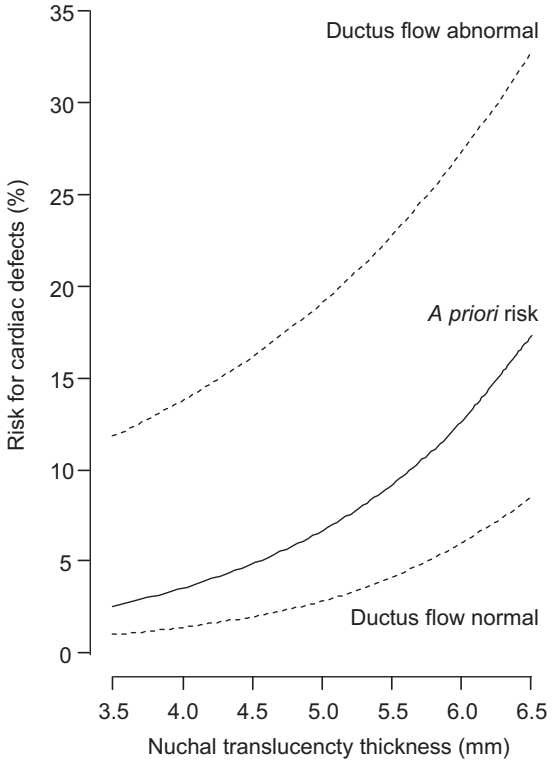

Fig. 6. Relationship between nuchal translucency (NT) thickness in chromosomally normal fetuses and risk of major cardiac defects. The a-priori NT-related risk (solid line) is multiplied by the positive and negative likelihood ratios for abnormal (upper dashed line) and normal (lower dashed line) A-waves in the ductus venosus, respectively, to derive the adjusted risk. Adapted from Maiz et al.[54]

Table 3
Performance of screening for major cardiac defects by various strategies combining fetal nuchal translucency and blood flow in the ductus venosus.

Strategy	DR (%)	FPR (%)
NT >99th centile	27 (10/37)	1.0
DV PI >99th centile	27 (10/37)	1.0
NT >95th centile	40 (15/37)	5.0
DV PI >95th centile	38 (14/37)	5.0
NT or DV PI >99th centile	35 (13/37)	1.9
NT and DV PI >99th centile	24 (9/37)	1.0
NT and DV PI >98th centile	30 (11/37)	2.0
NT and DV PI >97th centile	35 (13/37)	3.0
NT and DV PI >96th centile	35 (13/37)	4.0
NT and DV PI >95th centile	40 (15/37)	5.0
A-wave reversed/absent	39 (14/36)	1.8
A-wave reversed/absent or NT >99th centile	47 (17/36)	2.7
A-wave reversed/absent or NT >98th centile	50 (18/36)	3.6
A-wave reversed/absent or NT >97th centile	50 (18/36)	4.5
A-wave reversed/absent or NT >96th centile	53 (19/36)	5.5
A-wave reversed/absent or NT >95th centile	58 (21/36)	6.4
A-wave reversed/absent or risk from NT or DV PI >99th centile	44 (16/36)	2.8
A-wave reversed/absent or risk from NT or DV PI >98th centile	50 (18/36)	3.8
A-wave reversed/absent or risk from NT or DV PI >97th centile	53 (19/36)	4.6
A-wave reversed/absent or risk from NT or DV PI >96th centile	53 (19/36)	5.5
A-wave reversed/absent or risk from NT or DV PI >95th centile	56 (20/36)	6.5
A-wave reversed/absent or risk from NT and a-wave >99th centile	42 (15/36)	2.8
A-wave reversed/absent or risk from NT and a-wave >98th centile	44 (16/36)	3.8
A-wave reversed/absent or risk from NT and a-wave >97th centile	50 (18/36)	4.9
A-wave reversed/absent or risk from NT and a-wave >96th centile	50 (18/36)	5.6
A-wave reversed/absent or risk from NT and a-wave >95th centile	53 (19/36)	6.5

NT, nuchal translucency; DR, detection rate; FPR, false-positive rate; DV, ductus venosus; PI, pulsatility index.
Adapted from Borrell et al.[55]

6.3. Tricuspid regurgitation

Tricuspid regurgitation (TR) is a frequent finding in trisomic fetuses at 11–13 weeks of gestation[59,60] and it is also observed in euploid fetuses with CHDs.[8,35,61] The underlying mechanism for the association between CHD and TR, as well as increased NT and DV abnormal blood flow, has not been fully explored. The proposed theory, similar to that of NT and DV, is impairment in cardiac function that is manifested only during the first trimester because, at this gestation, the compliance of the fetal heart is low and cardiac afterload resulting from placental resistance is high.

The performance of TR in the detection of major CHDs was examined in a screening study at 11–13 weeks of gestation which included 85 cases with major CHDs and 40 905 without CHDs.[59] The prevalence of TR was ~1% in normal fetuses and in one-third of those with major CHD. The incidence of TR and DV reversed a-wave increased with NT thickness both in fetuses with and in those without major CHD. NT above the 95th centile, TR or DV reversed a-wave were observed in 35.3%, 32.9%, and 28.2% of the cases with major CHD, respectively, and in 4.8%, 1.3%, and 2.1% of those without CHD. Any one of the three markers was found in 57.6% of CHD cases and in 8% of those without.[61] The patient-specific risk and the

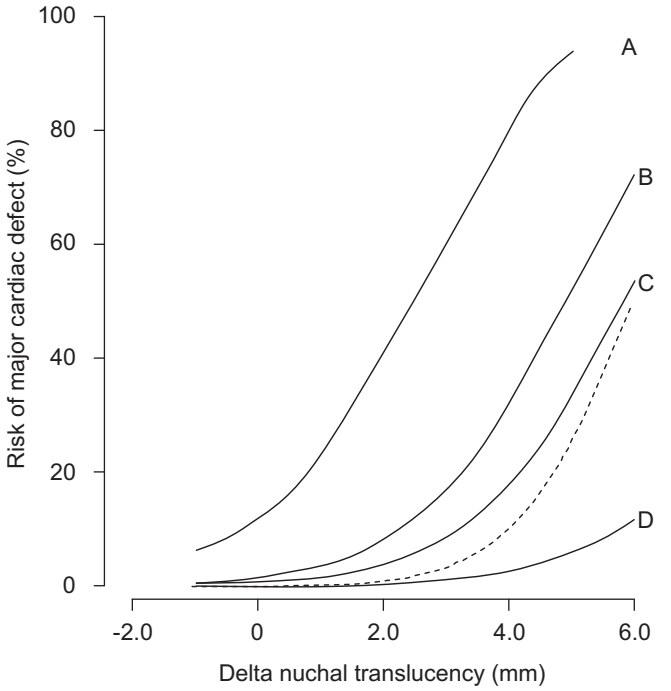

Fig. 7. Patient-specific risk for major cardiac defects according to fetal nuchal translucency thickness (interrupted line) and nuchal translucency combined with the results of blood flow in the ductus venosus and across the tricuspid valve (continuous lines) in a fetus with crown–rump length of 65 mm. (A) Tricuspid regurgitation and reversed A-wave in the ductus venosus. (B) Tricuspid regurgitation and normal flow in the ductus venosus. (C) Normal flow across the tricuspid valve and reversed A-wave in the ductus venosus. (D) Normal flow across the tricuspid valve and in the ductus venosus. Adapted from Pereira et al.[61]

performance of screening for major CHD using NT, DV Doppler and TR are shown in Fig. 7 and Table 4. The screening performance for major CHD using NT alone was improved by the addition of DV flow and further improved by the addition of TR. For fixed false-positive rates of 1%, 3%, and 5%, the detection rates of major CHD by a combination of NT, DV flow, and TR were 36.5%, 48.2%, and 54.1%, respectively.

The association between TR and CHD was also observed in another prospective study in which transabdominal fetal heart examination was performed by a well-trained obstetrician using a high-frequency linear transducer in 886 cases. TR was reported in 16 (61.5%) euploid fetuses with CHD and in 62 (9.2%) of 670 in euploid fetuses with normal heart.[35] Similar results have been reported in first-trimester study in 4445 pregnancies.[8] There was a higher prevalence of TR in fetuses with CHD compared with normal fetuses (33% vs 1.7%). In the same study the corresponding values for NT above the 95th centile and abnormal DV flow were 38%, 5.6%, 22% and 3.1%, respectively.

Two approaches have been proposed for the use of the algorithm combining NT, DV Doppler and TR to estimate the patient-specific risk for major CHD.[61] The first one is to define the risk cut-off that selects the patients requiring referral for specialist fetal echocardiography. The risk increases exponentially with NT thickness from 1 per 1000 in those with NT at or below the 95th centile to 7 per 1000 for NT between the 95th and 99th centile and 58 per 1000 for NT above the 99th centile. The risk is further increased if there is DV reversed a-wave, TR, or both and is decreased if flow in the DV and across the tricuspid valve is normal. The second approach is to define as high risk all cases with TR, DV reversed a-wave, or both, which constitute ~3% of the population and contain 48% of those with major cardiac defects. If cases with nuchal translucency above the 99th centile are also included, the screen-positive rate would increase to ~4% and the estimated detection rate would be 52%. If there are available resources for performing fetal echocardiography in 8% of the population, then the NT cut-off for defining the high-risk group could be reduced to the 95th percentile with an increase in the estimated detection rate to 58%.

Table 4
Performance of screening for major cardiac defects by fetal nuchal translucency and blood flow across the tricuspid valve and in the ductus venosus.

Screening test	Major cardiac defect	
	Present ($n = 85$)	Absent ($n = 40\,905$)
NT above the 99th centile	18 (21.2%)	290 (0.7%)
NT between the 95th and 99th centile	12 (14.1%)	1666 (4.1%)
NT above the 95th centile	30 (35.3%)	1956 (4.8%)
Reversed a-wave in ductus venosus	24 (28.2%)	856 (2.1%)
Reversed DV a-wave or NT above the 99th centile	33 (38.8%)	1118 (2.7%)
Reversed DV a-wave or NT above the 95th centile	40 (47.1%)	2732 (6.7%)
TR	28 (32.9%)	516 (1.3%)
Either TR or NT above the 99th centile	35 (41.2%)	792 (1.9%)
Either TR or NT above the 95th centile	43 (50.6%)	2405 (5.9%)
Either TR or reversed DV A-wave (Doppler)	41 (48.2%)	1309 (3.2%)
Either Doppler or NT above the 99th centile	44 (51.8%)	1669 (4.1%)
Either Doppler or NT above the 95th centile	49 (57.6%)	3265 (8.0%)

NT, nuchal translucency; DV, ductus venosus; TR, tricuspid regurgitation.
Adapted from Pereira et al.[61]

6.4. Maternal serum markers and congenital cardiac defects

A case–control study of 68 cases of isolated fetal CHDs and 340 normal controls at 11–13 weeks of gestation reported lower maternal serum placental growth factor (PLGF) levels in CHD (0.80 vs 1.00 multiple of median).[62] This decrease in PLGF was observed in conotruncal and valve defects but not in left heart defects. The decrease in serum PLGF was not related to impaired placental perfusion.[62]

A case–control study of 306 cases of fetal CHDs and 1224 no-CHD controls reported abnormal second-trimester serum α-fetoprotein (AFP), human chorionic gonadotrophin (hCG) and unconjugated estriol (uE_3) in the CHD group.[63] Cases with critical CHDs were more than twice as likely to have AFP multiple of the median (MoM) ≥95th centile and/or an hCG and/or uE_3 MoM ≤5th centile.[63]

The value of first- and second-trimester maternal serum biochemical markers in screening for fetal CHDs remains to be determined.

7. Conclusion

First-trimester detection of CHD is feasible, but early detailed assessment of the fetal heart requires a high level of expertise in early anomaly scanning and fetal echocardiography. However, the detection of major CHDs at 11–13 weeks is influenced by their association with easily detectable markers and a policy decision as to the objectives of this scan and the allocation of resources necessary to achieve them. The use of transvaginal ultrasound and newer techniques are likely to improve the detection rate. However, the limitations of fetal echocardiography in the first trimester must be borne in mind, and resort to follow-up mid-gestational echocardiography should always be considered.

Practice points

- The detection rate of CHD at the first trimester is low and varies according to the experience of the centre and the population studied.
- The detection rate varies according to the type of the cardiac abnormality, e.g. from around 51% for hypoplastic left heart to 18% for tetralogy of Fallot and transposition of the great arteries.
- The detection of major CHDs at 11–13 weeks could be improved if we use easily detectable markers for screening for CHD, e.g. nuchal translucency.
- The detection rate could be improved if the ultrasound assessment at the first trimester follows structured protocols.
- The detection rate of CHD could be improved by the use of transvaginal ultrasound and newer techniques.
- The limitations of fetal echocardiography in the first trimester must be borne in mind, and resort to follow-up mid-gestational echocardiography should always be considered.

Research directions

- The development of algorithms for the screening for CHD in the first trimester, using a combination of maternal and pregnancy characteristics, nuchal translucency, ductus venosus Doppler and tricuspid regurgitation.
- Prospective assessment of the routine implementation of tools, such as transvaginal ultrasound and STIC, for improving the detection rate of CHD.

Conflict of interest statement

None.

Funding sources

The study was supported by a grant from The Fetal Medicine Foundation (UK Charity No: 1037116).

References

1. Mensah GA, Brown DW. An overview of cardiovascular disease burden in the United States. *Health Affairs* 2007;**26**:38–48.
2. Garne E, Dolk H, Loane M, Boyd PA. EUROCAT website data on prenatal detection rates of congenital anomalies. *J Med Screen* 2010;**17**:97–8.
*3. Syngelaki A, Chelemen T, Dagklis T, Allan L, Nicolaides KH. Challenges in the diagnosis of fetal non-chromosomal abnormalities at 11–13 weeks. *Prenat Diagn* 2011;**31**:90–102.
4. D'Ottavio G, Mandruzzato G, Meir YJ, Rustico MA, Fischer-Tamaro L, Conoscenti G. Comparison of first trimester and second trimester screening for fetal anomalies. *Ann NY Acad Sci* 1998;**847**:200–9.
5. Taipale P, Ammala M, Salonen R, Hilesmaa V. Two-stage ultrasonography in screening for fetal anomalies at 13–14 and 18–22 weeks of gestation. *Acta Obstet Gynecol Scand* 2004;**83**:1141–6.
6. Chen M, Lam YH, Lee CP, Tang MH. Ultrasound screening of fetal structural abnormalities at 12 to 14 weeks in Hong Kong. *Prenat Diagn* 2004;**24**:92–7.
7. Cedergren M, Selbing A. Detection of fetal structural abnormalities by an 11–14-week ultrasound dating scan in an unselected Swedish population. *Acta Obstet Gynecol Scand* 2006;**85**:912–5.
8. Volpe P, Ubaldo P, Volpe N, et al. Fetal cardiac evaluation at 11–14 weeks by experienced obstetricians in a low-risk population. *Prenat Diagn* 2011;**31**:1054–61.
9. Kornman LH, Wortelboer MJM, Beekhuis JR, Morssink LP, Mantingh A. Women's opinions and the implications of first-versus second-trimester screening for fetal Down's syndrome. *Prenat Diagn* 1997;**17**:1011–8.
10. Department of Health. Abortion Statistics, England and Wales: 2008. *Statistical Bulletin 2009/1*. London: DoH; 2009.
11. Hernádi L, Töröcsik M. Screening for fetal anomalies in the 12th week of pregnancy by transvaginal sonography in an unselected population. *Prenat Diagn* 1997;**17**:753–9.
*12. Hyett J, Perdu M, Sharland G, Snijders R, Nicolaides KH. Using fetal nuchal translucency to screen for major congenital cardiac defects at 10–14 weeks of gestation: population based cohort study. *BMJ* 1999;**318**:81–5.
13. Bilardo CM, Pajkrt E, de Graaf I, Mol BW, Bleker OP. Outcome of fetuses with enlarged nuchal translucency and normal karyotype. *Ultrasound Obstet Gynecol* 1998;**11**:401–6.
14. Hafner E, Schuchter K, Liebhart E, Philipp K. Results of routine fetal nuchal translucency measurement at weeks 10–13 in 4233 unselected pregnant women. *Prenat Diagn* 1998;**18**:29–34.
15. Chen M, Lee CP, Lam YHH, et al. Comparison of nuchal and detailed morphology ultrasound examinations in early pregnancy for fetal structural abnormality screening: a randomized controlled trial. *Ultrasound Obstet Gynecol* 2008;**31**:136–46.
16. Dane B, Dane C, Sivri D, Kiray M, Cetin A, Yayla M. Ultrasound screening for fetal major abnormalities at 11–14 weeks. *Acta Obstet Gynecol Scand* 2007;**86**:666–70.
17. Mavrides E, Cobian-Sanchez F, Tekay A, et al. Limitations of using first trimester nuchal translucency measurement in routine screening for major congenital heart defects. *Ultrasound Obstet Gynecol* 2001;**17**:106–10.
18. Michailidis GD, Economides DL. Nuchal translucency measurement and pregnancy outcome in karyotypically normal fetuses. *Ultrasound Obstet Gynecol* 2001;**17**:102–5.
19. Schwarzler P, Carvalho JS, Senat MV, Masroor T, Campbell S, Ville Y. Screening for fetal aneuploidies and fetal cardiac abnormalities by nuchal translucency thickness measurement at 10–14 weeks of gestation as part of routine antenatal care in an unselected population. *Br J Obstet Gynaecol* 1999;**106**:1029–34.
20. Orvos H, Wyadaka K, Kozinszky YZ, Katona M, Pal A, Szabo J. Increased nuchal translucency and congenital heart defects in euploid fetuses. The Szeged experience. *Eur J Obstet Gynecol Reprod Biol* 2002;**101**:124–8.
21. Bahado-Singh RO, Wapner R, Thom E, et al. Elevated first-trimester nuchal translucency increases the risk of congenital heart defects. *Am J Obstet Gynecol* 2005;**192**:1357–61.
22. Bruns RF, Moron AF, Murta CGV, Goncalves LFA, Zamith MM. The role of nuchal translucency in the screening of congenital heart defects. *Arq Bras Cardiol* 2006;**87**:272–9.
23. Becker R, Wagner RD. Detailed screening for fetal anomalies and cardiac defects at the 11–13 weeks scan. *Ultrasound Obstet Gynecol* 2006;**27**:613–8.
24. Westin M, Saltvedt S, Almstro H, Grunewald C, Valentin L. By how much does increased nuchal translucency increase the risk of adverse pregnancy outcome in chromosomally normal fetuses? A study of 16 260 fetuses derived from an unselected pregnant population. *Ultrasound Obstet Gynecol* 2007;**29**:150–8.
25. Muller MA, Clur SA, Timmerman E, Bilardo CM. Nuchal translucency measurement and congenital heart defects: models association in low-risk pregnancies. *Prenat Diagn* 2007;**27**:164–9.
26. Oztekin O, Oztekin D, Týnar S, Adýbelli Z. Ultrasonographic diagnosis of fetal structural abnormalities in prenatal screening at 11–14 weeks. *Diagn Interv Radiol* 2009;**15**:221–5.
27. Hildebrand E, Selbing A, Blomberg M. Comparison of first and second trimester ultrasound screening for fetal anomalies in the southeast region of Sweden. *Acta Obstet Gynecol Scand* 2010;**89**:1412–9.
28. Grande M, Arigita M, Borobio V, Jimenez JM, Fernandez S, Borrell A. First-trimester detection of structural abnormalities and the role of aneuploidy markers. *Ultrasound Obstet Gynecol* 2012;**39**:157–63.
29. Carvalho JS, Mavrides E, Shinebourne AE, Campbell S, Thilaganathan B. Improving the effectiveness of routine prenatal screening for major congenital heart defects. *Heart* 2002;**88**:387–91.
30. Westin M, Saltvedt S, Bergman G, Almstro H, Grunewald C, Valentin L. Is measurement of nuchal translucency thickness a useful screening tool for heart defects? A study of 16,383 fetuses. *Ultrasound Obstet Gynecol* 2006;**27**:632–9.
31. Borrell A, Robinson JN, Santolaya-Forgas J. Clinical value of the 11- to 13 + 6-week sonogram for detection of congenital malformations: a review. *Am J Perinatol* 2011;**28**:117–24.
32. Allan L, Cook A, Huggon I. First trimester fetal heart scanning. In: Allan L, Cook A, Huggon I, editors. *Fetal echocardiography – a practical guide*. Cambridge: Cambridge University Press; 2009. p. 190–202.
33. von Kaisenberg CS, Kuhling-von Kaisenberg H, Fritzer E, Schemm S, Meinhold-Heerlein I, Jonat W. Fetal transabdominal anatomy scanning using standard views at 11 to 14 weeks' gestation. *Am J Obstet Gynecol* 2005;**192**:535–42.
34. Lombardi CM, Bellotti M, Fesslova V, Cappellini A. Fetal echocardiography at the time of the nuchal translucency scan. *Ultrasound Obstet Gynecol* 2007;**29**:249–57.
35. Persico N, Moratalla J, Lombardi CM, Zidere V, Allan L, Nicolaides KH. Fetal echocardiography at 11–13 weeks by transabdominal high-frequency ultrasound. *Ultrasound Obstet Gynecol* 2011;**37**:296–301.
36. Bennasar M, Martínez JM, Olivella A, et al. Feasibility and accuracy of fetal echocardiography using four-dimensional spatiotemporal image correlation technology before 16 weeks' gestation. *Ultrasound Obstet Gynecol* 2009;**33**:645–51.

37. Vinals F, Ascenzo R, Naveas R, Huggon I, Giuliano A. Fetal echocardiography at 11+0 to 13 + 6 weeks using four-dimensional spatiotemporal image correlation telemedicine via an Internet link: a pilot study. *Ultrasound Obstet Gynecol* 2008;**31**:633–8.
38. Turan S, Turan OM, TY-Torredes K, Harman CR, Baschat AA. Standardization of the first-trimester fetal cardiac examination using spatiotemporal image correlation with tomographic ultrasound and color Doppler imaging. *Ultrasound Obstet Gynecol* 2009;**33**:652–6.
39. Smrcek JM, Berg C, Geipel A, et al. Detection rate of early fetal echocardiography and in utero development of congenital heart defects. *J Ultrasound Med* 2006;**25**:187–96.
40. Haak MC, Twisk JWR, Van Vught MG. How successful is fetal echocardiography examination in the first trimester of pregnancy? *Ultrasound Obstet Gynecol* 2002;**20**:9–13.
41. Vimpelli T, Huhtala H, Acharya G. Fetal echocardiography during routine first-trimester screening: a feasibility study in an unselected population. *Prenat Diagn* 2006;**26**:475–82.
42. Hyett J, Moscoso G, Papapanagiotou G, Perdu M, Nicolaides KH. Abnormalities of the heart and great arteries in chromosomally normal fetuses with increased nuchal translucency thickness at 11–13 weeks of gestation. *Ultrasound Obstet Gynecol* 1996;**7**:245–50.
43. Hyett JA, Brizot ML, Von Kaisenberg CS, McKie AT, Farzaneh F, Nicolaides KH. Cardiac gene expression of atrial natriuretic peptide and brain natriuretic peptide in trisomic fetuses. *Obstet Gynecol* 1996;**87**:506–610.
44. Simpson JM, Sharland GK. Nuchal translucency and congenital heart defects: heart failure or not? *Ultrasound Obstet Gynecol* 2000;**16**:30–6.
45. Atzei A, Gajewska K, Huggon IC, Allan L, Nicolaides KH. Relationship between nuchal translucency thickness and prevalence of major cardiac defects in fetuses with normal karyotype. *Ultrasound Obstet Gynecol* 2005;**26**:154–7.
*46. Makrydimas G, Sotiriadis A, Hugon IC, et al. Nuchal translucency and fetal cardiac defects: a pooled analysis of major fetal echocardiography centers. *Am J Obstet Gynecol* 2005;**192**:89–95.
*47. Makrydimas G, Sotiriadis A, Ioannidis JP. Screening performance of first-trimester nuchal translucency for major cardiac defects: a meta-analysis. *Am J Obstet Gynecol* 2003;**189**:1330–5.
48. Snijders RJ, Noble P, Sebire NJ, Souka AP, Nicolaides KH. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10–14 weeks of gestation. Fetal Medicine Foundation First Trimester Screening Group. *Lancet* 1998;**352**:343–6.
49. Souka AP, Krampl E, Bakalis S, Heath V, Nicolaides KH. Outcome of pregnancy in chromosomally normal fetuses with increased nuchal translucency in the first trimester. *Ultrasound Obstet Gynecol* 2001;**18**:9–17.
50. Kiserud T, Eik-Nes SH, Hellevik LR, Blaas H-G. Ductus venosus blood velocity changes in fetal cardiac diseases. *J Matern Fetal Invest* 1993;**3**:15–20.
51. Kiserud T, Eik-Nes SH, Blaas H-G, Hellevik LR, Simensen B. Ductus venosus blood velocity and the umbilical circulation in the seriously growth-retarded fetus. *Ultrasound Obstet Gynecol* 1994;**4**:109–14.
52. Matias A, Huggon I, Areias JC, Montenegro N, Nicolaides KH. Cardiac defects in chromosomally normal fetuses with abnormal ductus venosus blood flow at 10–14 weeks. *Ultrasound Obstet Gynecol* 1999;**14**:307–10.
*53. Papatheodorou SI, Evangelou E, Makrydimas G, Ioannidis JP. First-trimester ductus venosus screening for cardiac defects: a meta-analysis. *Br J Obstet Gynaecol* 2011;**118**:1438–45.
*54. Maiz N, Plasencia W, Dagklis T, Faros E, Nicolaides K. Ductus venosus Doppler in fetuses with cardiac defects and increased nuchal translucency thickness. *Ultrasound Obstet Gynecol* 2008;**31**:256–60.
*55. Borrell A, Grande M, Bennasar M, et al. First trimester detection of cardiac defects with the use of ductus venosus blood flow. *Ultrasound Obstet Gynecol* 2012 Nov. http://dx.doi.org/10.1002/uog.12349. [Epub ahead of print].
56. Martínez JM, Comas M, Borrell A, et al. Abnormal first-trimester ductus venosus blood flow: a marker of cardiac defects in fetuses with normal karyotype and nuchal translucency. *Ultrasound Obstet Gynecol* 2010;**35**:267–72.
57. Berg C, Kremer C, Geipel A, Kohl T, Germer U, Gembruch U. Ductus venosus blood flow alterations in fetuses with obstructive lesions of the right heart. *Ultrasound Obstet Gynecol* 2006;**28**:137–42.
58. Gardiner HM, Belmar C, Tulzer G, et al. Morphologic and functional predictors of eventual circulation in the fetus with pulmonary atresia or critical pulmonary stenosis with intact septum. *J Am Coll Cardiol* 2008;**51**:1299–308.
59. Huggon IC, DeFigueiredo DB, Allan LD. Tricuspid regurgitation in the diagnosis of chromosomal anomalies in the fetus at 11–14 weeks of gestation. *Heart* 2003;**89**:1071–3.
60. Kagan KO, Valencia C, Livanos P, Wright D, Nicolaides KH. Tricuspid regurgitation in screening for trisomies 21, 18 and 13 and Turner syndrome at 11^{+0}–13^{+6} weeks of gestataion. *Ultrasound Obstet Gynecol* 2009;**33**:18–22.
*61. Pereira S, Ganapathy R, Syngelaki A, Maiz N, Nicolaides KH. Contribution of fetal tricuspid regurgitation in first-trimester screening for major cardiac defects. *Obstet Gynecol* 2011;**117**:1384–91.
62. Llurba E, Syngelaki A, Sánchez O, Carreras E, Cabero L, Nicolaides K. Maternal serum placental growth factor at 11–13 weeks' gestation and fetal cardiac defects. *Ultrasound Obstet Gynecol* 2012. http://dx.doi.org/10.1002/uog.12346. [Epub ahead of print].
63. Jelliffe-Pawlowski L, Baer R, Moon-Grady AJ, Currier RJ. Second trimester serum predictors of congenital heart defects in pregnancies without chromosomal or neural tube defects. *Prenat Diagn* 2011;**31**:466–72.