

# Fetal echocardiography at the time of the nuchal translucency scan

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**KEYWORDS:** chromosomal anomalies; congenital heart disease; fetal echocardiography; first trimester; nuchal translucency; prenatal diagnosis; trisomy 21

## ABSTRACT

**Objective** The fetal heart is not studied routinely in the first trimester because of technical and time limitations. Our aim was to assess the feasibility of performing a fetal cardiac study in pregnancies referred for nuchal translucency (NT) screening, using high-frequency linear transabdominal transducers with a specific ultrasound preset.

**Methods** A single trained operator assessed the fetal heart in pregnancies with a fetal crown–rump length (CRL) of 60–84 mm that had been referred for NT screening. A 15- or 6-MHz transabdominal linear transducer with a specific preset suitable mainly for color-flow mapping was used to confirm or refute normal cardiac anatomy rather than to establish a specific diagnosis. Fetuses having an increased risk for congenital heart disease were referred to a tertiary center for a further examination within 1 week. This group consisted of all fetuses with NT > 95<sup>th</sup> centile and those in which a family history or the initial heart scan increased the risk.

**Results** A total of 608 fetuses with a median CRL of 65 mm was examined between 2003 and 2005. A cardiac scan was performed successfully in 456 (75%) using a 15-MHz linear transducer alone, and the additional use of a 6-MHz transducer allowed diagnostic images to be obtained in a further 152. Normal cardiac anatomy was assessed confidently within 10 min in 517/608 (85%) pregnancies; in 85 (14%) a longer time was needed and six patients were rescheduled within 2 weeks because of non-diagnostic images at the initial scan. In 571/608 (94%) the risk for congenital heart disease (CHD) was not increased and the heart was considered normal at initial echocardiography; this was confirmed by later scans and at postnatal follow-up. In 37/608 (6%) fetuses the

risk for CHD was increased (35 for NT > 95<sup>th</sup> centile and two for family history). In this group normal heart anatomy was described in 34 fetuses and confirmed by subsequent specialist echocardiography. Cardiac defects were suspected in three fetuses (all with increased NT) and confirmed by a fetal cardiologist in each case.

**Conclusions** A trained operator can perform a fetal heart study during the NT screening test using transabdominal high-resolution transducers in an acceptable length of time. Copyright © 2007 ISUOG. Published by John Wiley & Sons, Ltd.

## INTRODUCTION

Interest in early examination of the fetal heart is related to the significant clinical impact of early detection of cardiac problems. Early fetal heart assessment using transvaginal sonographic transducers has been feasible since the early 1990s<sup>1,2</sup>, and by the late 1990s, improved spatial resolution of probes allowed the transabdominal route to be used as well in the assessment of high-risk patients<sup>3,4</sup>.

In recent years, nuchal translucency thickness (NT) and maternal serum biochemistry screening for trisomy 21 in the first trimester has been requested increasingly by women because of their proved effectiveness<sup>5,6</sup> and because of the opportunity to obtain at the same time additional information, including on the fetal anatomy. Other first-trimester sonographic markers of trisomy 21 have recently been proposed<sup>7</sup> as part of a two-stage assessment of risk. With the exception of the nasal bone<sup>8,9</sup>, these markers are related to the cardiovascular system, and include tricuspid valve regurgitation<sup>10–13</sup>, increased impedance to flow in the ductus venosus<sup>14</sup>, aberrant right

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subclavian artery<sup>15,16</sup> and vascular anomalies<sup>17</sup>. These may be explained in part by the theory of dysfunctional or abnormal angiogenesis occurring in cases of aneuploidy<sup>18</sup>. The emerging importance of these markers, as well as the long-recognized association between congenital heart disease (CHD) and trisomy 21, have caused renewed interest in the early study of the fetal heart. However, the degree of assessment of the early cardiovascular system that is feasible by the first-level operator remains unclear. The effectiveness in low-risk populations of such assessment, performed by operators who are trained but not specialists in echocardiography, has been the object of several studies<sup>19–21</sup>, with conflicting conclusions. Rustico *et al.*<sup>19</sup> deemed routine early cardiac assessment 'ill advisable' because of high costs in terms of time, equipment and involvement of operators, combined with a low sensitivity in detecting CHD, while Bronshtein and Zimmer<sup>21</sup> reported accurate results and suggested early fetal cardiac examination for all pregnant women. In both of these studies, transvaginal transducers were used and the assessments were not incorporated into existing screening tests such as NT.

The aim of this study was to assess whether the evaluation of the fetal heart (in terms of a distinction between normal and abnormal anatomy) routinely included in an NT examination, by means of the same transabdominal high frequency probe, is feasible and reliable in an acceptable length of time.

## MATERIAL AND METHODS

Included in the study were singleton pregnancies with a fetal crown–rump length (CRL) of 60–84 mm, referred between December 2003 and July 2005 for screening for trisomy 21 by fetal NT and maternal serum biochemistry.

Ultrasound examinations were carried out by a single operator (C.L.) who had obtained The Fetal Medicine Foundation Certificate of Competence in the 11–14-week scan and attended a 1-week intensive training course in fetal cardiology. Pregnant women were routinely offered an examination of the fetal extracardiac morphology and a complete fetal heart study (by B-mode, color Doppler and power Doppler imaging techniques). Written informed consent was obtained from all women having explained the limitations associated with early cardiac examination.

We first tested high-frequency linear transducers (6–15 MHz) using commercial and specially designed phantoms to define sensitivity and spatial resolution in B-mode and color-flow mapping applied to small-sized targets at 5.5–8 cm in depth. Because of its properties (velocity, angle independence and higher amount of signal at low power output), power Doppler flow mapping was considered optimal for our purposes. As a reference for the physics tests, a preliminary measurement of cardiac components was made on a 13-week fetal specimen. The tests performed by a physicist on built-in phantoms were focused to optimize color-flow imaging parameters at low power output, allowing spatial resolution to detect

and distinguish two adjacent flows as being separate, in parallel tubes simulating vessels at a distance of 0.2–0.5 mm from each other.

All patient scans were carried out transabdominally using an Acuson Sequoia 512 (Imagegate, Siemens, Erlangen, Germany) ultrasound machine equipped with either a 15-MHz (15L8w) or a 6-MHz (6L3) linear transducer. The 15-MHz transducer is usually used for imaging small parts and has an optimal resolution of 5–7.5 cm depth, which corresponds to the depth at which the fetus is lying in the majority of pregnancies at 12–14 weeks. The 6-MHz transducer has less resolution but deeper penetration (5–8.5 cm depth) and so is useful for studying the fetus when the images from the previous transducer are limited by a patient's anatomical features. The original preset of both transducers was modified in order to obtain images of diagnostic quality and to ensure adequate safety limits for an early cardiac scan: the mechanical index for B-mode (MI) and the soft tissue thermal index in color-flow modality (TIS) were set so as not to exceed a value of 1. Two presets were used with the 15-MHz probe: one for the heart position at a distance from the skin of 5–6.5 cm and one for a distance of 6.5–7.5 cm. For distances greater than 7.5 cm, a modified preset on the linear 6-MHz, transducer was used.

During the ultrasound examination, the operator measured the NT and visualized the nasal bones. For examination of the fetal extracardiac anatomy the following protocol was observed.

- Skull and brain: examination of the completeness of the skull and the presence of the falx and symmetrical choroid plexuses
- Face: examination of the orbits and the fetal profile; nasal bones studied in longitudinal and axial planes
- Spine: examination of the vertebrae
- Thorax: examination of diaphragm and mediastinum
- Abdomen: examination of stomach in the left upper abdomen, abdominal wall and umbilical cord insertion (including on the placenta)
- Urinary tract: examination of the kidneys and/or both renal arteries, and the bladder surrounded by two umbilical arteries
- Extremities: examination of the long bones, fingers, toes and the movement and posture of the joints.

For examination of the fetal cardiac anatomy, the operator looked for the following.

- Abdominal situs with the aorta to the left of the spine and the inferior vena cava anterior and to the right of the spine; the heart lying on the left side angled at 45° from the midline, occupying one quarter of the chest
- The four chambers of the heart with the left atrium in front of the spine and the right ventricle just below the sternum; atrial appendages; atrioventricular valve offsetting
- The aorta arising centrally in the heart from the left ventricle and the pulmonary trunk arising from the

anteriorly placed right ventricle and crossing to the fetal left side over the ascending aorta

- Interventricular septum: aortic continuity in the left outflow view
- The anteriorly positioned ductal arch and the transverse aortic arch on the left side, converging towards the fetal spine and being equal in size.

In order to increase the accuracy and to shorten the examination time<sup>22–25</sup>, a color-flow mapping investigation of the chambers and great vessels was carried out as follows.

- Four-chamber and septal aortic continuity: use of both power and color Doppler showing flow dynamics to visualize, recognize and compare the four chambers and pulmonary veins draining into the left atrium
- Outflows, arterial duct and aortic arch: visualization with power Doppler. 'X' sign (the crossing of the main pulmonary artery with the aorta); 'b' sign (the straight line of the pulmonary artery surrounded by aortic arch, when possible with three epiaortic vessel images); 'V' sign (the connection of the aorta and ductus arteriosus).

Tricuspid valve flow assessment was done in the last 125 examinations according to the criteria described by Hugon *et al.*<sup>10</sup>, with Doppler sampling in the right atrium at the level of the tricuspid valve, to search for significant regurgitation (occupying at least half of systole and with velocity > 80 cm/s). The long-axis view showing vessels arising from the aortic arch was also included in the last 93 fetuses.

In cases considered normal, reassessment of cardiac structures was recommended at 20 weeks, while those cases with suspicious or abnormal features were referred to a fetal cardiologist. In all fetuses with NT > 95<sup>th</sup> centile or with a familial risk for CHD, irrespective of the cardiac findings, an appointment for an expert examination was scheduled within 1 week and the operator (C.L.) observed this examination, in order to compare the findings, at the tertiary center where cardiac (V.F., M.B.) and extracardiac (M.B.) structures were examined.

In cases of termination of pregnancy, postmortem examination was performed by means of micro-dissection and subsequent histological study (A.C.). Operators involved in the screening and subsequent diagnosis were present during the postmortem examination. All cases, both normal and abnormal, that continued pregnancy underwent a complete scan with echocardiography at 20 weeks' gestation performed by one of the authors. Postnatal follow-up data were obtained directly from the parents or from the medical operators of maternity units at which the infants were delivered.

## RESULTS

The study group consisted of 623 pregnancies undergoing NT screening. The median maternal age was 34 (range, 28–41) years. The median gestational age at screening was 12 + 6 (range, 12 + 3 to 13 + 6) weeks, with a median

fetal CRL of 65 (range, 60–84) mm. Of these, 15 cases were excluded because of miscarriage ( $n = 3$ ) or because they were lost to follow-up ( $n = 12$ ).

The time necessary for the cardiac anatomy to be assessed confidently, in addition to the time required for the NT screening, was  $\leq 10$  min in 517/608 (85%) cases and longer in 85/608 (14%) cases. In the remaining six (1%) cases it was necessary to repeat the assessment within 2 weeks because of non-diagnostic images at the initial scan. A total of 456/608 (75%) cases were examined successfully using only the 15-MHz transducer, while the remaining 152 cases were also examined with the 6-MHz linear transducer.

In 573/608 (94.2%) fetuses, NT was < 95<sup>th</sup> centile. In the remaining 35 (5.8%) fetuses, 26 had an NT measurement between the 95<sup>th</sup> and 99<sup>th</sup> centiles and nine had NT > 99<sup>th</sup> centile. The group defined, according to NT and family history, as being at low risk for CHD included 571/608 (94%) fetuses. Heart anatomy was considered normal in all of these fetuses and this was confirmed at 20 and 32 weeks. No major CHD was found at the postnatal follow-up.

The 37 fetuses defined as being at increased risk for CHD (35 for NT > 95<sup>th</sup> centile and two with normal NT but with family history) were referred to a tertiary center for a further examination within 1 week. In 34 of these, the heart was classified as normal by the first-level operator and confirmed as such by the fetal cardiologist. In the remaining three fetuses, abnormal heart findings were suspected at the screening and, in all of these, major CHD was diagnosed by the fetal cardiologist. The defects were complete atrioventricular septal defect, truncus arteriosus, and simple transposition of the great arteries. In all three cases, the parents opted to terminate the pregnancy. Two of these fetuses had an abnormal karyotype (trisomy 21 in the fetus with atrioventricular septal defect and trisomy 18 in the one with truncus arteriosus) and a subsequent postmortem examination confirmed the cardiac diagnosis. In the fetus with simple transposition of the great arteries there was a normal karyotype and no other associated extracardiac anomaly; the parents, however opted for termination of pregnancy in another country and no postmortem confirmation was obtained.

Of the 125 patients in whom we checked for tricuspid regurgitation, holosystolic regurgitation was found in one case, with otherwise normal cardiac anatomy confirmed at 20 weeks and postnatally.

In 80 of the 93 fetuses in which we used power Doppler for long-axis view, three vessels were visible arising from the aortic arch. There were no false positives in our limited series.

## DISCUSSION

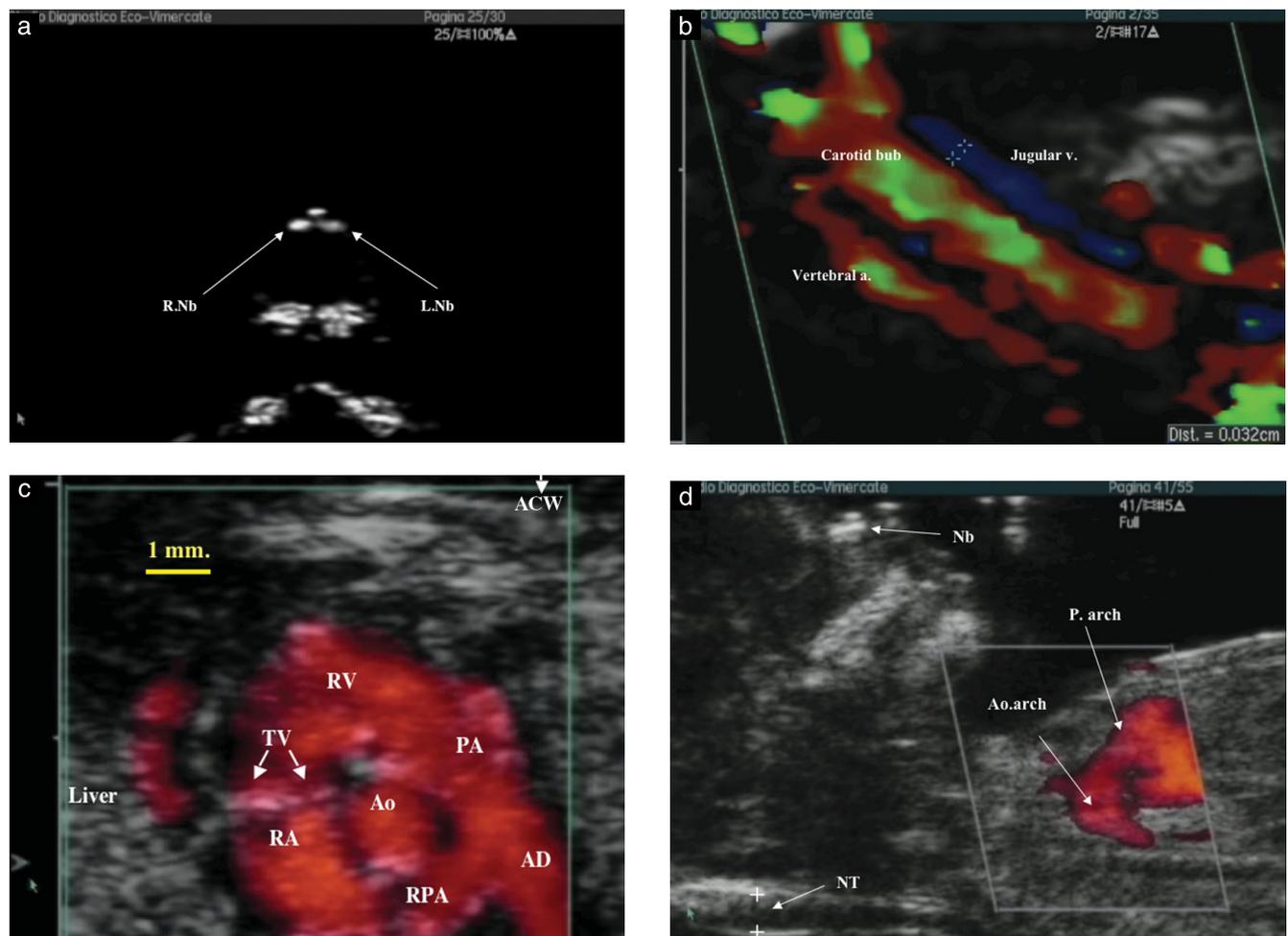
This study provides evidence that a routine study of the fetal heart during NT screening is feasible in a reasonable length of time when using high-frequency transabdominal transducers.

It is widely accepted that the measurement of NT to screen for aneuploidies should be combined with a search for early detectable malformations<sup>25–27</sup>. Currently, operators look only for extracardiac anomalies and not for cardiac defects. This is contradictory, because at this stage of gestation the heart has already almost completed its development<sup>2,28–30</sup>, whereas development of other fetal structures, in particular the brain, remains incomplete. Moreover, cardiac defects have a higher prevalence than do other fetal defects<sup>31,32</sup> and are more frequently associated with both chromosomal anomalies and genetic syndromes<sup>33,34</sup>.

The risk of a major CHD increases with increased NT thickness<sup>35</sup>, and this marker is more effective in defining a population at high risk than are family history, maternal diseases or exposure to teratogens<sup>36</sup>. However, increased NT is not an adequate method in isolation for screening for cardiac anomalies in euploid fetuses because of the relatively low sensitivity (30%)<sup>37–40</sup>. Thus we must rely

on the suspicions of the operator performing the routine scan, who remains the major potential contributor to the detection of CHD<sup>41,42</sup>.

Early cardiac screening is justified because fetal echocardiography in the first trimester performed by a specialist has been proved to be accurate in defining major cardiac anomalies present at this age<sup>43–46</sup>. However, a lack of operators who are trained specifically, as well as technical and time limitations, make questionable the routine scanning of the fetal heart in the first trimester. So far, the sensitivity of a routine cardiac scan in a non-selected population has been relatively low even at mid-gestation, despite persistent attempts to improve the detection rate<sup>42</sup>. If the study of the heart is challenging for operators at mid-gestation, its small size in the first trimester must make it even more challenging, and a lower sensitivity than that in the second trimester might be expected. Rustico *et al.*<sup>19</sup> argued against early screening of the heart because the low sensitivity (33%) does not justify

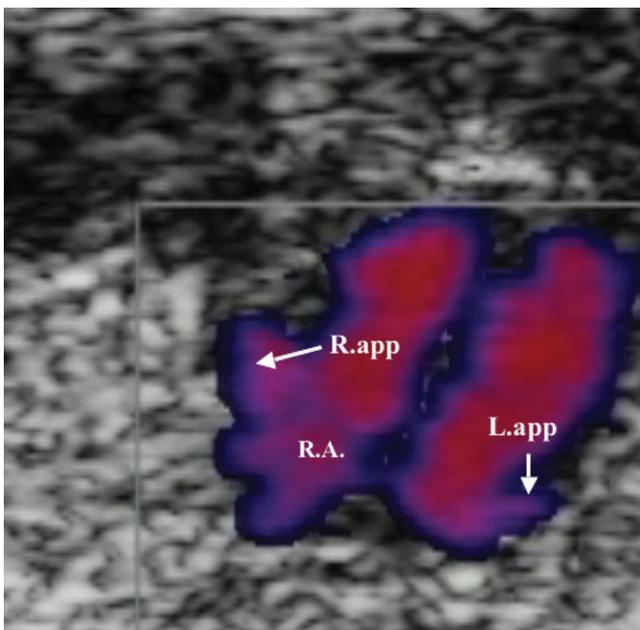


**Figure 1** Technical properties of a 15-MHz transabdominal linear transducer with a 50-mm footprint allow improved B-mode and color-flow mapping at 12–14 weeks. (a) B-mode assessment at 12 + 6 weeks of the two nasal bones in an axial plane. R.Nb and L.Nb, right and left nasal bones. (b) Details of the neck arteries at 13 + 0 weeks, with flow patterns of vertebral and carotid arteries and the jugular vein demonstrated by color Doppler; the calipers indicate the diameter of the jugular vein. (c) Detailed resolution using power Doppler of the heart structures at 13 + 1 weeks provides diagnostic images. ACW, anterior chest wall; AD, arterial duct; Ao, aorta; PA, pulmonary artery; RPA, right branch pulmonary artery; RA, right atrium; RV, right ventricle; TV, tricuspid valve. (d) At 12 + 5 weeks the optimal plane required for measuring nuchal translucency (NT) thickness and for visualizing the nasal bone (Nb) is adequate for describing the size and relationship of aortic and pulmonary arches (Ao.arch, P.arch).

its use as a single test. However, as recently explained by Campbell<sup>47</sup> when discussing the addition to NT screening of uterine artery Doppler examination as a screening test for severe pre-eclampsia, a test that cannot justifiably be performed alone could be 'piggy-backed' onto a screening program that is already in existence at no significant extra cost.

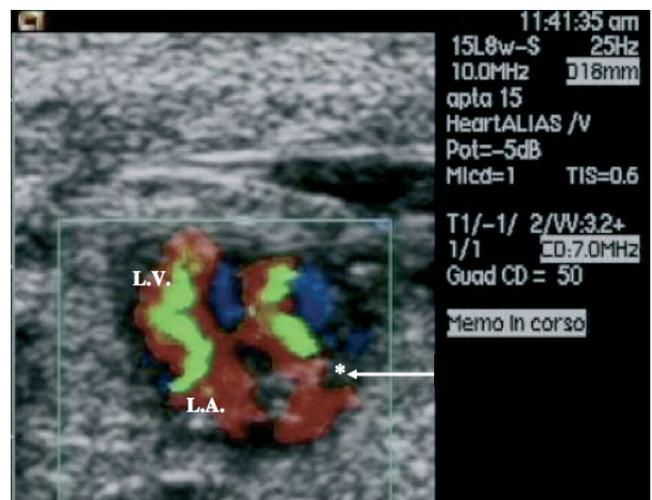
Currently, early cardiac scanning is offered to high-risk pregnancies in specialized centers, but circumstances are changing because of the wide dissemination of NT screening. The 11–14-week scan is demanding technically, requiring optimal use of image size, magnification, freezing, cine-loop, calipers and high resolution in order to measure accurately or observe clearly small structures such as NT or the nasal bones. NT screening requires good reliability and reproducibility in measuring structures that are fractions of millimeters in size, and so ongoing audit is mandatory. Arguably, NT measurement may be more acceptable to patients performed by a transabdominal rather than a transvaginal route, and the transabdominal route may also be preferable for morphological assessment, allowing a greater scope for varying viewing planes. All of these technical requirements for NT screening are also appropriate for an early cardiac study. The results of our physics tests were encouraging in terms of the potential application of these probes in the detailed study of fetal structures (Figure 1).

Another objection to early cardiac scanning is that it is too time-consuming. Our study shows, however, that after a learning period dedicated mostly to studying the technical optimization of real-time and color-flow presets, an average of 10 min should be added to the time for the routine NT examination and extracardiac evaluation.

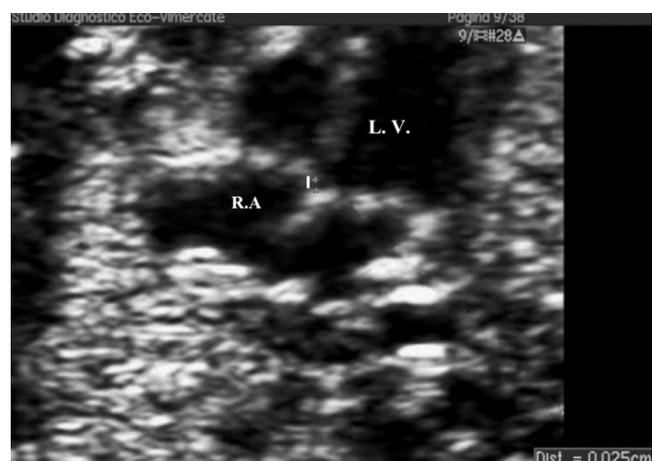


**Figure 2** Features of the atria at 12–14 weeks. Image in a 13 + 0-week fetus showing the atrial appendages on color power Doppler with a 6-MHz transducer. The right appendage (R.app.) is quadrangular in shape when filled and larger than the left, tubular appendage (L.app.). R.A., right atrium.

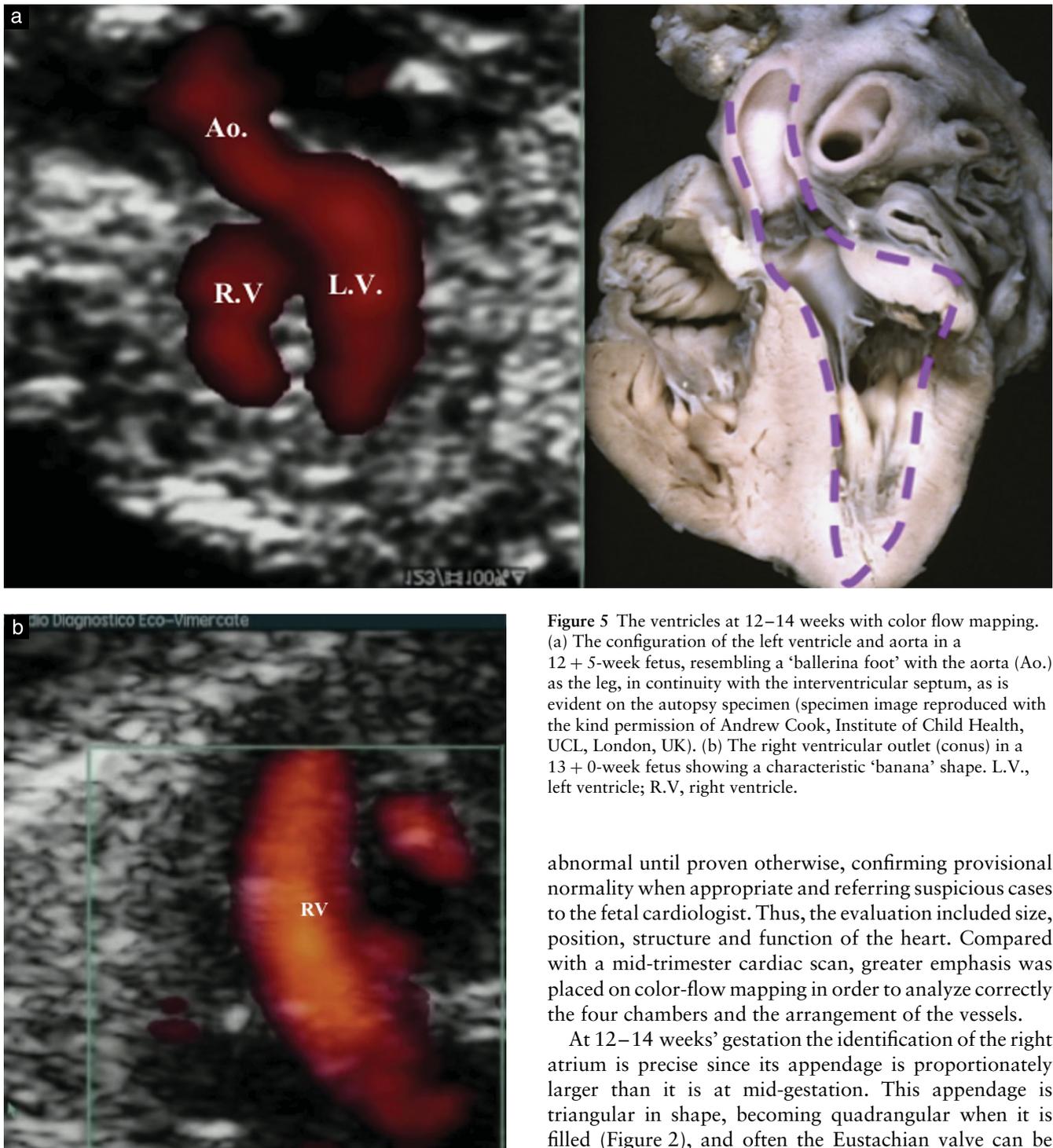
The operator who performed all the screening cardiac scans in this study was working at the time in a first-level unit and had attended a 1-week intensive training course in fetal cardiology. Aiming to detect normal versus abnormal heart findings rather than to make a diagnosis, he organized a multidisciplinary collaborative protocol with a team including a fetal cardiologist, an operator of a tertiary university unit and an experienced fetal cardiac morphologist. Postmortem examination of the fetal heart was carried out where appropriate after multidisciplinary review of the case with evaluation of the ultrasound images, allowing the pathologist to perform the most appropriate evaluation of the fetal heart. The first-level operator had easy access to discuss his cases with these experts, and compare his findings with the examination performed at the tertiary center, at follow-up or at autopsy. Thus, both his competence and his confidence in diagnosis improved.



**Figure 3** Power Doppler image of a 12 + 4-week fetal heart showing the Eustachian valve (\*) in the right atrium separating the blood stream. Images were obtained within the safety limits for acoustic output in B-mode and color Doppler, the thermal index for soft tissue (TIS) being 0.6.



**Figure 4** The crux of the heart and measurement of the displacement between the two inlet valves (I, calipers) in a 13 + 0-week fetus. R.A., right atrium; L.V., left ventricle.



**Figure 5** The ventricles at 12–14 weeks with color flow mapping. (a) The configuration of the left ventricle and aorta in a 12 + 5-week fetus, resembling a ‘ballerina foot’ with the aorta (Ao.) as the leg, in continuity with the interventricular septum, as is evident on the autopsy specimen (specimen image reproduced with the kind permission of Andrew Cook, Institute of Child Health, UCL, London, UK). (b) The right ventricular outlet (conus) in a 13 + 0-week fetus showing a characteristic ‘banana’ shape. L.V., left ventricle; R.V., right ventricle.

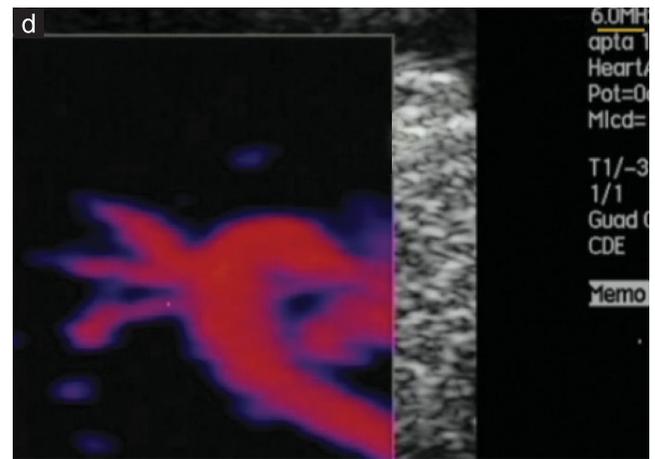
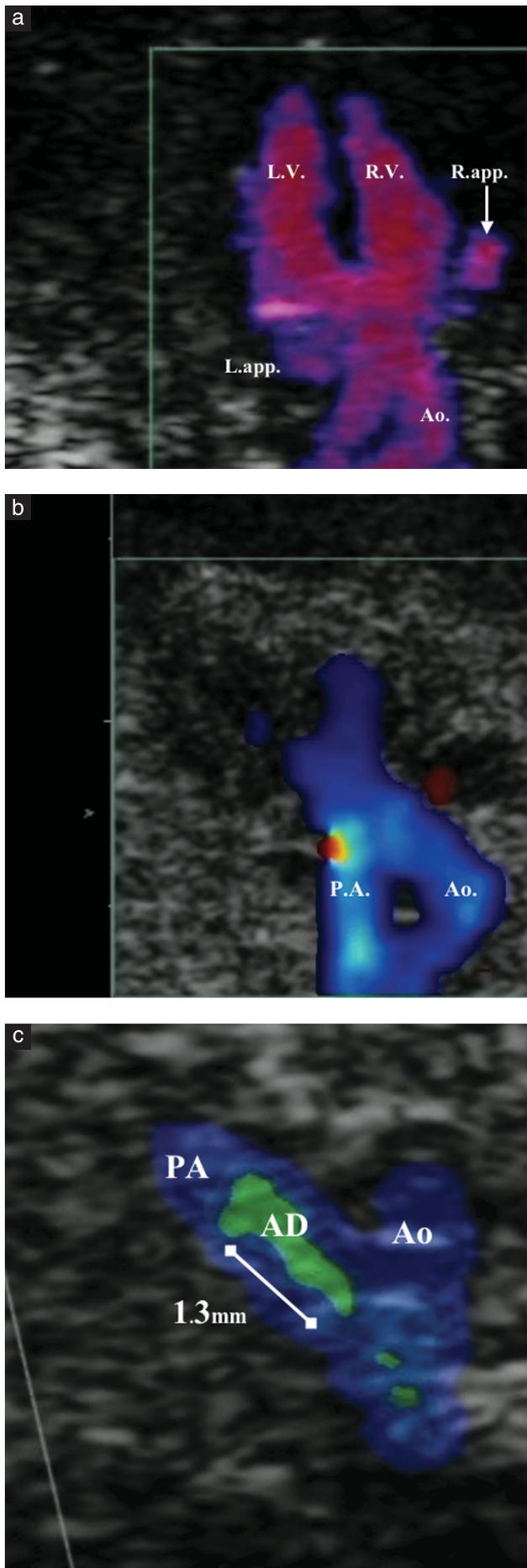
abnormal until proven otherwise, confirming provisional normality when appropriate and referring suspicious cases to the fetal cardiologist. Thus, the evaluation included size, position, structure and function of the heart. Compared with a mid-trimester cardiac scan, greater emphasis was placed on color-flow mapping in order to analyze correctly the four chambers and the arrangement of the vessels.

At 12–14 weeks’ gestation the identification of the right atrium is precise since its appendage is proportionately larger than it is at mid-gestation. This appendage is triangular in shape, becoming quadrangular when it is filled (Figure 2), and often the Eustachian valve can be seen as a second flap to the right of the foramen ovale (Figure 3). In comparison, the left atrium has a smaller appendage that is tubular in shape.

The veins draining into the left atrium were demonstrated in only a few cases by color-flow mapping. This limitation is related to suboptimal use of color flow: a smaller field of view was needed for color imaging but this was not possible with the transducers used.

Morphological right and left ventricles were distinguished by examining the offset of the inlet valves. The heart study was deferred until after 12 weeks of gestation because a delaminated septal leaflet of the tricuspid valve may not be seen at earlier gestational ages. The operator

A reason for the success of this study was because the operator tried to avoid early 12-week or late 13-week examinations deliberately. It was possible to schedule the patients optimally for the scan since they were previously booked at 9–11 weeks for the blood sample for the serum biochemistry tests. The fetal heart study was approached as a detailed evaluation of the whole cardiac anatomy rather than being restricted to any sonographic view. The aim and logical approach was the same as that used at the 20-week scan: the operator assumed that the heart was



**Figure 6** The outflow tract at 12–14 weeks. (a) In this 12 + 6-week fetus, the ‘X’ sign of the crossing of the great arteries is demonstrated using color power Doppler. In this plane, the atrial appendages are useful landmarks. (b) In this 12 + 4-week fetus, the ‘b’ sign is formed by the curved sweep of the aortic arch and the straight line of the pulmonary outflow and duct. (c) In this 13 + 0-week fetus, the ‘V’ sign is formed by the confluence of ductus arteriosus and aortic isthmus. The size of the two vessels was compared, without formal measurement. We consistently observed trivial aliasing in the ductus flow. (d) In this 13 + 0-week fetus, the vessels arising from the aortic arch were visualized with a 6-MHz transducer using adapted power Doppler settings. Ao, aorta; AD, arterial duct; L.app., left appendage; L.V., left ventricle; PA, pulmonary artery; R.app., right appendage; R.V., right ventricle.

could measure the displacement between the two inlet valves (0.25 mm) (Figure 4).

The optimum plane for visualizing the crux of the heart was that required for the correct placement of the Doppler sample volume in assessing tricuspid flow.

Morphological recognition of the ventricles was in some cases limited. The operator learned to rely on color power Doppler for identifying the typical appearance of a ‘banana-shaped’ right ventricle and a ‘ballerina shoe-shaped’ left ventricle (Figure 5).

The ‘X’ sign, produced by the normal crossing of the great arteries, is easy to obtain in different planes. The ‘b’ sign on color-flow mapping, formed by the curving sweep of the aortic arch adjacent to the straight line formed by the pulmonary artery and arterial duct, is also an indication of normally related great arteries. In the last 93 fetuses the operator tried to obtain views of the branches arising from the aortic arch in order to be more confident about the anatomy of the aortic arch. To do so only a further modification on the previous preset used for color power Doppler was necessary. The ‘V’ sign is formed by the confluence of the ductus arteriosus to the aortic isthmus. The operator compared, without measuring, the relative sizes of the two vessels and observed consistently trivial aliasing in the ductus arteriosus (Figure 6).

Our sample size was too small to give reliable results on the false-negative rate. In the literature, we could find only one study (Rustico *et al.*<sup>19</sup>) giving a false-positive rate (0.02%). We expect screening the heart at 12–13 weeks with high-frequency transducers to have a low false-positive rate, because of the lower variability

of dimensions and more homogeneous morphology of the structures compared with in mid- or late gestation, when the range or spectrum of normal features is wider in terms of both morphology and function. The detection of some cardiac anomalies is related to gestational age, but basic evaluation of the four chambers, outflow tracts and aortic and pulmonary arches is feasible if the trained operator can obtain adequate images. The key point is that at 12–13 weeks, the aim of fetal cardiac assessment is to verify normality and exclude major CHD that is detectable at this gestational age. Disproportion of chambers or vessels should be an indication for prompt referral to a tertiary center. Major anomalies of connection, such as transposition of the great arteries, double outlet right ventricle or truncus arteriosus are evident with the aid of color-flow mapping even in patients that are technically difficult to scan.

In conclusion, assessment of the fetal heart will become an essential part of the routine fetal evaluation in women examined at 12–13 weeks for NT and so will further improve the performance of screening for chromosomal anomalies and genetic syndromes. Our own experience suggests that the use of high-resolution transabdominal transducers with an appropriate preset is the key requirement for adequate cardiac evaluation in an acceptable length of time. Continuous training and audit to maintain and improve standards of accuracy are mandatory.

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## REFERENCES

- Gembruch U, Knopfle G, Bald R, Hansmann M. Early diagnosis of fetal congenital heart disease by transvaginal echocardiography. *Ultrasound Obstet Gynecol* 1993; 3: 310–317.
- Allan LD, Santos R, Pexieder T. Anatomical and echocardiographic correlates of normal cardiac morphology in the late first trimester fetus. *Heart* 1997; 77: 68–72.
- Carvalho JS, Moscoso G, Ville Y. First-trimester transabdominal fetal echocardiography. *Lancet* 1998; 351: 1023–1027.
- Smrcek JM, Berg C, Geipel A, Fimmers R, Axt-Flidner R, Diedrich K, Gembruch U. Early fetal echocardiography: heart biometry and visualization of cardiac structures between and 15 weeks' gestation. *J Ultrasound Med* 2006; 25: 173–178.
- Hyett J. Patient choice and the randomized controlled trial. *Ultrasound Obstet Gynecology* 2005; 25: 535–536.
- Spencer K, Spencer CE, Power M, Dawson C, Nicolaides KH. Screening for chromosomal abnormalities in the first trimester using ultrasound and maternal serum biochemistry in a one-stop clinic: a review of three years prospective experience. *BJOG* 2003; 110: 281–286.
- Nicolaides KH, Spencer K, Avgidou K, Faiola S, Falcon O. Multicenter study of first-trimester screening for trisomy 21 in 75 821 pregnancies: results and estimation of the potential impact of individual risk-orientated two-stage first-trimester screening. *Ultrasound Obstet Gynecol* 2005; 25: 221–226.
- Cicero S, Rembouskos G, Vandecruys H, Hogg M, Nicolaides KH. Likelihood ratio for trisomy 21 in fetuses with absent nasal bone at the 11–14-week scan. *Ultrasound Obstet Gynecol* 2004; 23: 218–223.
- Cicero S, Spencer K, Avgidou K, Faiola S, Nicolaides KH. Maternal serum biochemistry at 11–13 + 6 weeks in relation to the presence or absence of the fetal nasal bone on ultrasonography in chromosomally abnormal fetuses: an updated analysis of integrated ultrasound and biochemical screening. *Prenat Diagn* 2005; 25: 977–983.
- 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: 1071–1073.
- Faiola S, Tsoi E, Huggon IC, Allan LD, Nicolaides KH. Likelihood ratio for trisomy 21 in fetuses with tricuspid regurgitation at the 11 to 13 + 6-week scan. *Ultrasound Obstet Gynecol* 2005; 26: 22–27.
- Falcon O, Faiola S, Huggon I, Allan L, Nicolaides KH. Fetal tricuspid regurgitation at the 11 + 0 to 13 + 6-week scan: association with chromosomal defects and reproducibility of the method. *Ultrasound Obstet Gynecol* 2006; 27: 609–612.
- Falcon O, Auer M, Geroassili A, Spencer K, Nicolaides KH. Screening for trisomy 21 by fetal tricuspid regurgitation, nuchal translucency and maternal serum free beta-hCG and PAPP-A at 11 + 0 to 13 + 6 weeks. *Ultrasound Obstet Gynecol* 2006; 27: 151–155.
- 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: 307–310.
- Chaoui R, Heling KS, Sarioglu N, Schwabe M, Dankof A, Bollmann R. Aberrant right subclavian artery as a new cardiac sign in second and third-trimester fetuses with Down syndrome. *Am J Obstet Gynecol* 2005; 192: 257–263.
- Chaoui R. Prenatal ultrasound diagnosis of Down syndrome. After major malformations, soft markers, nuchal translucency and skeletal signs, a new vascular sign? *Ultrasound Obstet Gynecol* 2005; 26: 214–217.
- Berg C, Knuppel M, Geipel A, Kohl T, Krapp M, Knopfle G, Germer U, Hansmann M, Gembruch U. Prenatal diagnosis of persistent left superior vena cava and its associated congenital anomalies. *Ultrasound Obstet Gynecol* 2006; 27: 252–265.
- Li CM, Guo M, Salas M, Schupf N, Silverman W, Zigman WB, Husain S, Warburton D, Thaker H, Tycko B. Cell type-specific over-expression of chromosome 21 genes in fibroblasts and fetal hearts with trisomy 21. *BMC Med Genet* 2006; 7: 24.
- Rustico MA, Benettoni A, D'Ottavio G, Fischer-Tamaro L, Conoscenti GC, Meir Y, Natale R, Bussani R, Mandruzato GP. Early screening for fetal cardiac anomalies in an unselected population: the role of operator experience. *Ultrasound Obstet Gynecol* 2000; 16: 614–619.
- 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: 1029–1034.
- Bronshtein M, Zimmer EZ. The sonographic approach to the detection of fetal cardiac anomalies in early pregnancy. *Ultrasound Obstet Gynecol* 2002; 19: 360–365.
- Chaoui R, McEwing R. Three cross-sectional planes for fetal color Doppler echocardiography. *Ultrasound Obstet Gynecol* 2003; 21: 81–93.
- Carvalho JS. Early prenatal diagnosis of major congenital heart defects. *Curr Opin Obstet Gynecol* 2001; 13: 155–159.
- Yagel S, Cohen SM, Achiron R. Examination of the fetal heart by five short-axis views: a proposed screening method for comprehensive cardiac examination. *Ultrasound Obstet Gynecol* 2001; 17: 367–369.

25. Souka AP, Pilalis A, Kavalakis I, Antsaklis P, Papantoniou N, Mesogitis S, Antsaklis A. Screening for major structural abnormalities at the 11- to 14-week ultrasound scan. *Am J Obstet Gynecol* 2006; **194**: 393–396.
26. Weisz B, Pajkrt E, Jauniaux E. Early detection of fetal structural abnormalities. *Reprod Biomed* 2005; **10**: 541–553.
27. Souka AP, Von Kaisenberg CS, Hyett JA, Sonek JD, Nicolaides KH. Increased nuchal translucency with normal karyotype. *Am J Obstet Gynecol* 2005; **192**: 1005–1021.
28. Cook AC, Yates RW, Anderson RH. Normal and abnormal fetal cardiac anatomy. *Prenat Diagn* 2004; **24**: 1032–1048.
29. Anderson RH, Webb S, Brown NA, Lamers W, Moorman A. Development of the heart: (3) formation of the ventricular outflow tracts, arterial valves and intrapericardial arterial trunks. *Heart* 2003; **89**: 1110–1118.
30. de Lange FJ, Moorman AF, Anderson RH, Manner J, Soufan AT, de Gier-de Vries C, Schneider MD, Webb S, van den Hoff MJ, Christoffels VM. Lineage and morphogenetic analysis of the cardiac valves. *Circ Res* 2004; **95**: 645–654.
31. Garne E, Stoll C, Clementi M. Evaluation of prenatal diagnosis of congenital heart diseases by ultrasound: experience from 20 European registries. *Ultrasound Obstet Gynecol* 2001; **17**: 386–391.
32. Garne E, Loane M, Dolk H, De Vigan C, Scarano G, Tucker D, Stoll C, Gener B, Pierini A, Nelen V, Rosch C, Gillerot Y, Feijoo M, Tincheva R, Queisser-Luft A, Addor MC, Mosquera C, Gatt M, Barisic I. Prenatal diagnosis of severe structural congenital malformations in Europe. *Ultrasound Obstet Gynecol* 2005; **25**: 6–11.
33. Pajkrt E, Weisz B, Firth HV, Chitty LS. Fetal cardiac anomalies and genetic syndromes. *Prenat Diagn* 2004; **24**: 1104–1115.
34. Hyett JA, Perdu M, Sharland GK, Snijders RS, Nicolaides KH. Increased nuchal translucency at 10–14 weeks of gestation as a marker for major cardiac defects. *Ultrasound Obstet Gynecol* 1997; **10**: 242–246.
35. Ghi T, Huggon IC, Zosmer N, Nicolaides KH. Incidence of major structural cardiac defects associated with increased nuchal translucency but normal karyotype. *Ultrasound Obstet Gynecol* 2001; **18**: 610–614.
36. Maher JE, Colvin EV, Samdarshi TE, Owen J, Hauth JC. Fetal echocardiography in gravidas with historic risk factors for congenital heart disease. *Am J Perinatol* 1994; **11**: 334–336.
37. Mavrides E, Cobian-Sanchez F, Tekay A, Moscoso G, Campbell S, Thilaganathan B, Carvalho JS. Limitations of using first-trimester nuchal translucency measurement in routine screening for major congenital heart defects. *Ultrasound Obstet Gynecol* 2001; **17**: 106–110.
38. Hyett J. Does nuchal translucency have a role in fetal cardiac screening? *Prenat Diagn* 2004; **24**: 1130–1135.
39. Arzei A, Gajewska K, Huggon IC, Allan L, Nicolaides KH. Relation between nuchal translucency thickness and prevalence of major cardiac defects in fetuses with normal karyotype. *Ultrasound Obstet Gynecol* 2005; **26**: 154–157.
40. Makrydimas G, Sotiriadis A, Huggon IC, Simpson J, Sharland G, Carvalho JS, Daubeney PE, Ioannidis JP. Nuchal translucency and fetal cardiac defects: a pooled analysis of major fetal echocardiography centers. *Am J Obstet Gynecol* 2005; **192**: 89–95.
41. Carvalho JS. Fetal heart scanning in the first trimester. *Prenat Diagn* 2004; **24**: 1060–1067.
42. Carvalho JS, Mavrides E, Shinebourne EA, Campbell S, Thilaganathan B. Improving the effectiveness of routine prenatal screening for major congenital heart defects. *Heart* 2002; **88**: 387–391.
43. McAuliffe F, Hornberger L, Winsor S, Chitayat D, Chong K, Johnson J. Fetal cardiac defects and increased nuchal translucency thickness. *Am J Obstet Gynecol* 2004; **191**: 1486–1490.
44. Weiner Z, Lorber A, Shalev E. Diagnosis of congenital cardiac defects between 11 and 14 weeks' gestation in high-risk patients. *J Ultrasound Med* 2002; **21**: 23–29.
45. Huggon IC, Ghi T, Cook AC, Zosmer N, Allan LD, Nicolaides KH. Fetal cardiac abnormalities identified prior to 14 weeks' gestation. *Ultrasound Obstet Gynecol* 2002; **20**: 22–29.
46. Comas Gabriel C, Galindo A, Martinez JM, Carrera JM, Gutierrez-Larraya F, de la Fuente P, Puerto B, Borrell A. Early prenatal diagnosis of major cardiac anomalies in a high-risk population. *Prenat Diagn* 2002; **22**: 586–593.
47. Campbell S. First-trimester screening for pre-eclampsia. *Ultrasound Obstet Gynecol* 2005; **26**: 487–489.