FIRST TRIMESTER FETAL ECHOCARDIOGRAPHY. STATE OF THE PROBLEM

Javier Pérez-Pedregosa¹, María Begoña Adiego Burgos², Pilar Martínez-Ten²

REZUMAT

Anomaliile cardiace sunt printre cele mai frecvente malformaţii congenitale. Este cunoscut faptul că diagnosticul prenatal al acestor malformaţii are un impact major asupra managementului pre- şi postnatal al sarcinilor cu făt afectat. Evoluţia tehnologică şi supraspecializarea personalului au făcut posibile efectuarea ecocardiografiei precoce între 11-14 săptămâni de gestaţie. Încă de la acest stadiu de dezvoltare se pot depista în proporţie semnificativă anomaliile cardiace. Evaluarea ecocardiografică precoce este în prezent rezervată cazurilor cu risc crescut pentru defecte cardiace (NT crescută sau prezenţa unei leziuni extracardiace). Propunem însă că explorarea cordului să devină parte din evaluarea morfologică precoce, în rândul populaţiei cu risc scăzut, unde se întâlnesc 80% din anomaliile cardiace. Ecocardiografia fetală din trimestrul II continuă să rămână un standard de aur şi trebuie să fie efectuată pentru toate sarcinile în curs.

Cuvinte cheie: primul trimestru, explorare la 11-14 săptămâni, translucenţa nucală, defecte cardiace, ecocardiografie fetală, diagnostic prenatal

ABSTRACT

Cardiac anomalies are the most frequent congenital malformations and it has been shown that prenatal diagnosis has a major impact on the prenatal and postnatal management of affected pregnancies. Technical improvements and highly skilled operators, have demonstrated that early echocardiography, at 11-14 weeks scan, is feasible and a significant proportion of cardiac lesions present with abnormal ultrasound findings at this stage. Early evaluation is at this moment best reserved for cases at greater risk of cardiac defects (increased nuchal translucency and presence of extra cardiac lesions) but we proposed that it forms part of the early morphologic evaluation in low risk population where 80% of the cardiac anomalies happen. Second trimester fetal echocardiogram continues to be the gold standard and has to be performed for the ongoing pregnancies.

Key words: First trimester, 11-14 weeks scan, nuchal translucency, cardiac defects, fetal echocardiography, prenatal diagnosis

INTRODUCTION

11-14 weeks scan plays a main role for the screening of chromosomal abnormalities. First trimester nuchal translucency (NT) measurement is a well established and widely accepted method of screening for chromosomal defects and it is increasingly being incorporated into routine clinical practice. The method for measurement is well described and standardized. Fetal NT, in combination with maternal age and maternal serum markers (PAAP-A and free B-HCG), can detect approximately 90% of fetuses with trisomy 21 and other major chromosomal defects.¹ The detection rate of Down syndrome using this marker alone can reach 60-70% with a very low false–positive rate.² In addition, there is much more information hidden in the fetal NT. Several reports with thousands of pregnancies agree with the usefulness of this marker not only in detecting aneuploidies but also structural malformations and genetic syndromes, providing information about a general prognosis for the pregnancy.³ An increased fetal NT in a fetus with normal karyotype signifies greater risk for fetal cardiac defects and other syndromes.⁴ Atzei et al reported that the prevalence for major cardiac defects increases exponentially with fetal NT thickness.⁵ Many authors recommend fetal echocardiography in these cases, although a uniform approach has not yet been established.

Interest is focused in the last years in early morphologic evaluation at the time of the nuchal scan. Different studies have showed that a detailed and protocolized study, could led us to a high detection rate of structural malformations at this early stage.⁶ It is widely accepted that the measurement of NT to screen for aneuploidies should be combined with a search for early detectable malformations but currently sonographers look for extracardiac abnormalities and not for cardiac defects but this is contradictory because, at this stage of gestation the heart has almost already completed it’s development.⁷
First-trimester echocardiography provides an opportunity to examine the fetal heart early in gestation, especially in patients at risk for cardiac malformations because of a positive family history or in fetuses with increased nuchal translucency and/or abnormal flow at ductus venosus and/or tricuspid regurgitation. Fetal heart evaluation at this time is difficult but a trained operator can perform a fetal heart study during the NT screening test using transabdominal and/or transvaginal high-resolution transducers in an acceptable length of time.

The applications, methods, results, benefits and limitations of early echocardiography at 11-14 weeks scan will be reviewed at this paper.

EPIDEMIOLOGY.

Congenital heart defects (CHD) are the most frequent major congenital malformations with an incidence of 0.5 - 1/100 live born infants. Half of them are lethal or require major surgery with a minimum surgical mortality of 5-10%. There is a 25-35% of global mortality for the prenatally diagnosed cases, 60% during the first year. More than 50% of infant mortality and 20-30% of neonatal deaths are caused by congenital cardiac anomalies. CHD are 4 times more frequent than neural tube defects and 6 times versus chromosomal abnormalities and it is well known the big efforts that are focused in prevent (maternal folic prevention program) and diagnose this problems.

There is a strong association with genetic syndromes and aneuploidies, which is higher in prenatally diagnosed cases (5% in pediatric series, 25% in fetal series). Ninety percent of trisomy 18 fetuses, 90% of trisomy 13 fetuses and 35% of 45X0 fetuses have a cardiac malformation. If a congenital heart disease is present, there is a ten times increased risk of an additional malformation, even when 70-80% are isolated.11

Benefits of early detection are clear. Birth planning is fundamental especially in cases with ductus arteriosus (DA) dependant anomalies. In that cases, postnatal closure of DA precipitates acute hemodynamic compromise. If prenatal diagnosis is done, maintenance of patency of DA allows presurgical hemodynamic stabilization. It has been published that even for the worse prognosis subtypes, (hypoplastic left heart syndrome, great vessels transposition.) prenatal diagnosis produces a significant reduction of intra and postsurgical morbidity/mortality.15 Early detection will also allow us to inform parents and offer termination of pregnancy (TOP) in selected cases with bad prognosis with time enough for taking decisions. Demonstration of cardiac anomalies at this stage can also explain early fetal anomalies in some cases that otherwise would remain undiagnosed. On the other hand, a normal cardiac exam at 11-14 weeks will reduce parents anxiety with special interest in those families with high risk.

After this data, we should consider if the evaluation of the fetal heart should be performed in all the pregnant women or only in selected cases.

METHODOLOGY. TECHNICAL ASPECTS. HOW? WHEN?

It is obvious that at this early stage of pregnancy the size of the structures is the main limitation for the study but technical improvements with high resolution probes with specific presets have contributed to the development of the exam. It is important to reduce the scan area so that we can obtain more images per second of the region of interest. The probe frequency should be modified depending on the maternal habitus and position of the uterus. Colour Doppler should be adjusted with special attention at Pulse repetition frequency that has to be adapted for the velocities of the flow at this moment.

TRANSABDOMINAL VS TRANVAGINAL APPROACH

First reports published at the begginin of the 90’s employed transvaginal probes. In general transvaginal approach offers a better resolution of the fetal heart but it has some inconvenients. The main one is the limitation to obtain some planes because we are limited to a single axis. Fetal movements at this moment produce continous changes in the images so, experience of the operator is fundamental given that in many ocasions the visualization of certain structures will be on the screen for just a seconds. Some patiens experience transvaginal exam as cumbersome and is obvious that it is time consuming if we consider the early echocardiography as a future screening test for the whole population. The main advantage of the transabdominal approach is the higher number of different planes that can be obtained but with a lower resolution. Several reports differ on the results depending on the year of publication but in general they agree with the idea that transvaginal approach is better between 10-13 weeks and from that time, they both have similar results.12 Sometimes it can be necessary to combine both approaches and operator experience and preferences play an important role as well.
WHEN

Even with the newest high resolution equipments, heart embriology and development makes no possible an initial cardiac exam until 10 weeks. The rate of a complete cardiac evaluation improves as increases gestational age. Haak et al. reported 20% between 11-11 weeks and 92% between 13-13+6 weeks with a transvaginal probe. Souka et al. in 2004 and Smreck et al. in 2006 reported similar success rates with 100% of visualization at 14-15 weeks. The four-chamber view is the easiest plane to obtain. Haak reported 85% of success at 11 weeks and 98% at 13+6 weeks. The outflow tracts visualisation rate was 98% from

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**Figure 1.** Echocardiography at 12 weeks. (a) Four-chamber view, (b) color Doppler showing atrio-ventricular flow, (c) five-chamber view, long left ventricle axis, (d) Aorta and pulmonary artery crossing, (e) three vessels view (Voo), (f) three vessels view (V sign), (g & h) aortic arch, (i & j) ductal arch. L, left; Lv, left ventricle; R, right; Ra, right atrium; Rv, right ventricle; La, left atrium; PA. Pulmonary artery; SVC, right superior vena cava; Ao, aorta.

**Figure 2.** Echocardiography at 14 weeks. (a) Four-chamber view, (b) color Doppler showing atrio-ventricular flow, (c) Aorta and pulmonary artery crossing, (d) three vessels view (Voo), (e) three vessels view (V sign), (f & g) aortic arch, (h & i) ductal arch. L, left; Lv, left ventricle; R, right; Ra, right atrium; Rv, right ventricle; La, left atrium; PA. Pulmonary artery; SVC, right superior vena cava; Ao, aorta.
13 weeks. They also observed that pulmonar trunk was easier to observe than aortic between 11 and 11+6 weeks. It is also important to consider the possibility of evolving lesions principally valvular (mitral & tricuspid) and septal defects and follow up is necessary in most of the cases.

THE EXTENDED BASIC EXAM. ONLY FOUR CHAMBER VIEW IT’S NOT ENOUGH

Taking in to account the limitations due to the early gestational age, maternal habitus, fetal position and quality of the equipment the early heart exam should be performed as the conventional one at 20 weeks.

The extended basic study proposed by ISUOG includes the four-chamber view and outflow tracts. We recomend to extend the evaluation with a sequential study with 5 different planes from upper abdomen to mediastinum that allows the visualization of the main cardiovascular structures increasing the effectiveness of the exam, without a big increase in the complexity that can be obtain with subtle movements and tiltings of the probe.

Upper abdomen
Four-chamber view. (Fig. 1a,b, 2a,b)
Five-chamber view (connexion left ventricle - aortic root). (Fig. 1c)
Short axis - great vessels view (connexion right ventricle - pulmonary artery and its bifurcation)
Three vessels view (pulmonary artery with ductus arteriosus, aorta, right superior vena cava) also called line, dot, dot. (Fig. 1c, 2d)
The first two planes will allow us to determine the situs, situation and anomalies of auricles, ventricles, septum and valves. The evaluation of the outflow tracts will identify conotruncal malformations that remain undiagnosed with a single four-chamber view. We should take into account that until 15 gestational weeks the outflow tracts have an eliptic shape and depending on the view, we could obtain a false image of desproportion between both vessels. At this early stage it is also feasible the identification of the aortic and ductal arch (Fig. 1g,h,i,j, 2f,g,h,i) as well as anomalies of pulmonary and sistemic veins.

Color and pulsed Doppler can be very useful and there are different signs described as for conventional ecochocardiography at an advanced gestational age. Two parallel jets are seen in a normal four-chamber view with the flow passing from both auricles to the ventricles with similar color and without aliasing. (Fig. 1b, 2b) Pulsed Doppler with the sample gate at the level of the atrioventricular valves will show the typical pattern with the E and A wave. The first one, always smaller, it is produced by the early pass of the flow from the auricle to the ventricle at the first moment of diastole. The A wave is caused by the pass of the flow due to the auricle contraction at the late diastole. We can also study the presence of tricuspid regurgitation in a correct apical view. Color Doppler can be applied at the outflow tracts identifying the X sign (Fig. 1d, 2c) that represents the normal crossing of aorta and pulmonary artery and the V sign (Fig. 1f, 2c) that shows the connection between pulmonary artery with ductus arterioso and descending aorta.

In a recent study Lombardy reported that in 84% of the pregnancies less than 10 minutes were necessary for a complete exam. Other studies have reported examination times of around 20 minutes. Experience of the examiner, gestational age and maternal habitus are the main factors related to the lenght of the exam but we should consider that many of these reports are done by highly skilled specialists.

It’s very important to be used to this different views and signs that will allow us to understand and
identify abnormal findings in a fetus with a cardiac malformation at this early stage. (Figs. 3-6)

**Figure 5.** 14 weeks. Mitral estenosis with an aorta that overrides over a ventricular septal defect (VSD). (a) Abnormal four-chamber view showing a disproportion of chambers with a smaller left ventricle and normal right one. (b) Basal four-chamber view. (c) Five-chamber view showing a VSD (arrows). (d) Five-chamber view and aorta that overrides over the VSD. (e) Three vessels view and trachea. (f) color Doppler image of the three vessels view. L, left; Lv, left ventricle; R, right; Ra, right atrium; Rv, right ventricle; PA, Pulmonary artery; SVC, superior vena cava; T, trachea; Ao, aorta.

**Figure 6.** 14 weeks. Complete transposition of the great vessels. (a) Normal four-chamber view. (b) Normal color Doppler image of a four-chamber view showing two parallel jets. (c) Parallel outflow tracts, there is no X sign. (d) Upper mediastinum view that shows only two vessels (pulmonary artery and right superior vena cava). L, left; Lv, left ventricle; R, right; Ra, right atrium; Rv, right ventricle; PA, Pulmonary artery; SVC, right superior vena cava; T, trachea.

**RESULTS**

Early echocardiography requires highly experienced operators with adequate equipments and enough time. At this moment, this study is limited to tertiary centers and selected cases. But is well known that most of the cases affect low risk population (80%) where sensitivity of the exam is low (21%).

In the next years we should consider the posibility of the development of training programs for performing an early cardiac evaluation at the nuchal scan that will probably lead us to a higher detection rate. The size of the cardiac structures, at this moment below 22 mm, can explain why the results, even in series published by high expertise operators, are presented with an important false negative rates. In low risk population Rustico reported a 33% of sensitivity during first trimester. Gabriel et al reported better results in a high risk population on a multicentric study. The gestational age was higher (between 12 and 17 weeks) and the study was performed by highly skilled examiners (four chambers view + outflow tracts + venous return were obtained in 95% of the cases). The exam time was also higher than previously reported (30 minutes). There were 48 major cardiac defects and 38 were suspected in early evaluation. TOP was performed in 37 cases but necropsy only in 68%. This makes not possible to determine accurately sensitivity and specificity that ranges between 49-79 % and 94-100 % respectively.

Another important question is which subtypes are feasible to be diagnosed during the 11-14 weeks scan. Cardiac lesions can be evolutive and some cardiac defects are only evident in posterior stages (dysrhythmias, hypertrophic cardiomyopathies, tumors, blood flow obstructions). Huggon et al. reported true positive results in major cardiac defects like atrioventricular septal defects, hypoplastic left ventricle, Ebstein anomaly, truncus and tricuspid atresia and false negative in 7 cases affected by malformations of difficult diagnosis even at 20 weeks conventional echocardiography such as right aortic arch, ventricular septal defect (VSD) + coarctation, persistent left superior vena cava (2 cases), aortic arch hypoplasia, ventricular and great vessels desproportion, and aortic arch hypoplasia and perimembranous VSD + mild chambers disproportion.

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This results should be used to inform the parents about the possibilities of early echocardiography knowing, that in expert hands we can obtain a high detection rate for some subtypes with a high negative predictive value. A conventional examination has to be performed to the ongoing pregnancies at 20 weeks.

**FIRST TRIMESTER MARKERS AND CARDIAC ANOMALIES**

Screening for congenital heart disease using nuchal translucency measurement

Extensive studies have now established that increased NT is also a non specific finding in chromosomally normal fetuses, and it is associated
with a wide range of fetal structural defects, genetic syndromes and intrauterine lethality. The prevalence of birth defects and adverse outcome including miscarriage and intrauterine fetal death increases with increasing NT measurement. Among the structural anomalies, CHD are the most common in both chromosomally normal and abnormal fetuses. An association between increased NT and cardiac defects was first noted by Hyett and al, in pathologic studies after surgical termination in both chromosomally abnormal and normal fetuses. This has subsequently been confirmed by a number of studies. The combined data from nine series shows a high prevalence of major CHD, that increases exponentially with increasing NT thickness from 6 to 62/1000 in those with NT of 2.5 to 3.4 mm to 23 to 122/1000 in those with a NT of 3.5 mm or more. (Table 1)

**Table 1.** Studies reporting the prevalence of major CHD in chromosomally normal fetuses with increased NT.

<table>
<thead>
<tr>
<th>N</th>
<th>Cardiac defects (per mil)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT: 2.5-3.4 mm</td>
<td>NT ≥3.5 mm</td>
</tr>
<tr>
<td>Hyett (1997)</td>
<td>1389</td>
</tr>
<tr>
<td>Ghi (2001)</td>
<td>1319</td>
</tr>
<tr>
<td>Lopes (2003)</td>
<td>275</td>
</tr>
<tr>
<td>Galindo (2003)</td>
<td>353</td>
</tr>
<tr>
<td>McAuliffe (2004)</td>
<td>156</td>
</tr>
<tr>
<td>Bahado-Singh (2005)</td>
<td>378</td>
</tr>
<tr>
<td>Atzei (2005)</td>
<td>3444</td>
</tr>
<tr>
<td>Allan (2006)</td>
<td>766</td>
</tr>
<tr>
<td>Clur SA (2008)</td>
<td>967</td>
</tr>
</tbody>
</table>

Despite the association between increased NT and cardiac defects, it is not clear if NT screening can be an effective method to identify those pregnancies at risk for cardiac anomalies. The hypothesis that NT measurement may act as a screening test for CHD in fetuses without other risks factors has been extensively evaluated and several studies have reported on the screening performance of NT thickness for the detection of cardiac defects.

In a large retrospective study of an unselected low-risk population of over 29000 pregnancies, it was found that NT measurements 395th or 399th centile for gestational age identified 56% and 40% of the foetuses respectively with congenital heart abnormalities for a specificity of 93.8% and 99%. In this population the prevalence of major cardiac defects increased exponentially from 0.8 per 1000 for NT bellow than 95th percentile, 5.3/1000 for NT between 2.5 and 3.4 mm, 3% for NT between 3.5 and 4.4 mm, 9% for NT 4.5 to 5.4 mm, and 19.5% for NT above 5.5 mm. A normal NT was associated with a two-fold reduction in the background risk for major CHD and a NT 395th centile was associated with a nine-fold increase. This detection rate exceeds that expected from second-trimester cardiac screening in low-risk populations. If reproducible, universal first trimester NT assessment could surpass the traditional four-chamber view for routine CHD screening.

Other studies however have failed to reproduce these results and similar levels of diagnostic accuracy have not been reported in the literature. Josefsson, Michalidis and Hafner report detection rates of 38.5%, 36.4% and 25.9% respectively. The lowest detection rates are reported in two studies from the same group. Schwarzler reported the results of the screening in an unselected population with a detection rate of 11%, similarly a prospective observational study by Mavrides of over 7000 unselected pregnancies screened with first trimester NT measurement only detected 15% of cases of CHD. Recent studies by Bahado-Singh, Westin and Müller report similar detection rates of around 15% and conclude that NT measurement can not discriminate reliably between fetuses with and without CHD.

The most recent multicenter study by Simpson et al on a population of over 34000 unselected pregnancies reported an overall low performance of NT screening for CHD. Sensitivity, specificity and positive predictive value were 15.4%, 98.4% and 1.4% for a cut-off value of 2 MoM (98.3rd centile), 13.5%, 99.4% and 3.3 for a cut-off value of 2.5 MoM (99.4rd centile) and 9.6%, 99.7% and 5% for a cut-off value of 3 MoM (99.7rd centile). NT of 2.5MoM had a likelihood ratio of 22.5 for major CHD. Based on these data, for every 100 patients referred for fetal echocardiography with a NT of 99th centile or more, three will have a major cardiac anomaly.

Many causes may account for the different reported detection rates reported. The observed prevalence of cardiac defects varies substantially between studies what may indicate the use of different diagnostic criteria, cases with extra-cardiac anomalies are occasionally excluded and ascertainment and extended follow-up is not always optimal. The combined data of these studies of 134430 pregnancies included 327 fetuses with a major CHD. Overall 28.4% of major CHD were detected for a false positive rate of 3%.

A recent meta-analysis of the screening performance of first trimester NT for the detection
of major cardiac defects examined 8 studies involving over 58000 pregnancies reported that the use of the 95th and 99th percentile thresholds can identify approximately 37% and 31% respectively of CHD. This compares favourably with the 10% detection rate with specialist fetal echocardiography for pregnancies with a maternal history of diabetes mellitus or exposure to teratogens and a familiar history of cardiac defects. It was estimated that specialist fetal echocardiography in chromosomally normal fetuses with NT above 99th centile, 5% of the population would require fetal echocardiography, which would necessitate a substantial increase in dedicated resources.

A pooled analysis by the same author of 637 cases of CHD with known karyotype and first trimester NT measurement revealed that NT was 33.5mm in 23% of chromosomally normal fetuses and was not confined to specific types of CHD. Mean gestational age at diagnosis was 22 weeks with NT below 3.5mm and 16 weeks with NT of 33.5mm, suggesting that the finding of a NT of 33.5mm may select a group of high risk pregnancies that could potentially benefit of detailed cardiac scanning at 11-14 weeks, leading to an earlier diagnosis of all major types of CHD.

Simpson looked at various cut-offs of NT enlargement for referral to specialised units for fetal echocardiography. They suggest that a NT 399th centile (>3.5mm) should be considered as an indication for fetal echocardiography. Allan advocated performing a fetal echocardiogram at 14 weeks in all fetuses with a NT of 3.5mm or higher.

Thus, based on the currently available data, screening for CHD in the general population using NT has significant limitations. As with any screening test with such a low sensitivity, a negative test does not reliable exclude the risk of an abnormality and in fact the majority of fetuses affected by CHD will have a normal NT measurement. Notwithstanding, screening by NT yields a detection rate of around 30% which compares favourably with the reported sensitivity of 26% using the four chamber view of the heart at 16-22 weeks.

The CHD described in the literature in fetuses with an increased NT include septal defects and right and left obstructive lesions. Most studies have failed to identify obvious relationships between enlarged NT and particular types of cardiac anomaly. The finding that increased NT is not confined to a specific type of CHD has potentially important implications as major defects such as tetralogy of Fallot, transposition of the great arteries and aortic arc pathology are rarely detected by routine examination of the 4 chamber view at the second trimester.

Suggested mechanisms for increased NT include cardiac dysfunction, venous congestion on the head and neck, failure of lymphatic drainage, altered

<table>
<thead>
<tr>
<th>Author</th>
<th>Gestation</th>
<th>N</th>
<th>NT cut-off</th>
<th>CHD (%(n))</th>
<th>FPR</th>
<th>DR (%(n))</th>
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<tbody>
<tr>
<td>Josefsson (1998)</td>
<td>10-13+6</td>
<td>1460</td>
<td>≥2.5mm</td>
<td>0.75 (13)</td>
<td>8.9%</td>
<td>38.5% (5)</td>
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<td>Bilardo (1998)</td>
<td>10-13+6</td>
<td>1590</td>
<td>≥3mm</td>
<td>0.25 (4)</td>
<td>2.8%</td>
<td>50% (2)</td>
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<td>Hafner (1998)</td>
<td>10-13</td>
<td>4214</td>
<td>≥2.5mm</td>
<td>0.33 (14)</td>
<td>1.4%</td>
<td>28.6% (4)</td>
</tr>
<tr>
<td>Hyett (1999)</td>
<td>10-13+6</td>
<td>29154</td>
<td>≥95th centile</td>
<td>0.17 (50)</td>
<td>6.2%</td>
<td>56% (28)</td>
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<td>Schwarzer (1999)</td>
<td>10-13+6</td>
<td>4474</td>
<td>≥2.5mm</td>
<td>0.20 (9)</td>
<td>2.6%</td>
<td>11.1% (1)</td>
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<td>Michailidis (2001)</td>
<td>10-13+6</td>
<td>6606</td>
<td>≥95th centile</td>
<td>0.17 (11)</td>
<td>3.5%</td>
<td>36.4% (4)</td>
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<td>Mavrides (2001)</td>
<td>10-13+6</td>
<td>7339</td>
<td>≥2.5mm</td>
<td>0.35 (26)</td>
<td>3.5%</td>
<td>15.4% (4)</td>
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<td>Orvos (2002)</td>
<td>10-13+6</td>
<td>3655</td>
<td>≥3mm</td>
<td>0.96 (35)</td>
<td>2.3%</td>
<td>51.4% (18)</td>
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<td>Hafner (2003)</td>
<td>10-13+6</td>
<td>12978</td>
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<td>0.20 (27)</td>
<td>5%</td>
<td>25.9% (7)</td>
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<td>Bahado-Singh (2005)</td>
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<td>8167</td>
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<td>4.6%</td>
<td>14.3% (3)</td>
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<td>Westin (2006)</td>
<td>10-13+6</td>
<td>16383</td>
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<td>0.33 (52)</td>
<td>2.6%</td>
<td>13.5% (7)</td>
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<tr>
<td>Müller (2007)</td>
<td>10-13+6</td>
<td>4144</td>
<td>≥95th centile</td>
<td>0.31 (13)</td>
<td>2.4%</td>
<td>15.4% (2)</td>
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<tr>
<td>Simpson (2007)</td>
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<td>34266</td>
<td>≥99th centile</td>
<td>0.15 (52)</td>
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<td>Total</td>
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<td>0.24 (327)</td>
<td>3%</td>
<td>28.4% (93)</td>
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</tbody>
</table>
composition of the subcutaneous tissue, fetal anemia or hypoproteinemia and impaired fetal movements.\textsuperscript{30,31} Several hypotheses have been put forward regarding the underlying mechanism linking the increased NT and CHD. These include narrowing of the aortic isthmus causing excessive fluid accumulation in the first trimester, transient cardiac failure and a delay or disturbance in the development of lymphatic vessels in the neck that might explain the excessive nuchal fluid accumulation.\textsuperscript{32,33} Against the idea of cardiac failure is the fact that the heart is not enlarged and has normal systolic function.\textsuperscript{48,49} A further theory was put forward by Bekker who found abnormal lymphatic vessels in the neck region in fetuses with increased NT.\textsuperscript{53} They suggested that there was a primary disorder of the lymphangiogenesis or endothelial function which could cause both collections of nuchal fluid and also cardiac malformations. In summary, the studies describing an association between increased NT and major cardiac defects show that the prevalence of disease in chromosomally normal fetuses with NT \textsuperscript{3} 2.5mm (approx \textsuperscript{p}95) is similar to that reported in pregnancies with traditional risk factors such as a family history of a previously affected offspring or maternal diabetes, and that this prevalence increases with increasing fetal NT thickness. The clinical implication of these observations is that NT could be used concomitantly for both chromosomal and cardiac screening at 10 to 14 weeks of gestation and that patients found to have increased NT should undergo formal early fetal echocardiography complimentary to traditional second-trimester screening techniques. Improvements in the resolution of ultrasound equipments have made possible to undertake detailed cardiac scanning at the first trimester of pregnancy. Late first or early second-trimester echocardiography in referral centres may obtain diagnostic images in up to 98% of cases, with a sensitivity of 75 to 80%.\textsuperscript{54}

**Ductus venosus and congenital heart defects**

The ductus venosus (DV) is a venous shunt that provides a means of regulating the flow of well-oxygenated blood returning from the placenta via the umbilical vein. The ductus venosus allows flow to bypass the fetal liver, and by preferential streaming, directs blood into the right atrium, across the foramen ovale and into the left atrium providing the coronary and cerebral circulations with an oxygen-rich blood supply.

Absent or reversed flow during atrial contraction in the DV is abnormal and indicates impaired diastolic function with atrial contraction occurring against increased ventricular impedance to forward flow. Abnormal flow in the DV at 11 to 14 weeks of gestation is associated with an increased risk of chromosomal abnormalities and cardiac defects.\textsuperscript{55-57} In the combined data of 791 chromosomally normal fetuses with increased NT a major cardiac defect was observed in 45 (5.7%) and 39 (86.6%) had abnormal Doppler waveforms in the DV (Table 3). There are wide variations between the individual studies in the number of cases examined, the prevalence of cardiac defects and the incidence of abnormal DV waveforms in those with cardiac defects.

**Table 3.** Combined data of studies addressing the relationship between DV waveforms and major cardiac defects in chromosomally normal fetuses with increased NT above 95th centile

<table>
<thead>
<tr>
<th>Reference</th>
<th>Total (n)</th>
<th>Cardiac defects (n(%))</th>
<th>Abnormal DV Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No cardiac defect (n(%))</td>
<td>Cardiac defect (n(%))</td>
</tr>
<tr>
<td>Maiz (1999)</td>
<td>142</td>
<td>7(4.9)</td>
<td>4/135 (3)</td>
</tr>
<tr>
<td>Bilardo (2001)</td>
<td>69</td>
<td>4(5.8)</td>
<td>26/65 (40)</td>
</tr>
<tr>
<td>Murta (2002)</td>
<td>16</td>
<td>1(6.3)</td>
<td>0/15 (0)</td>
</tr>
<tr>
<td>Zoppi (2002)</td>
<td>115</td>
<td>2(1.7)</td>
<td>30/113 (26.5)</td>
</tr>
<tr>
<td>Haak (2003)</td>
<td>22</td>
<td>2(9.1)</td>
<td>8/20 (40)</td>
</tr>
<tr>
<td>Favre (2003)</td>
<td>95</td>
<td>9(9.5)</td>
<td>20/86 (23.3)</td>
</tr>
<tr>
<td>Maiz (2008)</td>
<td>191</td>
<td>16(8.4)</td>
<td>40/175 (22.9)</td>
</tr>
<tr>
<td>Total</td>
<td>791</td>
<td>45(5.7)</td>
<td>151/746 (20.2)</td>
</tr>
</tbody>
</table>

In the most recent and largest study by Maiz, multivariate analysis demonstrated that in fetuses with major cardiac defects the prevalence of an abnormal A-wave in the DV was not significantly associated with fetal NT thickness.\textsuperscript{65} The authors calculated the likelihood ratio for cardiac defects with an abnormal (absent or reversed) A-wave in the ductus venosus (Table 4). In the assessment of individual risk for major cardiac defects the a priori NT-dependent risk can be multiplied by the likelihood ratio depending on whether the A-wave in the ductus venosus is normal or abnormal. For example in a fetus with a NT of 3.5mm, the risk for cardiac defects is 2.6%, and this is increased to 11.9% if the A-wave is abnormal and reduced to 1% if the flow is normal.
Table 4. Relationship between fetal NT thickness and likelihood ratio (LR) for major cardiac defects depending on the findings of ductus venosus Doppler. To derive patient-specific risk the appropriate LR is multiplied by the a priori risk reported in a previous study (Atzei)

<table>
<thead>
<tr>
<th>NT (mm)</th>
<th>Major cardiac defect</th>
<th>A priori risk (%)</th>
<th>LR positive</th>
<th>LR negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5</td>
<td>2.6</td>
<td>4.58</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>4.0</td>
<td>3.5</td>
<td>3.89</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>4.5</td>
<td>4.9</td>
<td>3.32</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>5.0</td>
<td>6.7</td>
<td>2.85</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>5.5</td>
<td>9.2</td>
<td>2.47</td>
<td>0.43</td>
<td></td>
</tr>
</tbody>
</table>

Major differences in myocardial mechanics between early and late gestation may account for the transient nature of the increased NT and abnormal DV. The immature ventricles of the fetus are disadvantaged from the point of view of filling because they have a less organized myocardial arrangement, fewer sarcomeres per unit mass, smaller diameter, and operates at a significant higher heart rate leading to a lower compliance. Therefore myocardium develops a considerably greater tension at rest when stretched and there is an upward displacement of the end-diastolic pressure-volume relation with a higher pressure at any volume. This suggests that diastolic function in the first trimester is impaired compared with later gestation. In addition, in the first trimester, cardiac afterload is significantly greater than that in later gestation because of higher placental resistance. Also the fetus has not yet developed intrinsic renal function to counteract any tendency to fluid retention. Thus, in the first trimester, only a small impairment of cardiac diastolic function may be necessary for cardiac dysfunction to become evident as an increase in NT or abnormal A wave in the ductus venosus. Other causes of abnormal flow profile in the DV have been described including increased adrenergic drive, a relative restriction of the foramen ovale which is known to occur in fetal right heart disease, and an increase in the end-diastolic pressure in the left ventricle.

In summary, the high prevalence of abnormal flow in the ductus venosus in fetuses with major cardiac defects suggests that Doppler assessment of this vessel may provide an effective method for early screening for such defects. However the studies confirming this association are confined to fetuses with increased NT, and it is therefore uncertain whether in fetuses with cardiac defects and normal NT the ductus venosus is also abnormal.

Concern regarding the accuracy of Doppler study of the DV arises from possible methodological errors that may lead to misinterpretation of the results. First, the ductus venosus is located in an area where there is a confluence of veins that can confound the signal obtained. The Doppler signal can also be influenced by the angle of insonation, the sampling size and the wall filters. Considerable variability has been found in the semi-quantitative Doppler indices although qualitative classification of the flow as present, absent or reversed is reasonably reproducible. Thus caution must be exercised in introducing the evaluation of flow in the ductus venosus in clinical practice as Doppler measurements are prone error even in the presence of skilled technical ability.

First trimester tricuspid regurgitation and congenital heart defects

The presence of tricuspid regurgitation (TR) determined by pulsed wave Doppler has been shown to be a marker for trisomy 21 fetuses at 11 to 14 weeks of gestation but also for congenital heart diseases. In the first study by Huggon, in a series of 262 fetuses referred mostly because of increased nuchal translucency, the author reported a high prevalence of heart defects (25.6%). Tricuspid regurgitation was found in 46% (58/126) of chromosomally abnormal fetuses and in 8.8% (12/136) of chromosomally normal fetuses. The frequency of congenital heart defects in fetuses with TR was 50% in chromosomally normal fetuses and 58.6% in chromosomally abnormal fetuses. Faiola reported the association between TR and abnormal karyotype or congenital heart defects at the 11 to 13+6 week scan. Tricuspid regurgitation was present in 39 (8.5%) of the 458 chromosomally normal fetuses, in 82 (65.1%) of the 126 with trisomy 21 and in 44 (53%) of the 83 with trisomy 18 or 13. The study also demonstrated that the prevalence of TR decreases with gestation, increases with fetal NT thickness and is substantially higher in those with, than in those without a cardiac defect. In the chromosomally normal fetuses, the prevalence of TR in those with cardiac defects was 46.9% and 5.6% in those without cardiac defects, and the likelihood ratio of TR for cardiac defects was 8.4. A further study by the same group confirmed this findings.

The diagnosis of TR has been based on the presence of regurgitation during at least half of the systole and with a minimum velocity of 80 cm/s examined with the use of pulsed-waved Doppler, rather than color flow mapping. It has been found that at 11 to 14 weeks, color-flow mapping is unreliable for the detection of TR probably related to the small size of the tricuspid orifice (mean of 2mm) coupled with
the high heart rate at this time.67

The aetiology of the TR is questionable. It may be caused by an increase in preload or afterload presented to the right ventricle.66 Previous studies have reported TR in a wide range of pathological conditions characterized by increased cardiac preload, such as non-immune hydrops, arteriovenous fistulae and the recipient fetus in twin to twin transfusion syndrome, or increased cardiac afterload, such as severe fetal growth restriction and indomethacin-induced ductal constriction.

As with ducus venosus, its applicability in the general setting is limited due to the advanced skill level required of sonographers for reliable evaluation. It has been reported that the method for TR evaluation has a good reproducibility with a kappa coefficient of interobserver agreement of 0.87 and that tricuspid valve can be successfully examined in 99% of the fetuses at the 11 to 14 week scan.68

CONCLUSIONS

In addition to chromosomal anomalies the NT examination can provide an opportunity to screen for structural defects. Cardiac malformations are the most common form of congenital defects. Early diagnosis has several benefits. Birth planning for the ongoing pregnancies improves neonatal prognosis even for severe disease and parents can take decisions with enough time.

In expert hands with adequate equipment, early echocardiography can diagnose cardiac anomalies in high risk population. A complete exam has to include five different planes that can be extended to aortic arch. Transvaginal approach improves visualization of the heart until 13 weeks. Ultrasound follow up is necessary for the ongoing pregnancies and we have to consider the possibility of evolving lesions.

Educational programs and courses are fundamental for specialist to improve detection rate at an early stage. More studies are necessary to consider the possibility of including early echocardiography in low risk population.

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