Fetal heart and increased nuchal translucency: anatomical, pathophysiological, diagnostic and clinical aspects

Barker Clur, S.-A.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 2

The nuchal translucency and the fetal heart: a literature review

SAB Clur, J Ottenkamp and CM Bilardo

Prenat Diagn 2009; 29: 739-748
Chapter 2

Abstract

In this overview the current knowledge of the relationship between an increased nuchal translucency (NT) measurement and fetal heart structure and function in chromosomally normal fetuses is reviewed. Relevant pathophysiological theories behind the increased NT are discussed. Fetuses with an increased NT have an increased risk for congenital heart defects (CHDs) with no particular bias for one form of CHD over another. This risk increases with increasing NT measurement. Although the NT measurement is only a modestly effective screening tool for all CHDs when used alone, it may indeed be effective in identifying specific CHDs “likely to benefit” from prenatal diagnosis. The combination of an increased NT, tricuspid regurgitation and an abnormal ductus venosus Doppler flow profile, is a strong marker for CHDs. A fetal echocardiogram should be performed at 20 weeks’ gestation in fetuses with a NT ≥95th percentile but <99th percentile. When the NT measurement is ≥99th percentile, or when tricuspid regurgitation and/or an abnormal DV flow pattern is found along with the increased NT, an earlier echocardiogram is indicated, followed by a repeat scan at around 20 weeks’ gestation. The resultant increased demand for early fetal echocardiography and sonographers with this special expertise needs to be planned and provided for.
Introduction

For almost 20 years the association between an increased fetal neck thickness and chromosomal and cardiac abnormalities has fascinated researchers. In 1987 Benacerraf et al. published the association of Down’s syndrome with an increased nuchal fold thickness measured after 16 weeks gestation in 5500 fetuses. Nicolaides et al. (1992) subsequently described an increased risk of chromosomal anomalies in fetuses with an excessive nuchal fluid accumulation at 10-14 weeks gestation. The nuchal translucency (NT) was then defined as a transient subcutaneous collection of fluid behind the fetal neck seen ultrasonographically at 11-14 weeks gestation (Nicolaides et al., 1992). The definition of normal ranges for the NT measurement followed. The 95th percentile for NT measurement increases with gestational age between 11-14 weeks and is approximately 2.5mm depending on crown rump length, whereas the 99th percentile is fixed at 3.5mm. After 14 weeks the normal NT regresses, coinciding with a reduction in placental resistance and the beginning of fetal renal function (Pajkrt et al., 1995; Pandya et al., 1995, Snijders et al., 1998).

Quite soon it became clear that an increased NT is not only a marker for chromosomal anomalies, but also a nonspecific sign of a disturbance in normal early development. In the presence of a normal karyotype, an enlarged NT can be observed in fetuses affected by a variety of structural and genetic disorders, of which congenital heart defects (CHDs) are the most common (Hyett et al., 1996a, 1997; Hafner et al., 1998; Souka et al., 1998, 2001, 2005; Bilardo et al., 1998, 2001, 2007; Ghi et al., 2001; Orvos et al., 2002; Michailidis and Economides, 2001; Makrydimas et al., 2003, 2005; Westin et al., 2006, 2007). Hyett et al. (1996a) were the first to report an association between an increased NT measurement and CHDs in a small group of chromosomally normal fetuses. The idea that the NT could also be a marker for CHDs evolved from here.

Increased NT and the risk of a CHD

It was Hyett et al. again who, in 1999, reported that in a cohort of 29 154 pregnancies, 56% of the fetuses with a major CHD had an increased NT measurement. The prevalence of CHDs was seen to increase with increasing NT thickness. Based on this data, the NT measurement could be used as a first screening step in the detection of CHDs, identifying high-risk fetuses for referral to specialized centers for echocardiography. By performing an echocardiogram on the 1% of fetuses with a NT measurement ≥99th percentile, 40% of major CHDs could be identified. This report was welcomed with much enthusiasm as the NT measurement could lead to the improvement of the still rather disappointing prenatal CHD detection rate (15-55% depending on the expertise of the centre and screening protocol used), (Cooper et al., 1995; Tegnander et al., 1995; Rustico et al., 1995; Montana et al., 1996; Bull, 1999). Seven subsequent studies, however, tended to show less promising results (Bilardo et al., 1998; Hafner et al., 1998; Josefsson et al., 1998; Schwarzler et al., 1999; Mavrides et al., 2001; Michailidis and Economides, 2001; Orvos et al., 2002) (Table 1). In a meta-analysis of these eight studies, including 58 492 fetuses, Makrydimas et al. (2003) found that
Chapter 2

A NT measurement >99th percentile had a sensitivity and specificity of 31% and 98.7% respectively, with a positive likelihood ratio of 24 for the diagnosis of a major CHD. A sensitivity and specificity of 37% and 96.6% respectively was found using the 95th percentile cut-off.

Subsequent studies of large low-risk populations of chromosomally normal fetuses reported even lower detection rates for CHDs (Bahado-Singh et al., 2005; Westin et al., 2006; Müller et al., 2007; Simpson et al., 2007) (Table 1). Simpson et al. (FASTER Consortium 2007), for instance, in a prospective study of 34 622 fetuses, found a sensitivity of only 15.4% using 2.0 multiples of the median (MoM), (approximating the 98th percentile), cut-off. Similarly, our group found a sensitivity of 15.4% in 4144 low-risk pregnancies using the 95th percentile cut-off (Müller et al., 2007). The exclusion of septated cystic hygroma in the First And Second Trimester Evaluation of Risk (FASTER) study may partially explain their low detection rate. Had septated cystic hygroma been included, their CHD detection rate would have been 35.3% (Malone et al., 2005, Hyett et al., 2007, Simpson et al., 2007). Cystic hygroma was, however, included in the definition of an increased NT in the study of Müller et al. (Müller et al., 2007). Another recently published meta-analysis of seven studies chose a different approach and defined the relationship between an enlarged NT (cut-off 1.7 MoM at a false positive rate of 5%) and specific CHDs “likely to benefit” from prenatal diagnosis. The definition of CHDs likely to benefit from prenatal diagnosis included a defect that is not satisfactorily reparable and can lead to serious disability, and for which the offer of a pregnancy termination would be discussed, or a defect that is not satisfactorily reparable after birth, but in-utero treatment can reduce morbidity or a defect where prenatal diagnosis can lead to an altered postnatal management with proven improved prognosis, such as ductal dependant lesions (Wald et al., 2008). Wald et al. (2008) found an enlarged NT in 52% of these CHDs.

The comparison of all the above mentioned screening studies is not straightforward due to differences in cut-off points used to define an increased NT (95th or 99th percentile, 1.7, 2, 2.5 or 3 MoM), gestational ages at the time of NT measurement (10+4 to13+6 vs.11to14 weeks’ gestation), study populations (high vs. low-risk), study design (prospective vs. retrospective) and the definition of a major CHD. When using the 95th percentile cut-off, the reported prevalence of CHDs varied between 2 and 20%. Despite all the above mentioned variables, these studies do agree that the prevalence of CHDs is in the order of 6 times higher in fetuses with a NT ≥99th percentile than in an unselected population. As such, an increased NT is an indication to exclude a CHD. NT screening, when used alone, is only a modestly efficient strategy for detecting all CHDs, but may indeed be effective in detecting specific CHDs likely to benefit from prenatal diagnosis.

The median NT thickness is significantly higher in fetuses with major CHDs compared to those with normal hearts (Ghi et al., 2001). In a pooled analysis of data from four large fetal echocardiography centers, Makrydimas et al., (2005), found a NT measurement of ≥2.5mm and ≥3.5mm in 35.5% and 23% in 397 chromosomally normal fetuses with major CHDs respectively. The proportion of cases with an increased NT was similar for each CHD subtype. The median gestational age at CHD
Table 1. The risk of major cardiac defects and the cardiac defect detection rate related to NT measurement ≥95 and ≥99 in fetuses with normal chromosomes as found in different studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence CHD/1000 in euploid cohort (n)</th>
<th>Prevalence CHD/NT ≥95 + normal chromosomes</th>
<th>Prevalence CHD/NT ≥99 + normal chromosomes</th>
<th>CHD with NT ≥95/CHD total (%) = Detection rate</th>
<th>CHD with NT ≥99/CHD total (%) = Detection rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Josefsson et al., 1998</td>
<td>8.9/1000 (n=1,460)</td>
<td>5/134=3.7% (NT≥2.5mm)</td>
<td>0/6=0%</td>
<td>5/13=38.5%</td>
<td>0/13=0%</td>
</tr>
<tr>
<td>Bilardo et al., 1998</td>
<td>3.1/1000 (n=1,590)</td>
<td>2/47=4.3% (NT≥3mm)</td>
<td>–</td>
<td>2/4=50%</td>
<td>–</td>
</tr>
<tr>
<td>Hafner et al., 1998</td>
<td>3.3/1000 (n=4,214)</td>
<td>4/63=6.3% (NT≥2.5mm)</td>
<td>–</td>
<td>4/14=28.6%</td>
<td>–</td>
</tr>
<tr>
<td>Hyett et al., 1999</td>
<td>1.7/1000 (n=29,154)</td>
<td>28/1822=1.5% (NT≥p95)</td>
<td>20/315=6.3%</td>
<td>28/50=56%</td>
<td>20/50=40%</td>
</tr>
<tr>
<td>Schwarzler et al., 1999</td>
<td>2/1000 (n=4,474)</td>
<td>1/122=0.8% (NT≥2.5mm)</td>
<td>–</td>
<td>1/9=11.1%</td>
<td>–</td>
</tr>
<tr>
<td>Mavrides et al., 2001</td>
<td>3.5/1000 (n=7,339)</td>
<td>4/258=1.6% (NT≥2.5mm)</td>
<td>3/60=5%</td>
<td>4/26=15.4%</td>
<td>3/26=11.6%</td>
</tr>
<tr>
<td>Michailidis and Econo-mides 2001</td>
<td>1.7/1000 (n=6,606)</td>
<td>4/235=1.7% (NT≥p95)</td>
<td>3/73 = 4.1% (major)</td>
<td>4/11=36.4%</td>
<td>3/11=27.3%</td>
</tr>
<tr>
<td>Orvos et al., 2002</td>
<td>9.6/1000 (n=3,655)</td>
<td>18/101=17.8% (NT≥3mm)</td>
<td>–</td>
<td>18/35=51.4% (NT≥3mm) (all)</td>
<td>8/35=22.8%</td>
</tr>
<tr>
<td>Hafner et al., 2003</td>
<td>2.1/1000 (n=12,978)</td>
<td>7/649=1.1% (NT≥p95)</td>
<td>–</td>
<td>7/27=25.9%</td>
<td>–</td>
</tr>
<tr>
<td>Makrydimas et al., 2003</td>
<td>2.8/1000 (n=58,492)</td>
<td>66/2782=2.4% (NT≥p95)</td>
<td>26/454=5.7%</td>
<td>37%</td>
<td>31%</td>
</tr>
<tr>
<td>Bahado-Singh et al., 2005 (BUN)</td>
<td>2.6/1000 (n=8,167)</td>
<td>3/378=0.8% (NT≥2.5mm)</td>
<td>1/43=2.3% (NT≥3.5mm)</td>
<td>3/17=17.7% (22.5mm) (major)</td>
<td>1/17=5.9%</td>
</tr>
<tr>
<td>Westin et al., 2006</td>
<td>7.8/1000 (all)</td>
<td>13/424=3.1% (all)</td>
<td>4/49=8.2% (all)</td>
<td>13/127=10.2% (all)</td>
<td>4/127=3.1%</td>
</tr>
<tr>
<td>Moller et al., 2007</td>
<td>5.8/1000 (all)</td>
<td>2/100=2% (major)</td>
<td>2/21=9.5% (major)</td>
<td>2/24=8.8% (all)</td>
<td>2/24=8.8%</td>
</tr>
<tr>
<td>Simpson et al., 2007 (FASTER)</td>
<td>6.5/1000 (all)</td>
<td>19/569=3.3% (major)</td>
<td>7/209=3.4% (major)</td>
<td>19/224=8.5% (all)</td>
<td>15/224=6.7%</td>
</tr>
</tbody>
</table>

*As reported in Hyett, 2004.
**Hyett et al., 2007.

BUN, First trimester Maternal serum Biochemistry and Fetal Nuchal translucency Screening Study Group; CHD, congenital heart defects; FASTER, First and second Trimester Evaluation of Risk; MoM, multiples of the median (2.0 MoM = 98.3rd percentile, 2.5 MoM = 99.4th percentile); NT, nuchal translucency; p95, 95th percentile; p99, 99th percentile.
diagnosis was 16.1 weeks’ when the NT was ≥3.5mm compared to 22.1 weeks’ when <3.5mm, (Makrydimas et al., 2005).

The risk of a CHD increases exponentially with increasing NT measurement. In Table 2, the rates of CHDs per degree of NT enlargement reported in several studies are summarized. The frequency of CHDs varies from 0.6- 5% when the NT is between 2.5 and 3.5mm, to 64% when the NT measurement is above 8.5mm (Hyett et al., 1997, 1999, 2004; Ghi et al., 2001; Lopes et al., 2003; Galindo et al. 2003; McAuliffe et al., 2004; Bahado-Singh et al., 2005; Atzei et al., 2005; Simpson et al., 2007; Clur et al., 2008). The combined findings of ten studies are summarized in Figure 1 (Hyett et al., 1997, 1999; Ghi et al., 2001; Lopes et al., 2003; Galindo et al., 2003; McAuliffe et al., 2004; Bahado-Singh et al., 2005; Atzei et al., 2005; Simpson et al., 2007; Clur et al., 2008).

In conclusion, a NT measurement ≥95th percentile identifies fetuses with an increased risk of a CHD. They should be referred for fetal echocardiography, preferably in early pregnancy when the NT is ≥3.5mm or when additional markers of CHD are also present as will be discussed below.

Why is there an increased risk of CHDs when the NT is increased?

To help to understand the relationship between the increased NT and CHDs better, a few of the relevant hypotheses linking the increased NT and the heart structure and function will be discussed.

1) Cardiac failure or dysfunction

The idea that (transient) cardiac failure, either due to intrinsic myocardial dysfunction or secondary to the CHD itself, leads to the fluid accumulation causing the nuchal edema is commonly encountered, especially in the obstetric literature (Berger, 1999; Mol, 1999). The finding of an increased mRNA

![Prevalence of CHD/1000 against NT measurement](image)

**Figure 1.** Prevalence of congenital heart defects /1000 related to NT measurement.

NB: The data used for the construction of this graph are derived from Table 2. An exponential trend line has been added using Microsoft Excel 2007.

CHD=congenital heart defects, NT=nuchal translucency.
<table>
<thead>
<tr>
<th>Study</th>
<th>CHD/1000 NT &lt; p95</th>
<th>CHD/1000 p95 ≥ NT &lt; 3.5 mm</th>
<th>CHD/1000 NT 3.5-4.4 mm</th>
<th>CHD/1000 NT 4.5-5.4 mm</th>
<th>CHD/1000 NT 5.5-6.4 mm</th>
<th>CHD/1000 NT 6.5-8.4 mm</th>
<th>CHD/1000 NT ≥ 8.5 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyett et al., 1997</td>
<td>5.4 (31.4)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>(233)</td>
</tr>
<tr>
<td>Hyett et al., 1999</td>
<td>0.8 (5.3)</td>
<td>28.9 (90.9)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>(195.1)</td>
</tr>
<tr>
<td>Ghi et al., 2001*</td>
<td>–</td>
<td>24.9 (70.4)</td>
<td>31.3 (82.8)</td>
<td>–</td>
<td>190.5 (303.6)</td>
<td>(430)</td>
<td></td>
</tr>
<tr>
<td>Lopes et al., 2003</td>
<td>12.6 (215.7)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>(303.6)</td>
</tr>
<tr>
<td>Galindo et al., 2003</td>
<td>53.4 (112.6)</td>
<td>52.2 (NT ≥ 4.4 mm)</td>
<td>102 (NT ≥ 5.5 mm)</td>
<td>240 (NT ≥ 6.6 mm)</td>
<td>–</td>
<td>–</td>
<td>(242.4)</td>
</tr>
<tr>
<td>McAuliffe et al., 2004</td>
<td>1.6 (78.4)</td>
<td>10 (70)</td>
<td>70 (200)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>(300)</td>
</tr>
<tr>
<td>Souka et al., 2005*</td>
<td>1.9 (NT &lt; 2 mm)</td>
<td>6 (23.3)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>(300)</td>
</tr>
<tr>
<td>Bahado-Singh et al., 2005</td>
<td>18.2 (59.4)</td>
<td>35.2 (183.0)</td>
<td>64.4 (126.7)</td>
<td>140 (260)</td>
<td>–</td>
<td>–</td>
<td>(260)</td>
</tr>
<tr>
<td>Atzei et al., 2005</td>
<td>4.9 (median)</td>
<td>8.7 (median &lt; NT &lt; p95)</td>
<td>30.2 (71.4)</td>
<td>74.8 (150)</td>
<td>200 (290)</td>
<td>190.5 (293)</td>
<td>(277)</td>
</tr>
<tr>
<td>Simpson et al., 2007**</td>
<td>3.3 (14.1)</td>
<td>33.5 (14.1)</td>
<td>–</td>
<td>85.7 (195.1)</td>
<td>–</td>
<td>–</td>
<td>(277)</td>
</tr>
<tr>
<td>Clur et al., 2008</td>
<td>18.8 (78.7)</td>
<td>30.2 (132.5)</td>
<td>97.4 (195.1)</td>
<td>84/2 (190.5)</td>
<td>9/14 (643)</td>
<td>–</td>
<td>(277)</td>
</tr>
<tr>
<td>Total</td>
<td>78/5039</td>
<td>43/1284</td>
<td>30/401</td>
<td>9/60</td>
<td>8/42</td>
<td>9/14</td>
<td>643</td>
</tr>
</tbody>
</table>

CHD = congenital heart disease, MoM = multiples of the median (2.0 MoM = 98.3rd percentile, 2.5 MoM = 99.4th percentile, 3 MoM = 99.7th percentile); NT, nuchal translucency, p95, 95th percentile. *Not included in Total (review article or cohort is included in another study). **Cystic hygromas not included.
of cardiac atrial and brain natriuretic peptide in trisomic fetuses with an increased NT was seen as supportive evidence for this hypothesis (Hyett et al., 1996b). However, it may not be valid to extrapolate a postnatal fluid regulation process to the 11-14 week-old trisomic fetus. In monochorionic twins, discordancy for increased NT has been indicated as an early marker of twin-to-twin transfusion syndrome where cardiac failure is known to play a role (Nicolaidis et al., 2002). Here the early imbalance in the circulatory volume, (volume overload versus anemia), shared by the twins could cause the nuchal edema.

If cardiac failure causes the nuchal edema, then cardiomegaly, ascites, peripheral edema, and pericardial and pleural effusions would also be expected. Ascites, peripheral edema and effusions, however, are usually not seen in fetuses with an increased NT.

a) Abnormal ductus venosus Doppler flow profile

Much of the early data regarding cardiac hemodynamics in early pregnancy has been based on Doppler waveform analysis. An abnormal ductus venosus (DV) Doppler flow profile, where during late diastole, coincident with atrial contraction, reduced or reversed flow is seen, has been interpreted as indicative of cardiac failure as it was assumed to reflect increased central venous pressure (Montenegro et al., 1997; Matias et al., 1997, 1999). Martinez et al. (2003) however, failed to find a correlation between the pulsatility index in the jugular vein and that of the DV in 179 first trimester fetuses with an increased NT. Flow reversal during atrial contraction indicates that the pressure in the right atrium is higher than in the portal system but does not necessarily imply heart failure. It may be seen in situations of diastolic cardiac dysfunction, restricted flow through the foramen ovale, increased adrenergic drive and during hypoxia when the sphincter-like DV dilates and vessel wall compliance increases (Simpson and Sharland, 2000; Kiserud, 2001; Allan, 2006). The fluid balance in the 11-14 week fetus is taxed due to the tendency to increased preload as intrinsic renal function has not yet developed and the circulating blood volume is increasing. Also, the afterload is increased as placental resistance is still high. The immature ventricles are less compliant and thus small alterations in intravascular fluid volume may be enough to produce the abnormal DV flow patterns (Reed et al., 1986; Tulzer et al., 1994; van Splunder et al., 1996; Matias et al., 1999; Leiva et al., 1999). A temporary abnormality of the DV itself, possibly abnormal diameter regulation or increased vessel compliance, could also potentially cause the abnormal flow pattern. Bekker et al. (2005a) found the DV endothelium to be abnormally thick in trisomy 16 mice, the mouse model for human trisomy 21.

An abnormal DV flow profile in fetuses with an increased NT measurement is associated with CHDs, chromosomal malformations and an adverse pregnancy outcome (Montenegro et al., 1997; Borrell et al., 1998; Matias et al., 1998, 1999; Carvalho, 1999; Bilardo et al., 2001; Antolin et al., 2001; Haak et al., 2003, 2005; Favre et al., 2003; Sedmera et al., 2005; Oh et al., 2007). The abnormal DV flow is temporary, resolving as the increased NT disappears (Huisman and Bilardo, 1997; Matias et al., 1998). The combined data from seven studies, including 600 chromosomally normal fetuses with a NT ≥95th percentile, showed CHDs in 4.8% (29) of the fetuses, 96.6% (28) of which also had an abnormal DV flow pattern at 11-13+6 weeks’ gestation (Maiz et al., 2008). Maiz et al. (2008), in a
Literature review: NT and fetal heart

cohort of 191 11-13+6 week-old fetuses with a NT ≥3.5mm, observed an abnormal DV flow pattern in 11/16 (68.8%) fetuses with CHDs and 40/175 (22.9%) without CHDs. The prevalence of an abnormal DV flow increased with NT thickness in fetuses without CHDs but not in those with CHDs. The authors conclude that in fetuses with a NT ≥3.5mm the finding of an abnormal DV flow is associated with a three-fold increase in the likelihood of a CHD, whereas a normal flow pattern halves the risk.

b) Direct cardiac function measurement in fetuses with an increased NT

Direct measurements of cardiac function are required to determine if impaired cardiac function is responsible for the increased NT measurement or not. Simpson and Sharland (2000) measured the left ventricular ejection fraction in fetuses with a ventricular septal defect around 20 weeks’ and showed no significant difference between fetuses who had had an increased NT and those who had not. Their measurements of cardiac function were made after the increased NT would have resolved in most cases. The finding of a normal cardiac function at 20 weeks’ gestation does not exclude possible cardiac dysfunction at the time when the NT was increased, however. Rizzo et al. (2003) looked at cardiac function at 20-23 weeks’ gestation in chromosomally normal fetuses with an increased NT (>95th percentile) compared to normal controls. They found a significantly decreased E-wave velocity and E/A (E-wave divided by A-wave) and E/TVI (E-wave divided by time velocity integral) ratios across the atrioventricular valves in fetuses who had had an increased NT at 11-14 weeks’ gestation compared to controls, suggesting reduced myocardial relaxation. It seems illogical that diastolic dysfunction should be found at 20-23 weeks’ gestation when the increased NT will have already resolved in most cases. A possible explanation is that the diastolic dysfunction was also present at the time of the increased NT and may even have been more evident at that time. If this abnormal diastolic function is to be linked with the abnormal DV flow profiles seen in fetuses with an increased NT, abnormal A-waves during atrial contraction would also be expected, which was not found. They also found no evidence for systolic dysfunction in these fetuses using pulmonary and aortic peak velocities and time to peak velocity as indicators of systolic function (measures of outflow resistance).

To be absolutely sure that there was no cardiac failure at the time of the increased NT measurement direct measurements of fetal cardiac function at 11-14 weeks’ gestation were needed. Huggon et al. (2004) provided this when they measured the myocardial performance index and E/A ratio across the atrioventricular valves in a series of 638 fetuses at 11-14 weeks’ gestation. They found no significant differences in cardiac function between normal fetuses, fetuses with chromosomal defects, fetuses with CHDs and fetuses with an increased NT (>4mm) and normal chromosomes. Haak et al. (2005) also found no difference in atrioventricular valve flow velocities between normal fetuses and those with an increased NT at 11-14 weeks’ gestation. Within the group with an increased NT they also found no difference between those with and those without a CHD. These findings do not support a causal relationship between the increased NT and diastolic, systolic or global cardiac dysfunction.
c) **Tricuspid regurgitation at 11-14 weeks' gestation**

The phenomenon of tricuspid regurgitation (TR) in young fetuses is interesting. Atrio-ventricular valve regurgitation is present in 6.3% of 7-8 week-old normal fetuses. The prevalence increases to 44% at 10 weeks' gestation and falls to 3.5-6% at 11-13+6 weeks' gestation. The TR disappears with the disappearance of the NT (Huggon et al., 2003; Faiola et al., 2005; Mäkikallio et al., 2005). TR is highly associated with aneuploidy, particularly trisomy 21 and its prevalence increases with the NT thickness and is substantially higher in fetuses with, than those without CHDs (Huggon et al., 2003; Faiola et al., 2005). In chromosomally normal fetuses the finding of TR at 11 to 13+6 weeks' gestation is associated with an eight-fold increase in the risk for CHDs (Faiola et al., 2005). The etiology of the TR is uncertain and may be related to small alterations in the already taxed hemodynamic balance of the 11-14 week fetus. However, both increased afterload and preload cause right ventricular dilatation which is almost never seen in these fetuses with TR in the absence of CHDs. The decreased compliance of the fetal heart may explain this discrepancy, and delayed diastolic function maturation may be the clue to its causation. Delayed tricuspid valve delamination has also been proposed to explain the transient TR in aneuploid fetuses (Lammers et al., 1995; Allan, 2006).

2) **Do CHDs cause the increased NT?**

The initial findings of Hyett et al. (1995, 1996a) where narrowing of the aortic isthmus and ascending aorta abnormalities were documented in a significant proportion of chromosomally normal and abnormal fetuses with an increased NT, stimulated the idea that altered fetal hemodynamics secondary to the CHDs themselves, (e.g. overperfusion or venous congestion of the head and neck), could cause the increased NT. However, several forms of CHDs leading to different hemodynamic patterns, irrespective of the size of the aorta or aortic isthmus, have been encountered in fetuses with an increased NT. Many CHDs associated with cardiac failure in postnatal life do not cause cardiac failure in the fetus. The effect of intracardiac shunts on the fetal heart, (volume overload and cardiac failure), is limited by the increased fetal pulmonary vascular resistance and systemic pressure in the fetal right ventricle (Rudolph, 2001). Moreover, CHDs not associated with cardiac failure in prenatal or postnatal life are also associated with an increased NT. With cardiac failure cardiomegaly would be expected, as has been described in fetuses with non-immune hydrops (Skoll et al., 1991; Johnson et al., 1992). Simpson and Sharland (2000), however, found no increased cardiothoracic ratio, irrespective of nuchal measurement, in fetuses with hypoplastic left heart syndrome or an isolated ventricular septal defect at 20 weeks' gestation. This does not, however, exclude the possibility that cardiomegaly may have been present at the time of the increased NT.

3) **Disorders of vasculogenesis and neurogenesis**

a) **Lymphangiogenesis**

A primary disorder of lymphangiogenesis was suggested after the abnormal enlargement and persistence of jugular lymphatic sacs were found in the neck region of fetuses with an increased NT (Haak et al., 2002, Bekker et al., 2005b). A delay in the reconnection of the lymphatic sacs with the venous system may affect venous hemodynamics retrogradely causing the abnormal DV waveforms seen. Later, with
continued development, the lymphatic sacs may be remodeled into lymph nodes and the excess of fluid may drain away explaining the transient nature of the increased NT.

b) Neural crest migration abnormality
The neck, head and the adrenergic nerves of the DV have a common embryonic origin, the neural crest (Cocenai et al., 1984) and blood vessels and nerves share many developmental genes (Carmeliet, 2003), making the proposal of a neural crest developmental anomaly, to link the increased NT, CHDs and the DV flow abnormalities, very attractive. An overexpression of Neural Crest Adhesion Molecule (NCAM), affecting neural crest cell migration and neuronal differentiation (Walsh and Doherty, 1997), has been found in the neck, heart and DV of trisomy 16 mice (Bekker et al., 2005a). Neural crest ablation and subsequent migration abnormalities have been shown to lead to the development of CHDs (Kirby, 1991; Besson, 1986). However, if the problem is failure of neural crest cell migration, then the CHDs seen in association with an increased NT would only include defects of conotruncal septation, outflow tracts, great vessels and aortic arch. Despite an initial suggestion that abnormalities of the aortic arch are more commonly found with an increased NT (Hyett et al., 1996a), it appears that there is no definite bias towards one particular type of CHD over another in these fetuses (Simpson and Sharland, 2000; Ghi et al., 2001; Galindo et al., 2003; Makrydimas et al., 2005; Allan, 2006; Clur et al., 2008).

4) Early fetal flow disturbances
Normal flow patterns affect the expression of the normal sequence of growth factors required for the normal development of cardiac chambers (Sedmera et al., 2005). Studies in chick embryos have shown that intracardiac flow disturbances or hemodynamic disturbances induce structural malformations suggesting that they may be responsible for both CHDs and the distension of tissues (Harh et al., 1973; Stekelenburg-de Vos et al., 2003). Neural crest ablation results in flow disturbances and the flow disturbances, and not the failure of migration of the neural crest cells, may cause the CHDs (Allan, 2006).
Thus an insult at 6-8 weeks gestation (environmental e.g. hypoxia or nutritional, or genetic) may result in fluid retention (Allan, 2006). The ensuing disturbances in vascular endothelial development including lymphangiogenesis and hemodynamics at 7-10 weeks’ gestation could then lead to the increased NT and altered growth factor expression with the resultant CHD. The question why fluid collection occurs in response to these insults still needs to be answered.

Fetal echocardiography, when, on which fetuses and by whom?
A finding of an increased NT identifies a new group of fetuses at increased risk for CHDs bringing with it an increased demand for detailed fetal echocardiography. Adequate resources are required to accommodate this in the future. Using a NT measurement ≥295th percentile as a cut-off for referral for echocardiogram, one major CHD can be expected to be diagnosed per 33 referrals for a fetal echocardiogram. This can be increased to 1 in 16 by using the 99th percentile cut-off (Makrydimas
et al., 2003). In their consensus statement of 2008, The International Society of Ultrasound in Obstetrics and Gynaecology proposes fetal echocardiography at the time of detection of the increased NT measurement (11-14 weeks) if the NT is >3.5mm, with a second scan at 20-22 weeks' gestation. When the NT measurement is between 2.5 and 3.5mm the echocardiogram can be performed at 18-20 weeks' gestation along with the anomaly scan (Lee et al., 2008). Even when the early echocardiogram shows no sign of a CHD, it is important to perform a follow up scan later as trivial abnormalities at 11-14 weeks' may progress to major CHDs during the pregnancy (Yagel et al., 1997, 2007; Carvalho, 2004). Progressive hypoplasia of the respective ventricular chamber has been observed, for example, in the setting of semilunar valves stenosis (Carvalho, 2004).

Early fetal echocardiography

An early fetal echocardiogram (performed in the late first or early second trimester of pregnancy), has been shown to be feasible, accurate, and safe (Comas Gabriel et al., 2002; Haak et al., 2002; Huggon et al., 2002; Lopes et al., 2003; Carvalho, 2004; McAuliffe et al., 2005; Becker and Wegner, 2006; Smreck et al., 2006; Lombardi et al., 2007; Yagel et al., 2007; Bronshtein et al., 2008). Two studies have focused on low-risk populations using the transvaginal approach (Yagel et al., 1997; Rustico et al., 2000). However, transvaginal examination is not favoured by many women and caregivers, the CHD pickup rates were low and early echo-screening will not replace the need for a follow-up scan later in the pregnancy if a still developing CHD is not to be missed.

The performance of a complete fetal echocardiogram at the end of the first trimester requires expertise. With modern equipment, it is usually possible, using the abdominal approach, to define the situs and cardiac connections, identify the cardiac chambers and their symmetry, the crossing of the great vessels and to evaluate the flow in the chambers and the great vessels using Doppler and colour flow mapping (Carvalho, 2004; Allan, 2006; Johnson and Simpson, 2007). A thorough knowledge of the pathophysiology of CHDs, their progression during gestation, the surgical possibilities and prognosis are required to make a correct diagnosis and to adequately counsel families. Early fetal echocardiography should probably only be performed in centers experienced in the technique and be reserved for fetuses at high-risk for a CHD. It should be viewed as an adjunct to, and not a replacement of, the 20 week scan (Johnson and Simpson, 2007).

Earlier fetal echocardiography, performed soon after the NT measurement, allows for an earlier diagnosis of CHDs and gives the parents more time to make an informed decision regarding the continuation of the pregnancy. Should they decide to interrupt the pregnancy, then this can be performed earlier, more safely (Allan, 2006; Yagel et al., 2007; Bronshtein et al., 2008) and with less long-term psychological sequelae (Korenromp et al., 2005). If the pregnancy is continued, the timing, location (hospital with neonatal intensive care, pediatric cardiology and pediatric cardiac surgery facilities), mode of delivery and direct postnatal care (prostaglandin E1 infusion or balloon atrioseptostomy) can be planned. In this way the postnatal outcome of these babies can be improved.
Literature review: NT and fetal heart

(Bonnet et al., 1999; Fuchs et al., 2007). Where the early fetal echocardiogram shows no sign of a CHD it allows earlier reassurance of couples considered at high-risk for a CHD.

Conclusions

Although the NT measurement alone appears only to be a moderately effective screening tool for the detection of all CHDs, its role in the detection of specific CHDs likely to benefit from prenatal diagnosis seems more promising. An increased NT is an important criterion for identifying fetuses eligible for specialized echocardiography. When TR and/or an abnormal DV Doppler flow profile is found in association with an increased NT, the risk of a CHD increases and the early exclusion of a CHD is warranted. Hopefully this strategy will improve the prenatal CHD detection rate with a resultant reduction in perinatal mortality.

We recommend echocardiography at 18-22 weeks’ gestation in fetuses with a NT ≥95th percentile but <99th percentile. In fetuses with a NT measurement ≥99th percentile, or in which TR and/or an abnormal DV flow pattern is found in addition to the increased NT, an earlier echocardiogram is indicated. The stressful period between the finding of an increased NT and the making of a definite cardiac diagnosis is then reduced allowing for a well-informed and unrushed decision regarding pregnancy termination.

The need for an experienced echocardiographer and up to date equipment cannot be stressed enough if early echocardiography is to be accurate and beneficial.
References


45) Hyett J. 2004 Does nuchal translucency have a role in fetal cardiac screening? Prenat Diagn 24: 1130–1135.


