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INVITED COMMENTARY:
CURRENT ISSUES IN OBSTETRICS AND GENETICS

Increased nuchal translucency in fetuses with a normal karyotype

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Sonographic assessment of nuchal translucency (NT) thickness has been recognized as an effective means of screening for trisomy 21 and other chromosomal abnormalities at 11–14 weeks of gestation. Up to 80% of aneuploid fetuses have increased NT, but this feature is also found in 5% of karyotypically normal fetuses at this stage of pregnancy (Snijders *et al*., 1998). As this screening test examines the fetus directly, many parents equate a high-risk result with fetal abnormality more readily than screening by other techniques. Typically giving the news that the fetal karyotype is normal is followed by the question '*So what is wrong with my baby*?' As the use of first trimester ultrasound, and in particular screening by NT thickness, becomes more widespread it is important to develop a strategy for the further management of these pregnancies which will enable us to identify other associated anomalies at an earlier stage. Parents need to be aware that the majority of fetuses with increased NT and a normal karyotype will have a normal outcome. This information, together with a discussion about the plan for subsequent management, should help them to continue the pregnancy with confidence and avoid choosing to terminate on the basis of an ultrasound marker rather than the identification of a fetal abnormality.

INCREASED NT AND INTRAUTERINE/NEONATAL LETHALITY

Souka *et al*. (1998) reported a series of 4116 chromosomally normal fetuses with increased NT at 10–14 weeks of gestation and showed that although 94% of these fetuses were liveborn, the chance of a livebirth decreased as NT thickness increased (Table 1). Whilst the 95th centile increases with advancing gestation, the 99th centile is constant, with a value of 3.5 mm, so 80% of fetuses with an abnormal NT measurement are actually in the group that has a 96% live-birth rate. This rate is likely to be similar to that seen in a background population and we could therefore suggest that our efforts for further surveillance should be confined to pregnancies where the NT thickness measured over the 99th centile (3.5 mm). At this early stage 80% of parents, with a fetus with a mild increase in NT thickness could be reassured.

This view is supported by data from another study examining pregnancy outcome in 6650 women who had attended for first trimester ultrasound assessment (Michailidis and Economides, 2001). Nuchal translucency measurement was made by the same technique and increased NT was once again defined as being above the 95th centile. The authors showed that the relative risk of adverse pregnancy outcome (spontaneous abortion, intrauterine death or termination for fetal abnormality) was 4.7 times higher if the NT thickness was above the 95th centile. For cases above the 99th centile the relative risk was 12.2 times higher when compared to fetuses with normal NT. Further analysis of the data show that the increased level of risk is solely confined to fetuses with NT above the 99th centile, whilst the risk of an adverse outcome with NT measurement between the 95th and 99th centiles is not significantly different from that with a normal NT (Table 1). Within the group of fetuses with NT above the 99th centile the degree of thickening remains important, as larger measurements are associated with poor outcome.

One advantage of reviewing the sonographic findings after just a few weeks is to determine whether there has been intrauterine demise. Souka *et al*. (2001) recently showed that in 1320 chromosomally normal fetuses with increased NT ($\geq$3.5 mm), 68 (5.2%) miscarried or died *in utero* and 43 (63%) of these died by 15 weeks of gestation. Although the underlying cause of intrauterine death was only identified in about a quarter of cases, early review allowed delivery to be expedited and appropriate counselling could be provided.

UNDERLYING PATHOPHYSIOLOGY

As well as being associated with chromosomal abnormalities, increased NT is known to be associated with a variety of other fetal structural defects and genetic syndromes. Assuming that these defects all produce nuchal oedema by a common mechanism, it is appropriate to

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Table 1—Data from two series reporting pregnancy outcome in chromosomally normal fetuses with increased nuchal translucency at 10–14 weeks of gestation

Author	NT	*n*	Deaths	Survivors
Souka *et al*., (1998)	95th–3.4 mm	3423	125 (4.7%)	3298 (96.3%)
	3.5–4.4 mm	448	36 (8.0%)	412 (92.0%)
	4.5–5.4 mm	138	20 (14.5%)	118 (85.5%)
	5.5–6.4 mm	48	17 (35.4%)	31 (64.6%)
	>6.5 mm	59	33 (55.6%)	26 (44.4%)
	Total	4116	231 (5.6%)	3885 (94.4%)
Michailidis *et al*., (2001)	<95th centile	6371	92 (1.4%)	6279 (98.6%)
	95th–99th centile	162	3 (1.9%)	159 (98.1%)
	>99th centile	73	13 (17.8%)	60 (82.2%)
	Total	6606	108 (1.6%)	6498 (98.4%)

review our current understanding of the pathophysiology as this may influence further management.

Historically, pathological studies of nuchal abnormalities were confined to those found after second or third trimester intrauterine death (Van der Putte, 1977; Chitayat *et al*., 1989). By 20 weeks' gestation, nuchal swellings are divided by sonographic appearance into multiseptated cystic hygroma or the generalised soft-tissue thickening of nuchal oedema. Cystic hygroma are strongly associated with Turner's syndrome where generalised hypoplasia and partial agenesis of the lymphatic system result in overdistention of the jugular lymphatic sacs as a consequence of failure of communication with the internal jugular vein (Chervenak *et al*., 1983). Fetuses with nuchal oedema do not have the same type of lymphatic changes and it would appear that this anomaly has a different aetiology (Chitayat *et al*., 1989). This may represent a mild end of a spectrum of hydrops fetalis which is also seen in fetuses with cardiovascular defects, skeletal dysplasias, congenital infection, metabolic and haematological disorders.

Both nuchal translucency at 11–14 weeks' and nuchal oedema at 20 weeks of gestation are commonly seen in trisomic fetuses and there may therefore be a common underling aetiology. Most of the investigations of the underlying pathophysiology of increased NT have been based on this hypothesis and this has in turn focused clinical attention on the association of increased NT and structural defects in the fetus, particularly major cardiac defects.

INCREASED NT AND CARDIAC DEFECTS

Initial investigation of the underlying mechanism of increased nuchal translucency was based in pathological findings in fetuses terminated due to chromosomal abnormality (Hyett *et al*., 1997a). These studies suggested that there was an association between increased nuchal translucency and structural defects of the heart and great arteries. Further pathological and ultrasound studies found that chromosomally normal fetuses with increased NT also had a high prevalence of congenital heart disease, leading to the hypothesis that increased NT could be used as a marker for cardiac disease (Hyett *et al*., 1997b). A review of 29 154 singleton pregnancies screened for chromosomal abnormality by measuring NT thickness at 11–14 weeks' gestation found that NT was above the 95th centile in 56% of fetuses with major cardiac abnormalities (Hyett *et al*., 1999).

It is an appealing idea to suggest that the population could be screened for major cardiac defects by measuring NT at this early stage of pregnancy and referring those with an increased measurement for detailed echocardiography. Traditional screening and selection of patients for detailed echocardiography relies on two approaches. Identifying historical risk factors, such as a previous affected pregnancy, maternal illness or ingestion of teratogens will only identify about 5% of affected cases (Maher *et al*., 1994). Assessment of the four-chamber view and great arteries at the time of the routine 20-week anomaly scan can be very effective, but the value of this screening technique is highly dependent on operator training and experience (Sharland and Allan, 1992; Rustico *et al*., 1995). Although NT measurement also requires training, in many units it is already being used to screen for chromosomal abnormalities and this objective assessment is readily audited allowing good quality control. As the quality and resolution of ultrasound equipment has improved, earlier echocardiography will allow earlier diagnosis for parents—although further research on the sensitivity and specificity of these techniques is needed to determine whether decisions about terminating a pregnancy can safely be made at this stage (Carvalho *et al*., 1998; Sharland, 1998).

Data from two groups performing detailed echocardiography have shown that referral for assessment after finding increased NT is worthwhile. Twenty-nine (7.3%) of 398 chromosomally normal fetuses with NT above the 99th centile were found to have a major cardiac defect—double the prevalence seen in pregnancies of diabetic women who are traditionally referred for echocardiographic assessment (Zosmer *et al*., 1999; Meyers-Wittkopt *et al*., 1996). Twenty-eight of these cases were successfully diagnosed prenatally, identified at 13–17 weeks' gestation in 88% of those scanned at this earlier stage. The second study reported a series of 313 fetuses that had increased NT identified at a local hospital earlier in pregnancy (Simpson and Sharland, 2000). Fifty-one (16.3%) of these had congenial heart

disease, although the prevalence may be inflated by other selection criteria which guided referral.

There are now several studies that have examined the outcome of fetuses with increased NT but direct comparison is unfortunately often complicated by variations in the methodology used for measurement and differing definitions of increased NT. Hiippala *et al*. (2001) reported follow-up data on a series of children who had had NT assessment during pregnancy (at 10–15 weeks) with NT $\geq$3 mm. In the initial study of 10 507 pregnancies, NT was $\geq$3 mm in 84 (0.8%) cases and 61 of these infants were chromosomally normal livebirths. There were two neonatal deaths due to major cardiac defects and detailed follow-up showed that there were two other infants with a cardiac defect requiring surgical intervention—a prevalence of 6.6%. Two recent publications have examined the effectiveness of NT measurement as a tool to screen for major cardiac defects (Michailidis and Economides, 2001; Mavrides *et al*., 2001). Both studies used the same methodology as the Fetal Medicine Foundation making comparison with the screening study of 29 154 pregnancies more straightforward. The detection rates for major cardiac defects by NT assessment using both the 95th and 99th centiles are shown in Table 2. The sensitivity of this test appears to be lower than had initially been anticipated. Differences in detection rates may in part be due to differences in study design—the initial data were analysed retrospectively, whereas the more recent studies were designed prospectively. Similarly, the overall prevalence of cardiac defects was lower in the first study than would have been anticipated on the basis of other data in the literature.

The data do not support the use of NT screening as the sole means of screening for major cardiac defects but thorough evaluation of the fetal heart for fetuses with increased NT remains an important means of identifying affected fetuses. In Mavrides' study only 50% of the 22 cases missed by NT screening were detected at 18–22 weeks' gestation, whilst in Michailidis' study four were detected with increased NT, two after the 20-week scan and the remaining five were diagnosed postnatally. NT measurement will not replace traditional means of screening for major congenital cardiac disease but does provides a useful adjunct to current methods of screening which have proven to be far from perfect.

Table 2—Studies examining the effectiveness of increased nuchal translucency as a screening tool for major cardiac defects in chromosomally normal fetuses

Author	NT cut-off (centile)	Detection rate
Hyett *et al*. (1999)	95th	28/50 (56%)
	99th	20/50 (40%)
Michailidis and Economides (2001)	95th	4/11 (36%)
	99th	3/11 (27%)
Mavrides *et al*. (2001)	95th	4/26 (15%)
	99th	3/26 (12%)
Total	95th	36/87 (41%)
	99th	26/87 (30%)

OTHER STRUCTURAL ANOMALIES AND GENETIC SYNDROMES

The list of structural anomalies and genetic syndromes which have been reported as being observed with increased NT is very long, but a true association has only been identified in a few cases (Souka *et al*., 1998, 2001). Fetal exomphalos can be identified from 11 weeks of gestation and has an increased prevalence in fetuses with increased NT. Whilst this is usually associated with chromosomal abnormalities, such as trisomy 18, the prevalence remains increased in chromosomally normal fetuses.

Similarly the prevalence of diaphragmatic hernia is significantly higher in a population of fetuses with increased NT. At later gestations, haemodynamic changes associated with diaphragmatic hernia mimic those seen with coarctation of the aorta. Pathological studies of the underlying mechanism of increased NT show that narrowing of the aortic isthmus is a common finding in fetuses with increased NT and similar haemodynamic changes may therefore be occurring in these two groups. In a series of 19 cases of diaphragmatic hernia, seven (37%) had increased NT at 10–14 weeks and this included five of the six neonatal deaths due to pulmonary hypoplasia—NT thickness may therefore be a useful indicator for the prognosis of infants with this structural anomaly (Sebire *et al*., 1997a).

It is difficult to prove a strong association between genetic syndromes and increased NT, as most syndromes have extremely low prevalence in the population and we are therefore reliant on case reports rather than series. The prevalence of genetic syndromes and single gene disorders does, however, appear to be increased in fetuses with increased NT, being as high as 12.7% in one publication (Bilardo *et al*., 1998). It seems likely that syndromes such as Noonan's, where infants commonly have a webbed neck, are likely to have similar phenotypic expression *in utero* (Achiron *et al*., 2000). Fetal akinesia deformation sequence has frequently been associated with increased NT although the mechanism for this association is unclear (Hyett *et al*., 1997c). Many skeletal dysplasias appear to be associated with increased NT and this may be due to the effects of mediastinal compression or due to differences in collagen expression.

In the second and third trimesters of pregnancy, nuchal oedema and hydrops have been found to be associated with materno–fetal infection. It has therefore been suggested that a fetal infection may, on occasion, be the underlying cause of increased NT. There have been two case reports suggesting an association between parvovirus infection and increased NT (Smulian *et al*., 1998; Markenson *et al*., 2000). However, screening a population of 426 chromosomally normal pregnancies with increased fetal NT found evidence of recent maternal infection in six cases, but no evidence of fetal infection on any occasion (Sebire *et al*., 1997b). Screening for fetal infection may be useful in cases where there in no resolution of nuchal oedema by 16–20 weeks but there is no evidence to suggest that a routine screen for

fetal infection is useful in those cases where increased NT resolves.

BEYOND THE 20-WEEK SCAN

Although most mortality and morbidity associated with increased NT can be determined by the time of the 20-week scan we should also consider the residual risk of a fetal anomaly remaining undetected at this stage. Souka *et al*. (2001) found that in 980 cases of NT $\geq$3.5 mm where no anomalies were found at the 20-week scan, the residual risk of an adverse outcome was very small (2%)—including several cases of cardiac defects which were amenable to prenatal diagnosis. The risk of adverse outcome was significantly higher (18%) if nuchal oedema was still recognisable at the time of the 20-week scan.

Giving accurate data about long-term outcome, and specifically the incidence of neurodevelopmental delay, is hampered by differences in the length of follow-up and method of data acquisition used by different study groups. The prevalence of neurodevelopmental delay ranges from 0.0% to 5.3% in studies with no formal paediatric evaluation (Michailidis and Economides, 2001; Souka *et al*., 2001; Cha'ban *et al*., 1996; Van Vugt *et al*., 1998; Adelunke *et al*., 1999). Another comparison of neurodevelopmental outcome between 89 infants who had had increased NT and 302 infants with normal findings at the 11–14 week scan found no significant difference between the two groups (Brady *et al*., 1998). This study included paediatric evaluation but follow-up ranged from 6–42 months and neurodevelopmental delay may not always be detected in the early stages of infancy. The most detailed report of neurodevelopmental outcome is provided by Hiippala *et al*. (2001) who followed infants for 2.4–7.1 years and made a diagnosis of developmental delay in just one (2%) infant.

CONCLUSION

As well as being associated with chromosomal abnormality, increased NT is associated with perinatal death, major cardiac defects and other structural defects and has been reported to be associated with a number of genetic syndromes. There are now several studies reporting the outcome of chromosomally normal fetuses with increased NT and management strategies for the remainder of the pregnancy should be based on these. The high prevalence of early intrauterine death means that an early follow-up scan is indicated. Eighty percent of parents, with a NT measurement between the 95th and 99th centiles can be reassured that the outcome of pregnancy is likely to be the same as for those pregnancies with a normal NT at this stage. In some centres a more detailed examination of fetal anatomy, and in particular of the fetal heart, may be possible at this stage. A review of the extent of nuchal oedema is also useful, as persistence of this sign is associated with an underlying structural defect and poor prognosis. A detailed anomaly scan will be necessary at 20 weeks and examination of the fetal heart by a sonographer trained in fetal echocardiography is a priority. Although the list of genetic associations is extensive, it is important to bear in mind that many of these syndromes will have subtle features that will be difficult to detect by ultrasound. If the anomaly scan is normal then the chance of the fetus having an underlying abnormality falls to about 2%.

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The Invited Commentary: Current issues in Obstetrics and Genetics section of *Prenatal Diagnosis* aims to commentary in topical issues in prenatal diagnosis which are of relevance to both obstetricians and medical geneticists. These commentaries are invited and each represents a personal critical analysis of the current studies of a particular subject, putting the latest research into the context of earlier work, and providing implications for clinical practice.