

Incidence of major structural cardiac defects associated with increased nuchal translucency but normal karyotype

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KEYWORDS: Cardiac defects, First trimester, Nuchal translucency, Screening, Ultrasound

ABSTRACT

Objective To examine the association between increased nuchal translucency thickness and major cardiac defects in chromosomally normal fetuses.

Setting Tertiary referral unit for fetal medicine and fetal cardiology.

Methods During a 4-year period (January 1997 to January 2001), detailed echocardiography was performed in 1319 chromosomally normal fetuses with increased nuchal translucency thickness at 10–14 weeks of gestation. The incidence of major cardiac defects was examined in relation to the fetal NT at the 10–14-week scan.

Results Major cardiac defects were diagnosed in 60 (4.5%) of the 1319 fetuses. In fetuses with a nuchal translucency thickness in the range of 2.5–3.4 mm, the incidence of major cardiac defects was 2.5% (18/722; 95% confidence interval, 1.5–3.9) and in those with a nuchal translucency thickness ≥ 3.5 mm, it was 7% (42/597; 95% confidence interval, 5.1–9.4).

Conclusion Specialist echocardiography is indicated in all fetuses with increased nuchal translucency thickness because, in such fetuses, the incidence of major cardiac defects is substantially higher than in pregnancies with maternal diabetes, family history and exposure to drugs, where fetal echocardiography is widely considered to be necessary.

INTRODUCTION

Ultrasound measurement of fetal nuchal translucency (NT) thickness is the basis for a widely adopted and effective method of screening for chromosomal abnormalities^{1–4}. A significant association between increased NT and the occurrence of major cardiac defects has also been observed. This correlation has been documented in both chromosomally abnormal^{5–7} and normal fetuses^{8–11} and the risk of cardiac anomalies increases with the NT measurement.

In a large group of chromosomally normal babies, Hyett *et al.* have reported an overall risk of cardiac defect of 2% when the NT was above the 95th centile and a considerably higher risk (6%) when the NT was above the 99th centile⁹. This study indicated that 56% of all fetuses with major cardiac defects had NT measurements above the 95th centile. However, Schwarzler *et al.*¹² failed to demonstrate any strong association between increased NT and cardiac defects, and more recent publications from the same and another center, although demonstrating some association, have cast some doubt on the effectiveness of NT screening for cardiac defects in the general population^{13,14}. Mavrides *et al.*¹³ found that only 15% of major cardiac defects occurred within the group of chromosomally normal fetuses with NT above the 95th centile, whereas Michaildis *et al.*¹⁴ found that 36% of all major cardiac defects occurred in a similar group. Although both of these studies demonstrated that most fetuses with cardiac defects had normal NT, they also reported that the incidence of cardiac defects was increased in association with increased NT compared to the whole population. In these two studies, the incidence of cardiac defects was 1.6% and 1.7% in those with NT above the 95th centile and 5.0% and 4.1% in those with NT above the 99th centile (3.5 mm).

This study provides an update of the risk for cardiac defects associated with different levels of increased NT at our center and discusses the possible sensitivity of increased NT in screening for these defects.

METHODS

During a 4-year period (January 1997 to January 2001), detailed echocardiography was performed in all fetuses with increased NT at 10–14 weeks of gestation and normal or unknown karyotype seen at our center. During the early part of the study, fetuses with NT of 3.5 mm or greater (corresponding to the 99th centile of NT) were studied but, thereafter, fetuses with NT of 2.5 mm or greater, approximating the 95th centile, were included. Only fetuses seen

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Presented at The Fetal Medicine Foundation's meeting on Research and Developments in Fetal Medicine, London, August 30th–September 1st 2001.

prospectively as part of this NT follow-up program were included: fetuses seen later for other reasons were excluded whether a previous nuchal assessment elsewhere was normal, abnormal or unknown. Those with unknown karyotype at the time of the scan were included in the final analysis only if chromosomal abnormality was excluded postnatally. Fetuses previously reported from our unit by Zosmer *et al.*¹¹ (but not those reported by Hyett^{9,10}) were included in this study. In 1268 fetuses, chorionic villus sampling (CVS) had demonstrated a normal karyotype and in 41 fetuses the karyotype was not determined prenatally but clinical normality was verified postnatally. Fetuses subsequently demonstrated to have a 22q11 microdeletion were not excluded.

An initial fetal cardiac scan was performed at between 10 and 23 weeks of gestation, depending on the level of increased NT. Fetuses with initial negative cardiac findings had further fetal echocardiography at 18–23 weeks of gestation. If cardiac defects were identified, they were evaluated by follow-up scans, postnatal assessment or autopsy. Cardiac defects not considered major were excluded, even if they were detected prenatally. Major cardiac defects were those expected to require surgery or interventional cardiac catheterization within the first year of life, if the pregnancy continued.

The cardiac scan was performed by an expert in fetal echocardiography and included assessment of the position of the heart, the four-chamber view, the outflow tracts and venous return. An Acuson Aspen ultrasound machine (Acuson, CA, USA) with probes varying from 7 to 3.5 MHz of frequency was used for all the scans. The images were recorded on videotape and stored digitally.

Demographic details and ultrasound findings were entered into a computer database at the time of the scanning. Parents were requested to fill in and return a follow-up questionnaire a few weeks after delivery and telephone inquiries were made if reports were not returned.

The incidence of major cardiac defects was examined in relation to the fetal NT at the 10–14-week scan. Confidence intervals (CIs) were calculated for proportions using the exact method.

RESULTS

Inclusion criteria were satisfied for 1319 fetuses with a median NT measurement of 3.3 mm (range, 2.5–12.3 mm). Excluded were 11 fetuses with cardiac defects that were not considered to be major; there were two with mild pulmonary stenosis, three with persistent left superior vena cava, one with a small ventricular septal defect and five with ventricular and/or great artery disproportion not due to coarctation of the aorta.

Major cardiac defects were diagnosed in 60 (4.5%) of the 1319 fetuses. In fetuses with NT in the range of 2.5–3.4 mm, the incidence of major cardiac defects was 2.5% (18/722, 95% CI 1.5–3.9) and in those with NT equal or greater than 3.5 mm, it was 7% (42/597, 95% CI 5.1–9.4%). The results are summarized in Figure 1. The median NT thickness was significantly higher in the group of fetuses with major cardiac defects than those with normal hearts (4.3 vs. 3.3 mm).

All types of major cardiac defects were represented in this group of fetuses with increased NT and no predominance of a specific defect type was observed (Table 1). Four fetuses with cardiac defects and a normal initial karyotype had 22q11 microdeletions demonstrated on further analysis of the original CVS samples; there were two cases of pulmonary atresia with ventricular septal defect, one case of Fallot's tetralogy and one of common arterial trunk.

Cardiac defects were first diagnosed at a median gestational age of 16 weeks with eight abnormalities first detected before 14 weeks of gestation. The parents chose to have termination of pregnancy in 35 (58%) of the 60 cases with major cardiac defects, including three with additional major extracardiac anomalies. The median gestational age at termination was 15 weeks with eight terminations performed before 14 weeks of gestation following a first-trimester

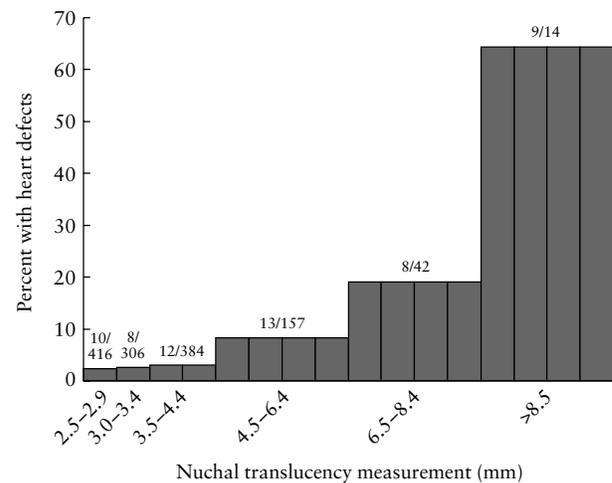


Figure 1 The incidence of major cardiac defects increases with nuchal translucency thickness. The numbers on the top of each column indicate number of major cardiac defects and the total number of fetuses examined in each nuchal translucency category.

Table 1 Major cardiac defects diagnosed in fetuses with increased nuchal translucency, classified according to the type of defect. Each fetus is included only once, in the single most appropriate category

Type of cardiac defect	n
Coarctation of the aorta (with or without VSD)	7
Hypoplastic left heart syndrome	5
Aortic valve stenosis	2
Atrioventricular septal defect (including complex defects)	12
Ventricular septal defect (large)	2
Fallot's tetralogy (including pulmonary atresia with VSD)	9
Double outlet right ventricle	4
Simple transposition	3
Pulmonary atresia (intact ventricular septum)	3
Other complex pulmonary atresias	4
Common arterial trunk	1
Double inlet left ventricle	2
Tricuspid atresia (with or without transposition)	4
Aortopulmonary window	1
Absent pulmonary and aortic valves (free regurgitation)	1
Total	60

VSD, ventricular septal defect.

echocardiography. In the 25 cases where the parents chose to continue with the pregnancy, there were three spontaneous intrauterine deaths and 22 livebirths. In four of the cases, there were major extracardiac abnormalities in addition to the cardiac defect. There was one case of pentalogy of Cantrell with Fallot's tetralogy, one case of cystic dysplasia of the kidneys with coarctation, one case of esophageal atresia with tracheo-esophageal fistula and Fallot's tetralogy and one case of rectal atresia and hypoplastic left heart syndrome. In the latter two cases, the extracardiac abnormality was not diagnosed prenatally.

Detailed postnatal follow-up was available in 21 of the 22 livebirths and, in all cases, the prenatal findings were confirmed. Autopsy results were available for 16 of the 39 fetuses following termination or intrauterine death and the presence of major cardiac defects was confirmed in all cases. Major cardiac defects were not identified postnatally in any of the 1259 cases with normal findings at fetal echocardiography.

To facilitate comparison with other studies and to predict the likely effectiveness of screening for major cardiac defects using NT, we calculated the expected proportion of cardiac defects that would be associated with increased NT in a theoretical unselected population. From large population studies of NT, approximately 5% of those with normal fetal karyotype will have NT measurements greater or equal to 2.5 mm and 1% greater or equal to 3.5 mm⁴. Patients referred to us with increased NT had some bias towards NT greater than 3.5 mm. There were similar numbers in the range of 2.5–3.4 mm as in the range equal or greater than 3.5 mm, rather than four times as many as expected in the whole population. We estimated the expected incidence of cardiac defects associated with increased NT in an unselected population based on the observed incidence in those with increased NT in our study. In an unselected population of 10 000 fetuses, 100 fetuses will have NT of 3.5 mm or greater and 7.0% of these (seven fetuses) will have a major cardiac defect. In the same population, 400 fetuses will have NT of 2.5–3.4 mm and 2.5% of these (10 fetuses) will have major cardiac defects. Thus, the incidence of cardiac defects which are associated with increased NT in the whole population is estimated as 1.7 per thousand. Estimates of the total incidence of cardiac defects in the population vary quite widely but reliable estimates lie in the range of 3–5 per thousand if only major defects are considered^{15–17}. Our data are thus consistent with approximately one-half of all major cardiac defects in chromosomally normal fetuses being associated with increased NT.

DISCUSSION

Our data confirm that increased NT during the first trimester is associated with major cardiac defects in fetuses with a normal karyotype and the risk of a cardiac defect increases markedly with increasing NT. In keeping with most recent studies, we have shown no obvious bias towards any particular type of defect in those presenting with increased NT¹⁸.

Unlike the studies of Mavrides *et al.*¹³ and Michailidis *et al.*¹⁴, this study does not attempt to consider a defined unselected population but, instead, a group selected on the

basis of increased NT with normal karyotype. Thus, although we can estimate the incidence of major cardiac defects in various bands of increased NT, we cannot make a direct comparison with the incidence of cardiac defects in the whole population. We have systematically examined only those with increased NT and not those with normal NT. The principal advantage of studying this referral population is that larger numbers with abnormal NT can be considered and estimates of the incidence of cardiac defects within this particular group are less susceptible to the statistical limitations inherent in a smaller sample size. However, in order to ascertain how the number of cardiac defects which have been detected by NT screening relates to those in the whole population, it is necessary to make assumptions about the overall incidence of major cardiac defects. Inconsistency in estimates of the incidence of congenital heart disease may be attributed to differences in which defects are classified as major or minor, inclusion or otherwise of those with major extracardiac conditions, incomplete ascertainment for serious conditions presenting late¹⁹ and dependence on reporting mechanisms which may be unreliable. The overall incidence of cardiac defects of 3.5 per thousand in the study of Mavrides *et al.*¹³ is consistent with complete ascertainment of defects within the population defined for study, whereas that of Michailidis *et al.*¹⁴ at 2.0 per thousand may indicate incomplete ascertainment. Although both of these studies show a lower incidence of cardiac defects than our own study, our own estimates fall within their quoted 95% confidence intervals both for the 2.5–3.4 mm NT group and for those with NT of 3.5 mm or greater.

A reliable estimate of the proportion of all major cardiac defects that are associated with increased NT might be considered important in predicting the effectiveness of screening for congenital cardiac defects using NT. In this respect, both of these studies suggest that screening is likely to be less effective than the estimates that our own study would suggest. They imply that 15% and 36% of major cardiac defects would be associated with NT equal or greater than 2.5 mm (approximately 95th centile) and 11% and 27% would be associated with NT equal or greater than 3.5 mm (or 99th centile)^{13,14}. Our own data suggest that, assuming an overall incidence of major cardiac defects of 3.5 per 1000, 56% of all those with major cardiac defects would have NT equal or greater than 2.5 mm and 32% would have NT equal or greater than 3.5 mm.

In practice, decisions to introduce NT assessment are likely to be influenced much more by its perceived effectiveness in screening for chromosomal abnormalities than to its value in screening for cardiac defects. From the fetal cardiologists' point of view, the main issue is likely to be how best to deal with those fetuses with increased NT arising from a program that is already established, rather than determining if such a program should be implemented in the first place. Broad agreement is likely on some of the main issues. First, a substantial though arguable proportion of fetuses with major cardiac defects does not have increased NT. Whatever NT-based screening program for cardiac defects may be in place, it will not replace the need for an adequate assessment of the fetal heart as part of the routine anomaly scan at

18–23 weeks of gestation. Second, fetuses with increased NT but a normal fetal karyotype are at increased risk of a cardiac defect and merit specialist cardiac assessment. The main area of contention and discussion is likely to be where the threshold of increased NT that initiates specialist fetal echocardiography should be set. There is no intrinsic cut-off point of NT below which cardiac defects suddenly become less likely. The lower the threshold set, the more cardiac defects will be diagnosed. However, as the threshold decreases, substantially more normal fetuses would need to be examined for each cardiac defect discovered. Our own data indicate that the incidence of major cardiac defects associated with NT of 2.5–2.9 mm at 2.4% is comparable with that associated with established indications for fetal echocardiography, such as family history²⁰ or maternal diabetes mellitus²¹. On this basis, detailed fetal echocardiography for all cases with NT of 2.5 mm or greater could be justified, but this would involve scanning 5% of pregnant women. Two other recent studies suggest a higher threshold of 3.5 mm would be more appropriate^{13,14}. In contrast to the situation with screening for chromosomal abnormalities, where proceeding to a definitive invasive test carries a significant risk to the fetus that must be balanced against the potential benefits, specialist fetal echocardiography performed competently carries essentially no threat to the fetus. In practice, the availability of the necessary skills and other resources is likely to be a major determinant of how many of the fetuses with increased NT have specialist fetal echocardiography. Major changes in the way that specialist fetal echocardiography services are provided would be required if as many as 5% of the pregnant population were to have specialist fetal echocardiography for this indication. The proportion of fetuses currently having specialist fetal echocardiography is unknown, but is certainly substantially smaller than this.

Research into the mechanisms underlying increased NT may lead to new and even more effective ways of identifying those at high risk of cardiac defects and chromosomal abnormality. Abnormal Doppler flow in the ductus venosus has already been shown to be closely related to both chromosomal abnormality and cardiac defects in those with increased NT, although this is unlikely to be suitable for first level screening^{22,23}. Currently, there are no methods suitable for general screening for cardiac defects at 10–14 weeks of gestation that are more effective than NT. Whilst there remains some dispute as to the most appropriate threshold for specialist echocardiography with increased NT, it is clear that NT measurements exceeding the 99th centile are a very strong indication. They are associated with a substantially higher risk of cardiac defect than longer-established indications for fetal echocardiography including maternal diabetes, family history and exposure to drugs.

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