

Using fetal nuchal translucency to screen for major congenital cardiac defects at 10-14 weeks of gestation: population based cohort study

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Abstract

Objectives To examine the utility of measuring fetal nuchal translucency thickness in screening for major defects of the heart and great arteries at 10-14 weeks of gestation.

Design Population based cohort study.

Subjects 29 154 singleton pregnancies with chromosomally normal fetuses at 10-14 weeks of gestation.

Setting Fetal medicine centre in London.

Main outcome measure Prevalence of major defects of the heart and great arteries.

Results Of 50 cases with major defects of the heart and great arteries (prevalence 1.7 per 1000 pregnancies) 28 (56%, 95% confidence interval 42% to 70%) were in the subgroup of 1822 pregnancies with fetal nuchal translucency thicknesses above the 95th centile of the normal range. The positive and negative predictive values for this cut off point of nuchal translucency thickness were 1.5% and 99.9% respectively.

Conclusions Measurement of fetal nuchal translucency thickness—traditionally used to identify fetuses at high risk of aneuploidy—at 10-14 weeks of gestation can identify a large proportion of fetuses with major defects of the heart and great arteries.

Introduction

Cardiac defects are the most common congenital abnormalities. The prevalence is 3-8 per 1000 pregnancies.^{1,2} In the United Kingdom, studies on screening women with low risk pregnancies by ultrasonography showed a prevalence of congenital abnormalities of 1.3-3.2 per 1000 pregnancies.^{3,4} About half of these defects are asymptomatic, and the other half are classed as major because they are either lethal or require surgery. Specialist fetal echocardiography at around 20 weeks of gestation can identify most of the major cardiac defects,^{5,6} but the main challenge in prenatal diagnosis is to identify those pregnancies at high risk that need referral to specialist centres. Currently, screening is based on examination of the four chamber view of the heart during routine ultrasonography at 16-22 weeks of gestation, but a recent study of 7459 pregnancies showed that an abnormal four chamber view can identify only 26% of major cardiac defects.⁷

A more sensitive method of screening may potentially be the ultrasonographic measurement of fetal nuchal translucency thickness at 10-14 weeks of gestation.⁸ Extensive studies have recently shown a strong association between cardiac defects and increased nuchal translucency thickness, which is thought to be the result of subcutaneous oedema in the nuchal region.⁹⁻¹¹ In four studies reporting on a total of 21 fetuses with major cardiac defects diagnosed at

Editorial by Mol

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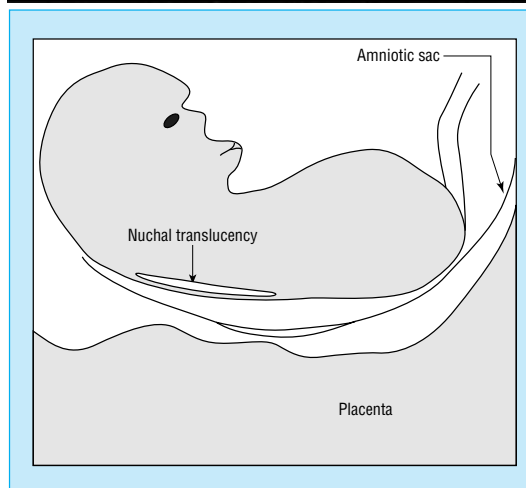


Fig 1 Ultrasonogram of 11 week old fetus showing measurement of crown-rump length and fetal nuchal translucency thickness

Table 1 Major defects of heart and great arteries that were diagnosed antenatally

Case	Nuchal translucency thickness (mm)	Diagnosis (weeks)	Outcome	Major abnormality of heart and great arteries
1	1.0	18	Termination	Ventricular septal defect, presented with congenital heart block
2	1.2	31	Termination	Ebstein's anomaly with pulmonary stenosis
3	4.0*	12	Termination	Exocardia
4	1.8	20	Termination	Tetralogy of Fallot
5	2.1	20	Termination	Hypoplastic left heart with double outlet right ventricle, asymmetrical pulmonary valve
6	2.3†	20	Termination	Atrioventricular septal defect
7	2.7†	16	Termination	Hypoplastic left heart syndrome
8	3.5*	19	Termination	Tetralogy of Fallot
9	4.0*	18	Termination	Mitral atresia, ventricular septal defect, double outlet right ventricle
10	3.6*	21	Termination	Hypoplastic left heart syndrome
11	5.0*	24	Termination	Hypoplastic right ventricle, atresia of tricuspid valve, ventricular septal defect, hypoplastic ductus arteriosus, right subclavian arterial ring
12	5.5*	18	Termination	Aortic atresia and atrioventricular septal defect to dominant right ventricle
13	1.8	25	Postnatal death‡	Atrioventricular septal defect
14	2.2	30	Postnatal death‡	Ventricular septal defect requiring surgery
15	2.7†	20	Live birth	Ventricular septal defect requiring surgery
16	2.8†	20	Live birth	Coarctation of the aorta, ventricular septal defect; arch repaired surgically
17	4.5*	18	Live birth	Transposition of great arteries
18	4.0*	21	Live birth	Transposition of great arteries, pulmonary stenosis, dextrocardia

*Thickness greater than 99th centile for gestational age. †Thickness greater than 95th centile for gestational age. ‡Death occurred after surgery for cardiac abnormality.

Table 2 Major defects of heart and great arteries diagnosed at postmortem examination after termination of pregnancy for extracardiac defects or intrauterine death

Case	Nuchal translucency thickness (mm)	Outcome	Pathological findings
19	3.0*	Termination at 13 weeks for limb abnormalities	Coarctation of the aorta, ventricular septal defect, bicuspid aortic valve
20	4.7†	Termination at 23 weeks for Smith Lemli Opitz syndrome	Hypoplastic right ventricle
21	9.0†	Termination at 13 weeks for exomphalos	Hypoplastic pulmonary trunk
22	14.0†	Termination at 15 weeks for hydrops	Interrupted aortic arch, ventricular septal defect
23	1.7	Intrauterine death at 37 weeks	Premature closure of foramen ovale with associated left heart hypoplasia
24	1.7	Intrauterine death at 20 weeks	Univentricular heart, absent tricuspid valve, pulmonary trunk arising from right atrium
25	1.9	Intrauterine death at 28 weeks	Truncus arteriosus
26	4.9†	Intrauterine death at 13 weeks	Coarctation of aorta
27	6.0†	Intrauterine death at 13 weeks	Coarctation of aorta, perimembranous ventricular septal defect
28	8.0†	Intrauterine death at 13 weeks	Narrow ascending aorta and aortic isthmus, imperforate aortic valve, dilated pulmonary trunk, ductus arteriosus
29	8.2†	Intrauterine death at 14 weeks	Coarctation of aorta, ventricular septal defect
30	9.4†	Intrauterine death at 16 weeks	Coarctation of aorta
31	11.0†	Intrauterine death at 15 weeks	Coarctation of aorta

*Thickness greater than 95th centile for gestational age. †Thickness greater than 99th centile for gestational age.

10-14 weeks of gestation, 17 (81%) had increased nuchal translucency thickness.¹²⁻¹⁵ In addition, pathological studies of both chromosomally abnormal and normal fetuses with increased nuchal translucency thickness have shown a high prevalence of abnormalities of the heart and great arteries.^{16 17} Furthermore, a study of 1389 chromosomally normal fetuses with increased nuchal translucency thickness reported that the prevalence of major cardiac defects increased exponentially with nuchal translucency thickness.¹⁸

Our study of 29 154 singleton pregnancies, presumed to be chromosomally normal, examined the utility of measuring fetal nuchal translucency thickness at 10-14 weeks of gestation as a method of screening for major abnormalities of the heart and great arteries.

Subjects and methods

We undertook a retrospective study to examine the prevalence of major cardiac defects in a population of 31 162 singleton pregnancies. The pregnancies were screened for chromosomal abnormalities by a combination of maternal age and fetal nuchal translucency thickness at 10-14 weeks of gestation.

The fetal crown-rump length and nuchal translucency thickness (fig 1) were measured as previously described by transabdominal ultrasonography, unless visualisation was poor in which case vaginal ultrasonography was carried out.⁸ Demographic details and ultrasound findings including number of fetuses, crown-rump length, and nuchal translucency thickness were entered into a computer database at the time of scanning. Karyotype results and details on pregnancy outcome were added as soon as these became available. Pregnancy outcome was obtained from maternity units, general practitioners, or the patients; the patients were given a questionnaire at the time of the initial scan. If no outcome data were received within two months of the expected date of delivery, we contacted the patients by telephone.

A computer search identified all singleton pregnancies with live fetuses at 10-14 weeks of gestation with a crown-rump length of 38-84 mm and an estimated date of delivery before 1 June 1997. The database was then searched for major abnormalities of the heart and great arteries, diagnosed before or after birth, in the group with a normal fetal karyotype or the birth of a baby with no dysmorphic features suggestive of a chromosomal abnormality.

The prevalence of major cardiac defects was determined and the utility of screening for nuchal translucency thickness including sensitivity, specificity, and positive and negative predictive values were calculated for the nuchal translucency thickness cut off points of the 95th and 99th centiles for crown-rump length. Nuchal translucency thickness normally increases with crown-rump length, and the 95th centile is 2.2 mm for a crown-rump length of 38 mm and 2.8 mm for a crown-rump length of 84 mm; the 99th centile does not change significantly with crown-rump length and is about 3.5 mm.⁹

Results

Our study group comprised 31 162 pregnancies. We excluded from further analysis 323 pregnancies with chromosomal abnormalities, 317 pregnancies with spontaneous miscarriages, and 1368 pregnancies where the women had changed address and despite repeated attempts through their general practitioners and maternity hospitals, it was impossible to obtain information on pregnancy outcome. In the remaining 29 154 pregnancies the median gestation at the time of screening was 12 weeks (range 10-14 weeks) and the median maternal age was 34 years (range 15-48 years). The fetal nuchal translucency thickness was above the

95th centile for crown-rump length in 1822 (6.3%) pregnancies and above the 99th centile in 315 (1.1%) pregnancies.

Major defects of the heart and great arteries were identified in 50 of the pregnancies. These included 18 pregnancies that were diagnosed antenatally by ultrasonography at 16-31 weeks of gestation (table 1), 13 that were diagnosed at pathological examination after intrauterine death or termination of pregnancy for conditions other than cardiac defects (table 2), and 19 that were diagnosed in live births (table 3).

The prevalence of major cardiac defects was 1.7 per 1000 pregnancies (50/29 154), which increased with nuchal translucency thickness from 0.8 per 1000 for those pregnancies with nuchal translucency thickness below the 95th centile to 63.5 per 1000 for those pregnancies with nuchal translucency thickness above the 99th centile (table 4). There were essentially six groups of cardiac defects; tetralogy of Fallot, hypoplastic left heart, transposition of the great arteries, coarctation of the aorta and aortic stenosis or atresia, ventricular and atrioventricular septal defects, and a sixth group of other complex defects (table 5). Table 6 shows the sensitivity, specificity, and positive and negative predictive values of nuchal translucency thickness cut off points of the 95th and 99th centiles in the detection of major cardiac defects, and figure 2 shows a receiver-operator characteristic curve.

Table 3 Major defects of heart and great arteries diagnosed postnatally

Case	Nuchal translucency thickness (mm)	Major abnormality of heart and great vessels
32	1.0	Tetralogy of Fallot
33	1.5	Large ventricular septal defect
34	1.5	Total anomalous pulmonary drainage
35	1.6	Tetralogy of Fallot
36	1.7	Tetralogy of Fallot
37	1.7	Transposition of great arteries
38	1.8	Transposition of great arteries, ventricular septal defect
39	1.9	Tetralogy of Fallot
40	1.9	Transposition of great arteries
41	2.0	Transposition of great arteries, ventricular septal defect
42	2.2	Tetralogy of Fallot
43	2.2	Tetralogy of Fallot
44	2.3	Ebstein's anomaly
45	2.3*	Transposition of great arteries
46	3.0*	Large ventricular and atrial septal defect
47	3.0*	Ventricular septal defect, double outlet right ventricle, pulmonary stenosis
48	3.5†	Tetralogy of Fallot
49	3.8†	Large ventricular septal defect
50	4.5†	Transposition of great arteries

*Thickness greater than 95th centile for gestational age.
†Thickness greater than 99th centile for gestational age.

Table 4 Prevalence of major defects of heart and great arteries in fetuses that were chromosomally normal

Nuchal translucency thickness	No of fetuses	No of major cardiac defects	Prevalence per 1000 fetuses
<95th centile	27 332	22	0.8
≥95th centile-3.4 mm	1 507	8	5.3
3.5-4.4 mm	208	6	28.9
4.5-5.4 mm	66	6	90.9
≥5.5 mm	41	8	195.1
Total	29 154	50	1.7

Table 5 Detection of specific cardiac defects using increased fetal nuchal translucency thickness

Cardiac defect	No (%) of fetuses	Nuchal translucency	
		No (%) >95th centile	No (%) >99th centile
Tetralogy of Fallot	9 (18)	2 (22)	2 (22)
Hypoplastic left heart	3 (6)	2 (67)	1 (33)
Transposition of great arteries	8 (16)	4 (50)	3 (38)
Coarctation of aorta, aortic stenosis, or atresia	10 (20)	10 (100)	8 (80)
Ventricular and atrioventricular septal defects	8 (16)	4 (50)	1 (13)
Other defects	12 (24)	6 (50)	5 (42)
Total	50 (100)	28 (56)	20 (40)

Table 6 Sensitivity and specificity of screening for major defects of heart and great arteries using fetal nuchal translucency thickness. Values are percentages (95% confidence intervals)

	Using 95th centile	Using 99th centile
Sensitivity	56.0 (42.0 to 70.0)	40.0 (26.0 to 54.0)
Specificity	93.8 (93.6 to 94.1)	99.0 (98.9 to 99.1)
Positive predictive value	1.5 (1.0 to 2.1)	6.3 (3.7 to 9.0)
Negative predictive value	99.9 (99.8 to 100.0)	99.9 (99.8 to 100.0)

Discussion

Our study shows that 55% of major abnormalities of the heart and great arteries are associated with increased fetal nuchal translucency thickness at 10-14 weeks of gestation. This method of screening compares favourably with the reported sensitivity of 26% using the four chamber view of the heart at 16-22 weeks of gestation. The clinical implication of our findings is that increased nuchal translucency thickness constitutes an indication for specialist fetal echocardiography. Certainly the overall prevalence of major cardiac defects in such a group of fetuses (about 2%) is similar to that found in pregnancies affected by maternal diabetes mellitus or with a history of a previously affected offspring, which are well accepted indications for fetal echocardiography.^{19 20}

At present there may be insufficient facilities for specialist fetal echocardiography to accommodate the potential increase in demand if the 95th centile of nuchal translucency thickness is used as the cut off point for referral. In contrast, a cut off point of the 99th centile would result in only a small increase in workload, and in this population the prevalence of major cardiac defects would be very high.

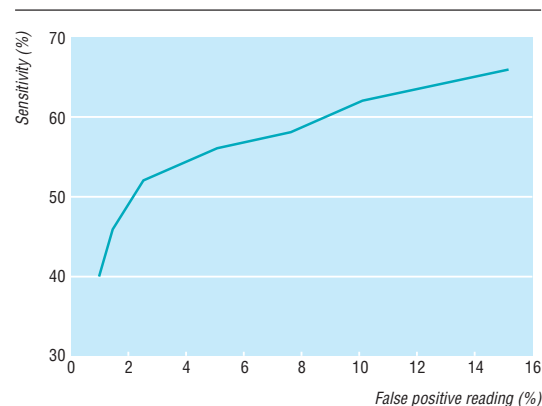


Fig 2 Receiver-operator characteristic curve showing detection rate for major cardiac defects at various false positive rates with increased nuchal translucency thickness

The consequence of combining data from terminations of pregnancy and intrauterine deaths with data from live births would be an overestimate of the true prevalence of cardiac defects in live births from a non-selected population; a proportion of cardiac defects diagnosed antenatally would have resulted in intrauterine death. However, the opportunity to determine such prevalence in “undisturbed” populations was lost in the early 1970s with the advent of prenatal diagnosis. In any case, as shown in the group of patients where the parents chose to continue with the pregnancy after the prenatal diagnosis of major cardiac defects, although the defect obviously persists throughout pregnancy, increased nuchal translucency thickness observed at 10-14 weeks of gestation often resolves by the second trimester and the babies are born alive. Similarly, information on intrauterine deaths is important both for offering a possible explanation for the death and in defining the risk of recurrence. This risk rises from 2% to 10% if there are two rather than one previously affected offspring, and the recurrence is frequently of the same severity or greater severity as the index case.²⁰

The prevalence of major cardiac defects in our population (1.8 per 1000 pregnancies) of presumed chromosomally normal fetuses is compatible with the previously reported prevalence for all cardiac defects in live births (3-8 per 1000 pregnancies); the higher prevalence was reported in studies using echocardiography for diagnosing lesions that are asymptomatic, minor, and even without murmurs. Our study did not include detailed cardiological assessment of all neonates, and since many of the asymptomatic defects would inevitably have been missed, we used major defects as the outcome measure. In contrast to previous studies, our population was confined to those pregnancies presumed to be chromosomally normal; about 25% of affected individuals are chromosomally abnormal. Another factor that may have underestimated our birth prevalence of cardiac defects is the short interval between delivery and obtaining outcome data (in most cases within one month); previous studies have reported that only about 60% of congenital cardiac defects are diagnosed by one month after birth.⁴

The distribution of different types of cardiac defects in our study (table 6) is similar to that described in previous prenatal and postnatal series.^{3 4 7 21 22} Although increased nuchal translucency thickness was observed with all types of major abnormalities of the heart and great arteries, there was a stronger association with left sided defects such as hypoplastic left heart and coarctation of the aorta.

Pregnancies identified by nuchal translucency scanning as being at high risk of cardiac defects need not wait until 20 weeks for specialist echocardiography. Improvements in the resolution of ultrasound machines have made it possible to undertake detailed cardiac scanning in the first trimester of pregnancy.^{13 23-25} Furthermore there are several case reports or small series on the ultrasonographic diagnosis of cardiac defects at 10-14 weeks of gestation, and it is interesting that in 21 fetuses with major cardiac defects, 17 (81%) had increased nuchal translucency thickness.¹²⁻¹⁵

Key messages

- The majority of congenital abnormalities of the heart and great arteries are associated with subcutaneous oedema in the neck region at 10-14 weeks of gestation
- Subcutaneous oedema in the neck region can be visualised by ultrasonography as increased nuchal translucency thickness
- The prevalence of major defects of the heart and great arteries increases with increasing fetal nuchal translucency thickness at 10-14 weeks of gestation
- Measurement of fetal nuchal translucency thickness at 10-14 weeks of gestation is a sensitive method of screening for major defects of the heart and great arteries

Measurement of fetal nuchal translucency thickness at 10-14 weeks of gestation—traditionally used to identify fetuses at high risk of aneuploidy²⁶—also identifies the majority of pregnancies with major defects of the heart and great arteries.

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Conflict of interest: None.

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Science commentary: What is fetal nuchal translucency?

In the fetus fluid collects behind the neck, much like it does in dependent ankle oedema in later life. This occurs partly because of the fetus's tendency to lie on its back and partly because of the laxity of the skin of the neck. As with ankle oedema this accumulation of fluid can represent the end point of several pathological processes, including heart failure. Fluid collecting behind the neck can be detected as nuchal translucency by ultrasound scanning, and it can be measured. The more fluid that has accumulated, the greater the risk of an abnormality being present.

Chromosomal abnormalities—for example, Down's syndrome—can cause fluid accumulation. Chromosome 21 contains the gene that codes for type VI collagen. In trisomy 21 one subunit of this collagen can be overexpressed, resulting in connective tissue that has a more elastic composition.

Failure of fetal movements is also likely to cause nuchal thickening. Neuromuscular abnormalities can cause poor breathing and body movements, both of which may lead to fluid collecting as happens in peripheral oedema. One example is arthrogyposis, which causes contractures and flexion deformities and can be fatal. Other causes are intrathoracic and extrathoracic compressive syndromes. If the thoracic cage is abnormally narrow or an intrathoracic lesion is present (such as a diaphragmatic hernia) the vessels in

the fetus's head and neck become congested and oedema occurs. Likewise, if heart failure occurs (due to congenital cardiac abnormalities or cardiac dysfunction) more extravascular fluid will form.

There is a brief opportunity between 10 and 14 weeks' gestation (when the fetal lymphatic system is developing and the peripheral resistance of the placenta is high) to detect abnormal fluid collections. After 14 weeks the lymphatic system is likely to have developed sufficiently to drain away any excess fluid, and changes to the placental circulation will result in a drop in peripheral resistance. So after this time any abnormalities causing fluid accumulation may seem to correct themselves and can thus go undetected by measuring nuchal translucency.

About 90% of fetuses with a nuchal translucency measurement of 3 mm ("high") at 12 weeks' gestation are normal at birth, while 10% have major abnormalities. Only 10% of babies with a measurement of 6 mm ("very high") at this time will be found to be normal. In centres that perform nuchal translucency measurements, once a fetus has been identified as having a high nuchal translucency, mothers are usually offered chorionic villus sampling and a repeat scan about two weeks later to exclude chromosomal or major physical abnormalities.

Abi Berger, *Science editor, BMJ*

Science
commentary

One hundred years ago

Special correspondence: Rome

Since Christmas the annual university disorders have recurred in Italy. This year they began in the University of Palermo, where the students were desirous of obtaining an additional session of examinations. Professor Baccelli, the Minister of Public Instruction, refused to grant the request and threatened to close the University for the academic year if they did not cease the disorders, which had also extended to the University of Naples. This firm action soon put a stop to the disturbances in both Universities. Later the students attending the anatomical school of the University of Turin, by way of protest against the appointment of Dr. Fusari to the Chair of Human Anatomy, made such disturbances that it was impossible for him to continue his lectures. The Rector of the University published a manifesto, with the sanction of Professor Baccelli, in which he stated that the school of anatomy would not be reopened until the students pledged themselves in writing that order would be kept at Professor Fusari's lectures. If the students did not agree to this, the school would be closed for the whole year, and the

summer and autumn examinations would not be held. On February 24th the course was reopened for those students who had complied with the Rector's demand. While these students were entering the school the anti-Fusarians tried to prevent them, crying out "*Tutti o nessuno!*" The latter were dispersed by the police, and they went to the University, where they tried in vain to get the support of the students of the other faculties. On February 26th they endeavoured forcibly to enter the school of anatomy, and came into collision with the public authorities. Many of them were arrested, and they are now being tried in Turin. The Academic Council then decreed the closure of the course of anatomy for the current year. Why the students object to Professor Fusari is not very clear, as he is a very able man, has had a distinguished university career, and has the warm support of all his colleagues. The firm action of Professor Baccelli in reference to these disorders has been warmly praised in the Chamber of Deputies and by the press. (*BMJ* 1899;i:629)