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Fetal nuchal translucency: ultrasound screening for fetal trisomy in the first trimester of pregnancy

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ABSTRACT

Objective To investigate a new method of screening for fetal trisomies on the basis of maternal age and fetal nuchal translucency thickness at 10 to 13 weeks of gestation.

Design A prospective screening study.

Setting Tertiary referral centre.

Subjects One thousand two hundred and seventy-three women with singleton pregnancies undergoing first trimester fetal karyotyping because of advanced maternal age, parental anxiety, or family history of a chromosomal abnormality in the absence of balanced parental translocation.

Methods Estimates of maternal age-related risks for fetal trisomies 21, 18 and 13 at this gestation were used to derive the expected incidence of these trisomies in fetuses with nuchal translucency < 3 mm, 3 mm and > 3 mm, respectively, and the ratio of observed to expected number of cases was calculated.

Results The nuchal translucency was $\geqslant 3$ mm in 86% of the trisomic and in 4·5% of the chromosomally normal fetuses. The observed number of trisomies in the 1185 cases with nuchal translucency < 3 mm was approximately five times less than the number expected on the basis of maternal age. In the groups with translucency of 3 mm ($n = 52$) and > 3 mm ($n = 36$), the observed numbers of trisomies were approximately five times and 24 times higher than the respective numbers expected on the basis of maternal age.

Conclusion The risk of fetal trisomy can be derived by combining maternal age and fetal nuchal translucency thickness at 10 to 13 weeks of gestation. It is predicted that for a false positive rate of 5%, the sensitivity of the new method of screening would be at least 85%, which compares favourably with the respective 20 to 30% and 50 to 60% of screening based on maternal age alone or the combination of maternal age with maternal serum biochemistry.

This study proposes a new method of screening for fetal trisomies based on the combination of maternal age and fetal nuchal translucency thickness at 10 to 13 weeks of gestation. Previous studies have established the background to the introduction of such a method of screening. Firstly, several ultrasonographic studies have reported a high association between collection of fluid behind the fetal neck (nuchal translucency) and chromosomal abnormalities in the first trimester of pregnancy; in the combined data from nine series on nuchal translucency, 172 (53%) of 327 fetuses had abnormal karyotype (Cullen *et al.* 1990; Nicolaides *et al.* 1992a; Shulman *et al.* 1992; Suchet *et al.* 1992; van Zalen-Sprock *et al.* 1992; Ville *et al.* 1992; Johnson *et al.* 1993; Nadel *et al.* 1993; Savoldelli *et al.* 1993). Secondly, the prevalence of fetal trisomies at 9 to 14 weeks of gestation was reported by Snijders *et al.* (1994); they examined 15793 pregnancies undergoing first trimester fetal karyotyping and derived estimates of maternal age-related risks for trisomies 21, 18 and 13. Thirdly, a preliminary study of 827 women with singleton pregnancies undergoing first trimester fetal karyotyping has reported that the prevalence of translucency $\geqslant 3$ mm in chromosomally normal and trisomic fetuses was 4% and 80%, respectively (Nicolaides *et al.* 1992a). The aim of the present study is to define the incidence of translucency $\geqslant 3$ mm in chromosomally normal and trisomic fetuses in an expanded series of 1273 pregnancies and to derive risks for fetal trisomies on the basis of fetal translucency thickness and maternal age.

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Table 1. Nuchal translucency thickness and fetal karyotype.

Nuchal translucency thickness	Total no. cases	Fetal karyotype: Normal	Abnormal: Trisomy 21	Trisomy 18	Trisomy 13	Other
< 2 mm	1013	1001	3	1	—	8[a]
2 mm	172	171	1	—	—	—
3 mm	52	43	6	—	1	2[b]
4 mm	14	6	5	2	1	—
5 mm	10	2	7	1	—	—
6 mm	6	3	1	2	—	—
7 mm	2	—	—	2	—	—
8 mm	2	1	1	—	—	—
9 mm	2	—	1	1	—	—
TOTAL	1273	1227	25	9	2	10

[a] 46,XX, 18p-; 47,XXX ($n = 2$); 47XXY ($n = 2$); 47,XXX/46XX; 47XX+21/46XX; 47XX+8/46XX.
[b] 47,XX+22; 47,XY+fragment.

Subjects and methods

This was a prospective screening study of 1273 women with viable singleton pregnancies undergoing amniocentesis or chorion villus sampling (CVS) for fetal karyotyping at 10 to 13 weeks plus six days of gestation. Findings in the first 827 of 1273 patients have been published previously (Nicolaides *et al.* 1992*a*). The indications were advanced maternal age ($n = 1058$), parental anxiety ($n = 101$), or family history of a chromosomal abnormality in the absence of balanced parental translocation ($n = 56$). Karyotyping also was performed in 58 pregnancies undergoing CVS for prenatal diagnosis of haemophilia, beta-thalassemia, sickle cell disease, or Duchenne muscular dystrophy. Gestational age was determined from the maternal menstrual history ($n = 1243$) and for those with irregular periods or uncertain dates by measurement of fetal crown–rump length ($n = 30$). The mothers gave written informed consent for fetal karyotyping.

In all cases transabdominal ultrasound examination (curvilinear 5 MHz transducer, Aloka 650, Aloka Limited, Tokyo, Japan) was performed to obtain a sagittal section of the fetus for measurement of crown–rump length and the maximum thickness of the subcutaneous translucency between the skin and the soft tissue overlying the cervical spine. Care was taken to distinguish between fetal skin and amnion because at this gestation both structures appear as thin membranes (Nicolaides *et al.* 1992*a*). The ultrasound machine used was calibrated to record measurements to the nearest 1 mm. In each case two measurements of nuchal translucency were taken and the highest was considered. Intra-observer variation was assessed on the basis of two measurements taken by one operator in 100 patients; a difference of 1 mm was found on three occasions. The inter-observer variation was examined by comparing measurements by two operators in 100 cases; a difference of 1 mm was found on five occasions.

Estimates of maternal age-related risks for fetal trisomies 21, 18 and 13 at 9 to 14 weeks of gestation (Snijders *et al.* 1994) were used to calculate the expected incidence of these trisomies and the ratio of observed to expected number of cases was calculated. Rank correlation was used to examine the association between nuchal translucency thickness and age.

Results

The median maternal age was 38 years (range 22–47) and the median gestational age was 11 weeks (range 10–13). The fetal karyotype was normal in 1227 cases and abnormal in 46, including 36 with trisomies 21, 18 or 13. Data on nuchal translucency thickness and karyotype are summarised in Table 1. The three cases of mosaicism were from chorion villus samples, but they were subsequently confirmed by amniocentesis or cordocentesis to be true fetal mosaics.

The nuchal translucency was ≥ 3 mm in 86% of the trisomic and in 4·5% of the chromosomally normal fetuses; the corresponding values for translucency of ≥ 4 mm are 66% and 1%, respectively (Table 1). In the group with the normal fetal karyotype there was no significant association between nuchal translucency thickness and maternal age ($r = 0{\cdot}02$, $n = 1227$, $P = 0{\cdot}41$). The observed number of trisomies in the 1185 cases with fetal nuchal translucency < 3 mm was approximately 0·22 times that expected on the basis of maternal age (Tables 2 & 3). In the groups with translucency equal to 3 mm ($n = 52$) and > 3 mm ($n = 36$), the observed numbers of trisomies were approximately five times and 24 times higher than the respective numbers expected on the basis of maternal age.

Figure 1 illustrates the estimated risks for fetal trisomies 21, 18 or 13 on the basis of maternal age and nuchal translucency thickness at 10 to 13 weeks of gestation based on data from Snijders *et al.* (1994). To calculate risks on the basis of nuchal translucency thickness and age, the left hand side of the odds ratio for age-related risk was multiplied by the appropriate factor for nuchal translucency thickness. For example, in a 20 year old woman in

Table 2. Observed incidence of fetal trisomies 21, 18 and 13 compared to incidences expected on the basis of maternal age.

Nuchal translucency thickness	Total no. cases	Observed incidence		Expected incidence		Observed:expected	
		21	21 or 18 or 13	21	21 or 18 or 13	21	21 or 18 or 13
< 3 mm	1185	4	5	16·05	22·97	0·25	0·22
3 mm	52	6	7	1·10	1·57	5·50	4·50
> 3 mm	36	15	24	0·71	1·01	21·10	23·8

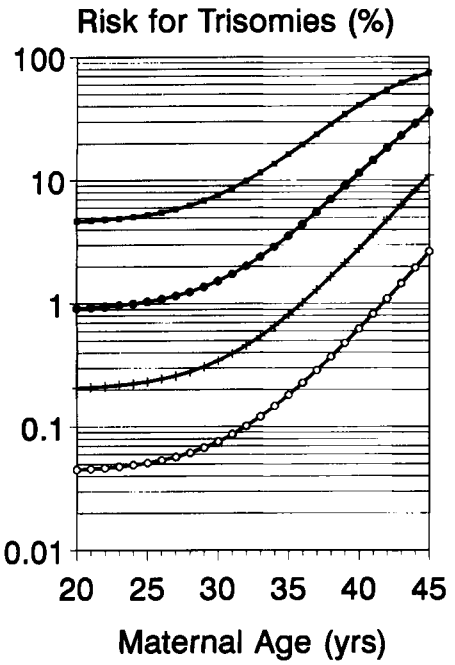

Fig. 1. Semilogarithmic graph illustrating estimated risks for fetal trisomies 21, 18 or 13 at 10–13 weeks' gestation on the basis of maternal age alone (+—+; Snijders *et al.* 1994) and maternal age with fetal nuchal translucency thickness of < 3 mm (○—○), 3 mm (●—●) and > 3 mm (■—■).

whom the fetal nuchal translucency is 3 mm, the risk increases from approximately 1:480 to 4·5:480 or 1/110. In contrast, in a 40 year old woman in whom the fetal nuchal translucency is < 3 mm, the risk decreases from 1:35 to 0·22:35 or 1/160.

In 44 of the 46 cases of fetal chromosomal abnormalities, the pregnancies were terminated at the request of the parents; two pregnancies (47,XXX and 47,XXY) continued and resulted in live births. The chromosomally normal group with nuchal translucency ⩾ 3 mm was investigated further by detailed ultrasound examination and echocardiography at 20 weeks of gestation and by screening for maternal toxoplasmosis, cytomegalovirus, rubella virus, herpes virus, parvo B19 virus, and coxsackie B virus. The infection screen was negative in all cases. In the group with nuchal translucency of 3 to 4 mm the pregnancies continued uneventfully, and in all cases the translucency had resolved by 20 weeks of gestation. Similarly, there was resolution of nuchal translucency and normal outcome in two fetuses: one with translucency of 5 mm and one with translucency of 6 mm. In all other cases with translucency ⩾ 5 mm, pregnancies were terminated because there were additional abnormalities (e.g., one

Table 3. Maternal age and fetal karyotype in 13 cases of fetal chromosomal abnormalities with nuchal translucency thickness < 3 mm.

Case no.	Maternal age (years)	Karyotype
1	33	47,XXX
2	36	Mosaic 47,XXX
3	36	Mosaic 47,XX+8
4	38	46,XX del18p
5	39	47,XX+21
6	39	Mosaic 47,XX+21
7	41	47,XY+18
8	41	47,XXY
9	41	47,XXY
10	42	47,XY+21
11	42	47,XX+21
12	42	47,XY+21
13	45	47,XXX

Table 4. Sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively) for trisomies 21, 18 or 13 with different cut-off points for fetal nuchal translucency thickness.

Nuchal translucency thickness	Sensitivity	Specificity	PPV	NPV
⩾ 2 mm	32/36 (88·9%)	1001/1227 (81·6%)	32/258 (12·4%)	1001/1005 (99·6%)
⩾ 3 mm	31/36 (86·1%)	1172/1227 (95·5%)	31/86 (36·0%)	1172/1177 (99·6%)
⩾ 4 mm	24/36 (66·7%)	1215/1227 (99·0%)	24/36 (66·7%)	1215/1227 (99·0%)
⩾ 5 mm	16/36 (44·4%)	1221/1227 (99·5%)	16/22 (72·7%)	1221/1241 (98·4%)
⩾ 6 mm	8/36 (22·2%)	1223/1227 (99·7%)	8/12 (66·7%)	1223/1251 (97·8%)
⩾ 7 mm	5/36 (13·9%)	1226/1227 (99·9%)	5/6 (83·3%)	1226/1257 (97·5%)
⩾ 8 mm	3/36 (8·3%)	1226/1227 (99·9%)	3/4 (75·0%)	1226/1259 (97·4%)
⩾ 9 mm	2/36 (5·6%)	1227/1227 (100·0%)	2/2 (100·0%)	1227/1261 (97·3%)

case each of hypoplastic left heart, exomphalos and neural tube defect, amnion disruption sequence, and hydrops).

Table 4 shows how nuchal translucency would have performed if it had been used as a screening test in our population. It should be borne in mind that this type of analysis, applied retrospectively, usually overestimates the performance of the same test applied prospectively.

Discussion

This prospective screening study of women undergoing fetal karyotyping confirms the previously reported association between chromosomal abnormalities and fetal nuchal translucency $\geqslant 3$ mm at 10 to 13 weeks of gestation. Furthermore, the pattern of associated chromosomal defects, trisomies rather than Turner's syndrome, is similar to that observed in second trimester fetuses with nuchal oedema (subcutaneous oedema producing a characteristic tremor on ballotment of the fetal head), rather than with cystic hygromata which are bilateral, septate, cystic structures (Azar *et al.* 1991; Nicolaides *et al.* 1992b). Nevertheless, we use the term translucency because this was the ultrasonographic feature that was observed (Nicolaides *et al.* 1992a).

The finding that in the group with a normal fetal karyotype the incidence of nuchal translucency $\geqslant 3$ mm was independent of maternal age has made it possible to derive estimates of risks for fetal trisomies on the basis of maternal age (Snijders *et al.* 1994) and fetal nuchal translucency. The data suggest that translucency of < 3 mm is associated with a fivefold reduction and translucency of $\geqslant 3$ mm a 12-fold increase in maternal age related risk for trisomies 21, 18 and 13. In a series of 560 fetuses with nuchal translucency $\geqslant 3$ mm, which included cases that were referred to our centre for karyotyping because the translucency was $\geqslant 3$ mm, it was possible to derive risks for trisomies with increasing translucency thickness. Thus, translucencies of 3 mm, 4 mm, 5 mm and $\geqslant 6$ mm were associated with fourfold, 21-fold, 26-fold and 41-fold increases in maternal age-related risks (Pandya *et al.* 1994).

In the present study, 84% of trisomy 21 fetuses and 4·5% of chromosomally normal fetuses had nuchal translucency of $\geqslant 3$ mm. In England and Wales approximately 1% of deliveries are of women $\geqslant 40$ years old (Office of Population Census and Statistics 1991) and from estimates of maternal age-related risks (Snijders *et al.* 1994). This group contributes approximately 12% of trisomy 21 infants. On the basis of these data, it is predicted that a policy which offers fetal karyotyping to women younger than 40 years of age if the fetal nuchal translucency is $\geqslant 3$ mm and to all women 40 years old or older could potentially identify more than 85% of trisomy 21 fetuses with a false positive rate of approximately 5%. Therefore, for the same false positive rate, the sensitivity of the new method of screening compares favourably with the respective values of 20 to 30% and 50 to 60% for screening by maternal age alone or maternal age and serum biochemistry (Haddow *et al.* 1992; Phillips *et al.* 1992; Wald *et al.* 1992). Furthermore, the uptake of invasive testing for fetal karyotyping following the identification of a visible marker in the fetus is likely to be higher than with risks derived from maternal factors.

A major criticism of screening by ultrasound, in contrast to biochemical testing, is that scanning requires highly skilled operators. This is certainly true for many of the subtle markers of chromosomal abnormalities detectable at 18 to 20 weeks of gestation. However, the skill necessary for measurement of nuchal translucency at 10 to 13 weeks is no greater than that required to obtain a reliable measurement of the crown–rump length, which is essential for accurate dating of pregnancy and correct interpretation of serum biochemistry results.

It is important to note that the women screened presented for the usual clinical indications of maternal age, anxiety and past history, rather than with a diagnosed fetal abnormality seen on ultrasound. For this reason, we believe the results can be extrapolated to the general population requesting screening. The sensitivity and specificity of nuchal translucency $\geqslant 3$ mm as a marker of chromosomal defects in routine transabdominal ultrasonographic examination of the whole population remains to be determined. Furthermore, the cost of implementing a routine ultrasound scan at 10 to 13 weeks, in addition to the fetal abnormality scan at 20 weeks, needs to be considered. Nevertheless, maternal serum biochemistry screening is being introduced widely and, as part of this screening, it is recommended that a scan should be performed before biochemical testing (Wald *et al.* 1992). The findings of the present study suggest that this scan should be undertaken at 10 to 13 weeks of gestation and the fetal nuchal region also should be examined.

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