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Screening for Down's syndrome by fetal nuchal translucency measurement in a high-risk population

E. Pajkrt, B. W. J. Mol, J. M. M. van Lith, O. P. Bleker and C. M. Bilardo*

Department of Obstetrics and Gynecology and *Department of Clinical Epidemiology and Biostatistics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Key words: NUCHAL TRANSLUCENCY, ULTRASOUND SCREENING, FETAL ANEUPLOIDIES, DOWN'S SYNDROME, PRENATAL DIAGNOSIS

ABSTRACT

Objective *To examine the discriminative capacity of nuchal translucency measurement in the detection of trisomy 21 and other chromosomal anomalies.*

Design *Prospective cohort study.*

Subjects *A total of 2247 women with viable singleton pregnancies between 10 and 14 weeks' gestation attending a prenatal diagnosis center for fetal karyotyping.*

Methods *The fetal nuchal translucency was measured transabdominally in all women before invasive prenatal testing.*

Results *Chromosomal abnormalities were found in 63 fetuses, including 36 with Down's syndrome. The likelihood of the presence of chromosomal abnormalities increased with larger nuchal translucency thickness. A nuchal translucency of 3 mm or more identified 25 out of 36 fetuses (69%) with trisomy 21 at the expense of a 4.0% false-positive rate. Correction of nuchal translucency measurements for differences due to variation of the measurement with gestational age, either by using the 'delta-value' or multiples of the median (MoM), did not improve the detection rate in our patient data set.*

Conclusions *The discriminative capacity of nuchal translucency measurement makes it a useful tool in screening for trisomy 21 and other chromosomal anomalies.*

INTRODUCTION

Nuchal translucency, an ultrasound measurement, has been introduced as a potential screening method for the detection of chromosomal abnormalities in the late first and early second trimesters of pregnancy[1]. Several studies have reported that an increased nuchal translucency is a useful marker for fetal aneuploidies, mainly trisomies[2]. The detection rate for Down's syndrome by this ultrasound measurement varies considerably among these studies, from 29% to 85%[3–14]. Several issues can explain the heterogeneity in the results of these studies. The inclusion of fetuses with sonographically detected structural anomalies may lead to overestimation in the detection rate. Since these fetuses are already at increased risk for aneuploidy[15], the role of nuchal translucency measurement as a marker for aneuploidies in these cases may be redundant. Many studies include patients referred because of an increased nuchal translucency. These studies therefore overestimate the sensitivity and underestimate the specificity of the measurement. This mechanism is known as verification bias[16]. The combined use of fetal karyotype and neonatal outcome as a reference standard may also lead to bias, since a fetus with an abnormal karyotype is far less likely to result in a live birth than a fetus with a normal karyotype[17,18].

Another issue that has rarely been addressed is that most studies use a fixed cut-off point as a criterion for abnormality. In the majority of studies a cut-off point of 3 mm is used to decide whether or not an invasive test for fetal karyotyping should be offered. The use of the nuchal translucency measurement as a continuous test, without fixed cut-off points, may improve its diagnostic performance.

The aim of the present study was to examine, after exclusion of all possible bias, the discriminative capacity of nuchal translucency measurement in the detection of fetuses affected by Down's syndrome and other chromosomal anomalies ascertained by fetal karyotyping.

Correspondence: Dr E. Pajkrt, Academic Medical Center, University of Amsterdam, Department of Obstetrics and Gynecology, H4-205, PO Box 22700, 1000 DE Amsterdam, The Netherlands

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MATERIALS AND METHODS

Consecutive women with viable singleton pregnancies attending the prenatal diagnostic center at the Academic Medical Center for fetal karyotyping at 10 to 14 completed weeks of gestation, were included in our study, between February 1994 and July 1997. Indications for fetal karyotyping were advanced maternal age, family history of a chromosomal abnormality, risk of a Mendelian disorder or parental anxiety. All women were informed and gave consent to participate in the study, which was approved by the Hospital Ethics Committee.

The nuchal translucency was measured at the intake visit before the scheduling of women for amniocentesis or immediately before chorionic villus sampling. The nuchal translucency was defined as the hypoechoic area between the skin outline echo and the soft tissues overlying the cervical spine, regardless of the presence of septa[1]. Fetuses with ultrasonographically detected abnormalities at the time of the nuchal translucency measurement were excluded from the study. Experienced sonographers performed all examinations. In all cases, a transabdominal ultrasound examination was performed with a curvilinear 3.5-MHz or 5-MHz transducer (Hitachi EUB 515A and Hitachi EUB 565, Tokyo, Japan and Toshiba SSA 250A, Tokyo, Japan). The maximum thickness of the nuchal translucency was visualized on a sagittal section of the fetus. If imaging of the nuchal translucency was impossible because of fetal position or maternal obesity, the measurement was recorded as failed. In cases in which the translucent area could not be visualized, because it was so thin that it was impossible to part the calipers from each other, the measurement was considered to be zero. Gestational age was calculated by crown–rump length[19] or biparietal diameter (BPD) measurement[20].

The nuchal translucency results were matched with the final diagnosis, i.e. fetal karyotype. The detection rate of trisomy 21 was calculated by using a fixed cut-off point of 3 mm. Likelihood ratios were calculated for different ranges of nuchal translucency measurement.

The median nuchal translucency thickness is known to increase with gestational age[21]. To correct for this variation with gestation two methods were used. From the distribution of nuchal translucency measurements in normal fetuses and in those with trisomy 21, for each fetus the difference between the observed nuchal translucency measurement and the appropriate normal median for gestational age was calculated and expressed as a 'delta-value'[9,22]. In order to facilitate comparison with maternal serum screening studies the nuchal translucency measurement in fetuses with Down's syndrome was also expressed as multiples of the median (MoM)[23].

Moreover, to compare the use of fixed cut-off points and 'delta-values', performance of the nuchal translucency measurement was also expressed by constructing receiver operating characteristic (ROC) curves for different ranges of nuchal translucency thickness and for different ranges of 'delta-values'. To estimate the likelihood ratio for the presence of trisomy 21 as a function of the 'delta-value', logistic regression incorporating spline transformation was used[24].

The association between maternal age and the nuchal translucency result was evaluated by calculating a correlation coefficient.

To investigate the effect of increased experience with this screening method, the results were analyzed separately for the 3 years of the study. The detection rate of trisomy 21, as well as the number of failed measurements and measurements equal to zero, were calculated separately for each year.

RESULTS

During the study period, 2247 women with a live fetus with a crown–rump length of more than 32 mm and a BPD of less than 30 mm participated in the study. The indications for karyotyping were advanced maternal age (n = 2004), family history of a chromosomal abnormality (n = 99), risk of Mendelian disorder (n = 63) and parental anxiety (n = 81). Twenty-three women (1.0%) were excluded from further analysis because of sonographically detected fetal anomalies at the time of the nuchal translucency measurement (Table 1). The mean maternal age of the 2224 women included in the analysis was 37.6 years (range 22–46 years). On the basis of the maternal age distribution in this study population and maternal age-specific risks between 9 and 14 weeks' gestation, the expected prevalence of Down's syndrome, trisomy 18 or triploidy was 1.3%, 0.4% and 0.05%, respectively[25,26]. The mean gestational age was 11 weeks plus 3 days.

Twelve pregnancies (0.5%) ended in a spontaneous abortion in the interval between the nuchal translucency measurement and amniocentesis. In these fetuses karyotyping was not performed. In 54 of the 2224 fetuses a good measurement could not be obtained (2.4%). The total prevalence of chromosomal abnormalities in the study population was 2.8%. Trisomy 21 was detected in 36 fetuses (1.6%), trisomy 18 in five fetuses (0.2%), triploidy in two fetuses (0.09%) and other chromosomal anomalies were found in 21 fetuses (0.9%). Data on nuchal translucency thickness in relation to fetal karyotype are shown in Table 2. In Figure 1 the obtained measurements in trisomy 21 fetuses are plotted against the normal range for gestation[21].

When a fixed cut-off point of 3 mm was used, an enlarged nuchal translucency was detected in 119 cases (5.4%). Of these 119 fetuses, 30 had an abnormal karyotype (25%), including 25 of the 36 fetuses affected by trisomy 21 (69%). Of the fetuses with other chromosomal abnormalities, five of the 27 were identified by increased nuchal translucency (18.5%), including four of the seven fetuses (57%) with trisomy 18 or triploidy. The remaining 89 fetuses with nuchal translucency of 3 mm or more included 86 of the 2149 fetuses with a normal karyotype (4.0%) and three of the 12 cases (25%) resulting in a spontaneous abortion before fetal karyotyping.

Table 1 Detected fetal anomalies, crown–rump length (CRL) and biparietal diameter (BPD) in the 23 cases excluded from the analysis at the time of nuchal translucency measurement (NT) and fetal karyotyping

Number	*Anomaly*	*CRL* (mm)	*BPD* (mm)	*NT* (mm)	*Karyotype*
1	cystic hygroma	52	—	—	46,XY
2	cystic hygroma	58	—	—	46,XY
3	cystic hygroma	68	21	—	46,XY
4	cystic hygroma	—	23	—	45,X
5	cystic hygroma	—	24	—	45,X
6	cystic hygroma	—	26	—	45,X
7	cystic hygroma	—	28	—	45,X
8	cystic hygroma	—	27	—	47,XX,+21
9	lateral cervical cysts	40	—	2.2	46,XY
10	Dandy–Walker malformation	36	—	0	69,XXX
11	Dandy–Walker malformation	43	—	2.3	46,XY
12	Dandy–Walker malformation	72	25	3.0	46,XY
13	anencephaly	38	—	4.7	46,XX
14	anencephaly	39	—	0	46,XY
15	anencephaly	56	—	1.2	46,XY
16	omphalocele*	39	—	1.3	46,XX
17	omphalocele*	44	—	0	46,XX
18	omphalocele*	50	—	0.8	46,XX
19	intra-abdominal cyst	43	—	0.8	46,XX
20	hydrops fetalis	49	—	1.5	47,XX,+18
21	obstructive uropathy	50	—	3.8	47,XX,+13
22	multiple anomalies	57	—	4.4	46,XY
23	choroid plexus cyst	—	29	5.0	47,XX,+21

—, no measurement performed; *, omphalocele persisting beyond 13 weeks' gestation

Table 2 Nuchal translucency thickness (NT), fetal karyotype and likelihood ratio

NT (mm)	*Number of cases*	*Karyotype*			*Spontaneous abortions*	*Likelihood ratio*			
		Normal	*Trisomy 21*	*Other*		*Normal*	*Trisomy 21*	*Other*	*All*
Failed	54	52	0	1[a]	1	1.5	0.0	1.5	0.6
0	192	188	2	1[b]	1	1.9	0.6	0.4	0.5
0.1–0.9	553	547	0	4[c]	2	5.4	0.0	0.6	0.2
1.0–1.9	1078	1053	8	13[d]	4	1.4	0.5	1.0	0.7
2.0–2.9	228	223	1	3[e]	1	1.7	0.3	1.0	0.6
3.0–3.9	64	52	8	2[f]	2	0.2	9.0	2.6	6.5
4.0–4.9	35	23	8	3[g]	1	0.06	18.6	7.5	16.1
5.0–5.9	10	7	3	0	0	0.07	25.9	0.0	14.4
6.0–6.9	4	2	2	0	0	0.03	60.4	0.0	33.6
≥ 7.0	6	2	4	0	0	0.01	120.9	0.0	67.1
Total	2224	2149	36	27	12				

a, 46,XX,+der(2);t(2;8); b, 47,XXY; c, trisomy 18; 47,XX,+marker; 47,XXY (*n* = 2); d, 47,XX,+der(13),t(13;17); 46,XX,+der(2);t(2;8); 46,XX,t(2;6) *de novo*; 45,XX,der(13;14) *de novo*; 47,XY,+13/46,XY (9:3); 47,XXX/46,XX (20:6); 47,XX,+18/46,XX (13:3); 47,XY/45,X (29:3); 46,XX/47,XX,+21 (19:1); 47,XYY; 69,XXX; 47,XXY (*n* = 2); e, trisomy 18; 47,XX,+22; 46,XX,der(4),t(4;8); f, trisomy 18; 46,XX/47,XX+12 (20:3); g, 69,XXX; trisomy 18 (*n* = 2)

Table 3 Detection rate of trisomy 21 using different cut-off points for delta-value

	Total (*n* = 2224)		*Normal* (*n* = 2149)		*Trisomy 21* (*n* = 36)		*Other* (*n* = 27)		*Abortions* (*n* = 12)	
Delta (mm)	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Failed	54	2.4	52	2.4	0	0	1	3.7	1	8.3
≥ 3.0	51	2.3	32	1.5	15	42	3	11	1	8.3
≥ 2.5	78	3.5	49	2.3	22	61	5	19	2	17
≥ 2.0	108	4.9	75	3.5	25	69	5	19	3	25
≥ 1.5	162	7.3	125	5.8	26	72	7	26	4	33
≥ 1.0	309	14	269	13	27	75	8	30	5	42
≥ 0.5	779	35	730	34	31	86	12	44	6	50
≥ 0.0	1478	66	1414	66	35	97	21	78	8	67

Likelihood ratios for different ranges of nuchal translucency thickness for the presence of a normal fetus, a fetus with trisomy 21, a fetus with another chromosomal anomaly or a fetus with any chromosomal anomaly, including Down's syndrome, are presented in Table 2. The likelihood ratio for the presence of an aneuploid fetus becomes larger with increasing nuchal translucency. The opposite is true for fetuses with a normal karyotype; in these the likelihood ratio decreases with increasing measurement.

When applying 'delta'-correction, the detection rate of trisomy 21 in this study remains 69%, for an invasive testing rate of 4.9% and a false-positive rate of 3.5% (Table 3). Similarly, converting the nuchal translucency measurements in MoM does not improve the detection rate of trisomy 21 in this study. In order to achieve a detection rate of 69% by this method, the invasive testing rate increases to 7.5% and the false-positive rate to 6.0% (Table 4).

Figure 2 shows the ROC curves constructed for different classes of nuchal translucency measurements and after 'delta'-correction. The area under the curve before 'delta'-correction is 0.86 (SE 0.02) and after 'delta'-correction 0.87 (SE 0.02). The likelihood ratio as a function of 'delta-value', as obtained after logistic regression with spline transformation, is illustrated in Figure 3.

In the group with a normal karyotype there was no clinically relevant association between nuchal translucency measurement and maternal age ($r = -0.09$, $p = 0.0005$).

Finally, calculation of the detection rate of trisomy 21 fetuses, as well as the number of measurements of zero and failed measurements, was carried out separately for each year of the study. In the first year, six (50%) out of the 12 fetuses with Down's syndrome were identified by a nuchal translucency of 3 mm or more (95% CI: 19%, 81%); in the second year seven (70%) out of ten (95% CI: 35%, 93%); and in the third year 12 (86%) out of 14 (95% CI: 57%, 98%). A nuchal translucency measurement of zero was obtained in 17% of the measurements performed in 1994.

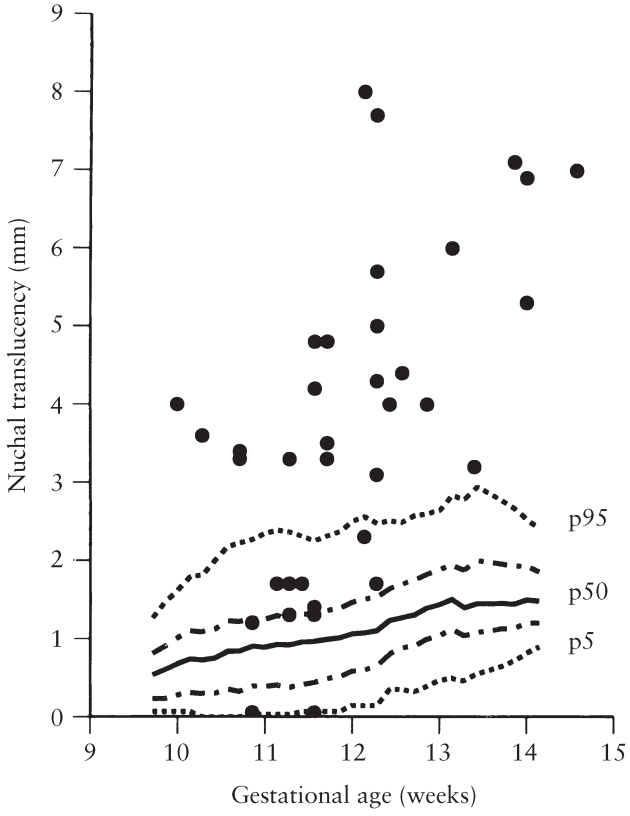

Figure 1 Nuchal translucency measurements in trisomy 21 fetuses plotted on the normal range. Adapted from reference 21

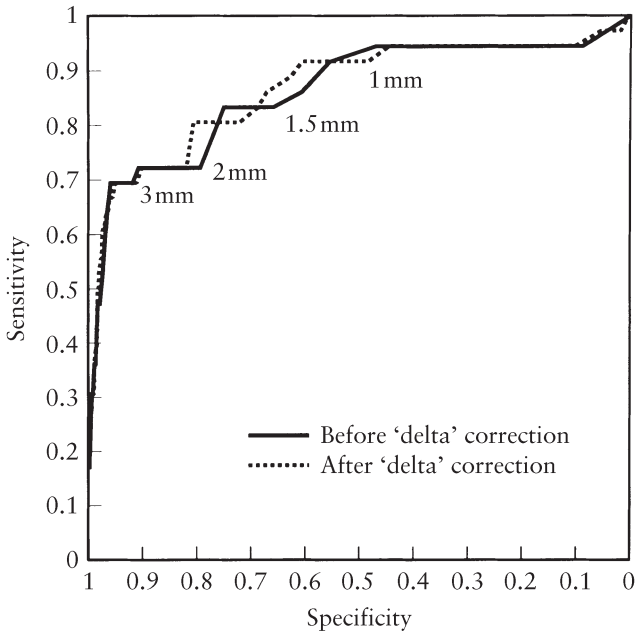

Figure 2 Receiver operating characteristic curves constructed for different classes of nuchal translucency measurements and after 'delta'-correction

Table 4 Detection rate of trisomy 21 using different cut-off points for multiples of the median (MoM)

	Total (*n* = 2224)		*Normal* (*n* = 2149)		*Trisomy 21* (*n* = 36)		*Other* (*n* = 27)		*Abortions* (*n* = 12)	
MoM	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Failed	54	2.4	52	2.4	0	0	1	3.7	1	8.3
≥ 4.0	57	2.6	37	1.7	15	42	3	11	2	17
≥ 3.5	77	3.5	51	2.4	20	56	3	11	3	25
≥ 3.0	107	4.8	76	3.5	23	64	5	19	3	25
≥ 2.5	166	7.5	130	6.0	25	69	7	26	4	33
≥ 2.0	325	15	285	13	27	75	8	30	5	42
≥ 1.5	783	35	734	34	31	86	12	44	6	50
≥ 1.0	1457	66	1393	65	35	97	21	78	8	67

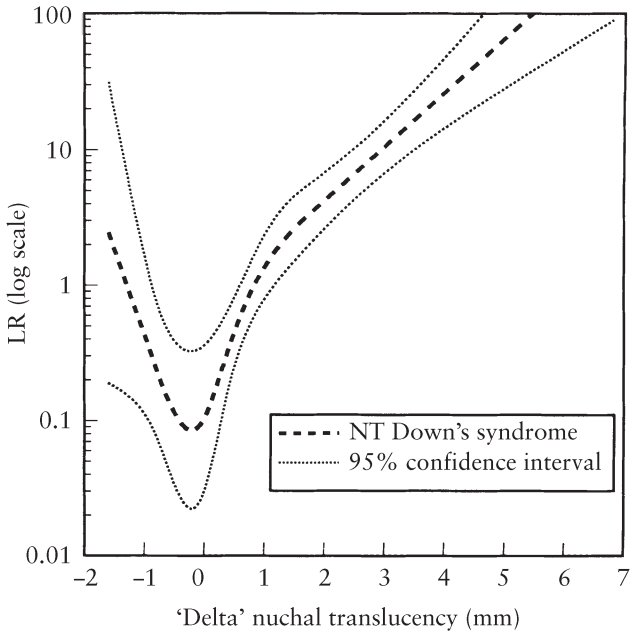

Figure 3 Likelihood ratio (LR) as a function of 'delta' nuchal translucency thickness (NT)

In the course of the study this declined to an incidence in 1997 of 0.5%. The failure rate to obtain a measurement fell from 3.2% in 1994 to 1.5% in 1997.

DISCUSSION

In this prospective screening study the nuchal translucency was 3 mm or more in 69% of the fetuses with trisomy 21 and in 4.0% of the chromosomally normal fetuses. The likelihood of the presence of chromosomal abnormalities increased with larger nuchal translucency thickness.

Since the introduction of screening by nuchal translucency measurement, numerous prospective studies have been published[2–14]. With a fixed cut-off point used as normal, the detection rate of trisomy 21 has been reported to range from 29%[11] to 85%[6], with false-positive rates ranging from 0.9%[8] to 6.0%[7]. A comparison of results between this and other studies is not always possible, owing to differences in methodology that could partially explain some of the heterogeneity in the results.

To evaluate the discriminative capacity of the nuchal translucency measurement, all fetuses with structural anomalies detected at the time of the measurement were excluded from the analysis. It is known that fetuses with congenital abnormalities are already at increased risk of chromosomal anomalies[15], irrespective of the size of the nuchal translucency. The measurement of nuchal translucency in these cases could therefore be superfluous. In some of the above-mentioned studies, these cases were included[3,4,9,12]. Although Comas and colleagues[5] reported that they had excluded cases of cystic hygroma, most reports do not state whether fetuses with structural anomalies have been excluded or not. In this study patients were referred for the usual indications for fetal karyotyping without having been pre-selected on the basis of an increased nuchal translucency. The inclusion of pre-selected patients[6,8,9,11] may cause verification bias and consequently overestimation of the accuracy of the diagnostic test[16]. Similarly, it is important that patients with failed or uninterpretable test results are included in the analysis, since failure to do so may also artificially inflate the performance of a test[16]. Finally, the chosen reference standard in this study was fetal karyotype as determined by invasive diagnostic procedures. In this way, the presence of trisomy 21 was always demonstrated. This is in contrast to other studies[5,6,8,9,11], in which, instead of using a single outcome measure, fetal karyotype and neonatal outcome were used alternatively. In these studies, women with a low maternal age-specific risk for Down's syndrome, but with an increased fetal nuchal translucency, were offered invasive prenatal diagnosis and in this group, trisomy 21 was always detected. In contrast, women with a low a priori risk for Down's syndrome and a normal measurement did not undergo fetal karyotyping, and neonatal outcome was used in this group as outcome measure. In the latter group, approximately half of the pregnancies affected by Down's syndrome ended spontaneously[17]. These cases were excluded from analysis and this may thus lead to verification bias. It is only after the accuracy of the nuchal translucency measurement in detecting trisomy 21 has been assessed in an unbiased way, that implementation may take place and pregnancy outcome may be used to evaluate the detection rate of this screening method. The possible absence of bias in this study is suggested by the similarity between the expected and the observed prevalence of trisomy 21, trisomy 18 and triploidy.

Taking these methodological problems into account, the results of this study can at best be compared to other prospective screening studies in women undergoing fetal karyotyping[2–4,10,12–14]. Our detection rate of 69% for trisomy 21 fetuses compares favorably with detection rates of 30%[4,10], 44%[13], 53%[14], 54%[2] and 57%[12], but is worse than the 84% detection rate reported by Nicolaides and colleagues[3].

Differences in gestational age at the time of measurement may explain some of the variation in performance among these studies. One center measures from 8 weeks' gestation[4], one from 9 weeks[14], whereas others do not start measuring until 10 weeks' gestation[2,3,10,12,13]. Another possible cause of difference in performance may be the effect of a learning curve. Increased experience with the technique of nuchal translucency measurement may improve the test results. This is strongly suggested by the declining incidence of failed measurements and by the decreasing occurrence of measurements of 0 mm in the course of this study. The striking improvement in detection rate for Down's syndrome fetuses in the third year of the study (86%) compared to that of the first year (50%) further supports the effect of a learning curve, despite the overlap of the 95% confidence intervals. A similar effect was reported by Salvoldelli and co-workers[2] who found the detection rate to be about twice as high in the last 2 years of their study as compared to the preceding 4-year period. Brambati and associates[4] commented on the differences in

results between the two units involved in their study: a private practice setting and a public health clinic. Differences in skill and motivation of the operators may be responsible for the diverging results.

In order to express the performance of the nuchal translucency at different levels, likelihood ratios were calculated. The likelihood ratio for the presence of chromosomal abnormalities increases with larger nuchal translucency thickness. However, as clearly illustrated in Figure 3, measurements around the normal median reduce the risk for trisomy 21 more than measurements of 0 mm. This could be explained by the fact that all fetuses develop a measurable nuchal translucency between 10 and 14 weeks' gestation and measurements of 0 mm before 12 weeks can theoretically still become abnormally larger at a later gestation[27]. As the likelihood ratio for the presence of aneuploidy increases with larger nuchal translucency measurement, the use of a fixed cut-off point for normality does not seem appropriate in a screening program based on this measurement. The diagnostic performance of the nuchal translucency measurement may improve when it is used as a continuous test. As maternal age does not influence the nuchal translucency measurement, the combination of maternal age and nuchal translucency thickness in relation to gestational age may give the best detection rate for trisomy 21. Correction for gestational age by both 'delta-value' and MoM did not improve the detection rate in this study. This was due to the distribution of nuchal translucency measurements in the trisomy 21 fetuses in this study and therefore cannot be extrapolated to other studies. Biagiotti and colleagues[14] suggested that the use of MoM correction might be advantageous in decreasing the false-positive rate. The opposite was found in this study. However, for the same detection rate of trisomy 21, the higher invasive testing rate obtained by MoM correction as opposed to 'delta'-correction may be purely coincidental.

In conclusion, the discriminative capacity of nuchal translucency measurement, as assessed in this study, makes it a useful tool in screening for trisomy 21 and other chromosomal anomalies in a high-risk population. However, prior to a widespread introduction of this screening method, its effectiveness should also be examined in a general obstetric population.

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REFERENCES

1. Nicolaides KH, Azar G, Byrne D, Mansur C, Marks K. Fetal nuchal translucency: ultrasound screening for chromosomal defects in first trimester of pregnancy. *Br Med J* 1992;303: 867–9
2. Savoldelli G, Binkert F, Achermann J, Schmid W. Ultrasound screening for chromosomal anomalies in the first trimester of pregnancy. *Prenat Diagn* 1993;13:513–18
3. Nicolaides KH, Brizot ML, Snijders RJM. Fetal nuchal translucency: ultrasound screening for fetal trisomy in the first trimester of pregnancy. *Br J Obstet Gynaecol* 1994;101: 782–6
4. Brambati B, Cislaghi C, Tului L, Alberti E, Amindani M, Colombo U, Zuliani G. First-trimester Down's syndrome screening using nuchal translucency: a prospective study in patients undergoing chorionic villus sampling. *Ultrasound Obstet Gynecol* 1995;5:9–14
5. Comas C, Martinez JM, Ojuel J, Casals E, Puerto B, Borrell A, Fortuny A. First-trimester nuchal edema as a marker of aneuploidy. *Ultrasound Obstet Gynecol* 1995;5:26–9
6. Szabó J, Gellén J, Szemere G. First-trimester ultrasound screening for fetal aneuploidies in women over 35 and under 35 years of age. *Ultrasound Obstet Gynecol* 1995;5:161–5
7. Bewley S, Roberts LJ, Mackinson A-M, Rodeck CH. First trimester fetal nuchal translucency: problems with screening the general population 2. *Br J Obstet Gynaecol* 1995;102: 386–8
8. Hafner E, Schuchter K, Philipp K. Screening for chromosomal abnormalities in an unselected population by fetal nuchal translucency. *Ultrasound Obstet Gynecol* 1995;6:330–3
9. Pandya PP, Snijders RJM, Johnson SP, Brizot ML, Nicolaides KH. Screening for fetal trisomies by maternal age and fetal nuchal translucency thickness at 10 to 14 weeks of gestation. *Br J Obstet Gynaecol* 1995;102:957–62
10. Scott F, Boogert A, Sinosich M, Anderson J. Establishment and application of a normal range for nuchal translucency across the first trimester. *Prenat Diagn* 1996;16:629–34
11. Kornman LH, Morssink LP, Beekhuis JR, De Wolf BTHM, Heringa MP, Mantingh A. Nuchal translucency cannot be used as a screening test for chromosomal abnormalities in the first trimester of pregnancy in a routine ultrasound setting. *Prenat Diagn* 1996;16:797–805
12. Hewitt B, de Crespigny L, Sampson AJ, Shekleton P, Robinson HP. Correlation between nuchal thickness and abnormal karyotype in first trimester fetuses. *Med J Aust* 1996;165: 365–8
13. Martinez JM, Borrell A, Antolin E, Puerto B, Casals E, Ojuel J, Fortuny A. Combining nuchal translucency with umbilical Doppler velocimetry for detecting fetal trisomies in the first trimester of pregnancy. *Br J Obstet Gynaecol* 1997;104: 11–14
14. Biagiotti R, Periti E, Brizzi L, Vanzi E, Cariati E. Comparison between two methods of standardization for gestational age differences in fetal nuchal translucency measurement in first-trimester screening for trisomy 21. *Ultrasound Obstet Gynecol* 1997;9:248–52
15. Snijders RJM, Farrias M, von Kaisenberg C, Nicolaides KH. Fetal abnormalities. In Snijders RJM, Nicolaides KH, eds. *Ultrasound Markers for Fetal Chromosomal Defects*. Carnforth, UK: Parthenon Publishing, 1996:2–62
16. Begg CB, McNeil BJ. Assessment of radiologic tests: control of bias and other design considerations. *Radiology* 1988;167: 565–9
17. Macintosh MCM, Wald NJ, Chard T, Hansen J, Mikkelsen M, Therkelsen AJ, Petersen GB, Lundsteen C. Selective miscarriage of Down's syndrome fetuses in women aged 35 years and older. *Br J Obstet Gynaecol* 1995;102:798–801
18. Mol BWJ, Pajkrt E, van Lith JMM, Bilardo CM. Screening for fetal trisomies by maternal age and fetal nuchal translucency thickness at 10 to 14 weeks of gestation [Letter]. *Br J Obstet Gynaecol* 1996;103:1051–2
19. Robinson HP, Fleming JEE. A critical evaluation of sonar crown–rump length measurements. *Br J Obstet Gynaecol* 1975;82:701–10
20. Chitty LS, Altman DG, Henderson A, Campbell S. Charts of fetal size: 2. Head measurements. *Br J Obstet Gynaecol* 1994;101:35–43
21. Pajkrt E, Bilardo CM, van Lith JMM, Mol BWJ, Bleker OP. Nuchal translucency measurement in normal fetuses. *Obstet Gynecol* 1995;86:994–7

22. Royston P. Constructing time-specific reference ranges. *Stat Med* 1991;10:675–90
23. Cuckle HS, Wald NJ, Thompson SG. Estimating a woman's risk of having a pregnancy associated with Down's syndrome using her age and serum alpha-fetoprotein level. *Br J Obstet Gynaecol* 1987;94:387–402
24. Harrell FE, Lee KL, Pollock BG. Regression models in clinical studies: determining relationships between predictors and response. *J Natl Cancer Inst* 1988;80:1198–202
25. Snijders RJM, Holzgreve W, Cuckle H, Nicolaides KH. Maternal age-specific risks for trisomies at 9–14 weeks' gestation. *Prenat Diagn* 1994;14:543–52
26. Snijders RJM, Sebire NJ, Nicolaides KH. Maternal age and gestational age-specific risk for chromosomal defects. *Fetal Diagn Ther* 1995;10:356–67
27. Pajkrt E, de Graaf IM, Mol BWJ, van Lith JMM, Bleker OP, Bilardo CM. Weekly nuchal translucency measurements in normal fetuses. *Obstet Gynecol* 1998;91:208–11