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A mixture model of nuchal translucency thickness in screening for chromosomal defects

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KEYWORDS: chromosomal defects; first trimester; nuchal translucency; risk assessment; screening; trisomy 21

ABSTRACT

Objective *Fetal nuchal translucency (NT) thickness increases with crown–rump length (CRL). In screening for chromosomal defects patient-specific risks are derived by multiplying the* a priori *maternal age-related risk by a likelihood ratio, determined from the deviation of the measured NT from the expected median. To quantify this deviation the measured NT is either subtracted (delta NT) or divided by the expected median (multiple of the median method, MoM). This study examines the validity of these methods.*

Methods *NT was prospectively measured at 11 + 0 to 13 + 6 weeks in screening for chromosomal defects. The distribution of NT in euploid and chromosomally abnormal fetuses was examined.*

Results *There were 37 078 normal pregnancies and 264 with trisomy 21, 81 with trisomy 18, 38 with trisomy 13 and 27 with Turner syndrome. We found that firstly, contrary to the assumption underlying the delta NT method, the distribution of delta NT changes with CRL and secondly, contrary to the assumption underlying the MoM method the distribution of NT was not Gaussian. Fetal NT followed two distributions, one that was dependent on CRL and one that was independent of CRL. The distribution in which NT increases with CRL was observed in about 95% of euploid fetuses, 5% with trisomy 21, 30% with trisomy 18, 15% with trisomy 13 and 10% with Turner syndrome. The median CRL-independent NT was 2.0 mm for the euploid group and 3.4, 5.5, 4.0 and 7.8 mm for trisomies 21, 18, 13 and Turner syndrome, respectively.*

Conclusions *The NT thickness in chromosomally normal and abnormal fetuses follows a mixture of a gestation-dependent and gestation-independent distribution. Copyright © 2008 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Fetal nuchal translucency (NT) thickness is the single most effective marker of trisomy 21 and all other major chromosomal defects. It increases with crown–rump length (CRL), and it is important to take gestational age into account when determining whether a given NT thickness is increased[1]. In screening for chromosomal defects patient-specific risks are derived by multiplying the *a priori* maternal age and gestation-related risk by a likelihood ratio, determined from the deviation of the fetal NT measurement from the normal median for CRL.

There are essentially two approaches to quantifying the deviation of NT from the normal median. One approach is to subtract the normal median from the NT measurement and to produce a deviation in mm referred to as delta NT. The other approach is to divide NT by the normal median to produce a multiple of the median (MoM) value[2,3]. In the calculation of patient-specific risks for trisomy 21 the *a priori* maternal age-related risk is multiplied by the likelihood ratio for a measured NT, which is the ratio of the heights of distributions of measurements in trisomy 21 and unaffected pregnancies. In the delta method it is assumed that there is a common distribution of NT delta values independent of CRL in the trisomy 21 pregnancies and another common distribution in unaffected pregnancies. In the MoM method it is assumed that the distributions of the log transformed MoM values in trisomy 21 and unaffected pregnancies are Gaussian.

In this paper we examine departures from the assumptions underlying the delta and MoM approaches

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and suggest a model based on two-component mixtures of distributions. We propose that in unaffected pregnancies the majority of fetuses demonstrate an increase in NT with CRL and in a minority of cases NT tends to be relatively large and is independent of CRL. In the chromosomally abnormal pregnancies there is a different mixture of NT distributions, with a minority of cases following the same CRL-dependent distribution as in the unaffected pregnancies, but in the majority of cases there is a distribution that is independent of CRL, with a higher mean and standard deviation (SD) than in unaffected pregnancies.

METHODS

At the Fetal Medicine Centre, London, screening for trisomy 21 is carried out by a combination of maternal age, fetal NT thickness and maternal serum pregnancy-associated plasma protein-A (PAPP-A) and free β-human chorionic gonadotropin (β-hCG) in a one-stop-clinic for first-trimester assessment of risk (OSCAR) at 11 to 13 + 6 weeks of gestation[4]. Transabdominal ultrasound examination is performed to diagnose any major fetal defects and for measurement of CRL and fetal NT thickness[1]. The Kryptor system (Brahms AG, Berlin, Germany) is used to measure PAPP-A and free β-hCG. Maternal demographic characteristics, ultrasononographic measurements and biochemical results are recorded in a computer database, and karyotype results and details on pregnancy outcomes are added into the database as soon as they become available.

A search of the database was done to identify all singleton pregnancies in which first-trimester screening by fetal NT, PAPP-A and free β-hCG was carried out from July 1999 to July 2005. In this study we examine the distribution of NT in chromosomally abnormal fetuses and in unaffected pregnancies.

Statistical analysis

Distribution of logMoM (NT) and delta NT

The adequacy of the MoM approach was assessed firstly by examining non-parametric centile curves to show how the distribution of log(NT) changes with CRL, and secondly by examining Gaussian probability plots of logMoM (NT), stratified by gestational age, to determine whether there are departures from the assumed Gaussian form; throughout this paper logs are to base 10.

The delta NT approach does not assume a Gaussian distribution, but it is implicit in this approach that the CRL-specific centile curves in the trisomy 21 and unaffected pregnancies should be parallel. We assessed the adequacy of this method by examining non-parametric centile curves for NT by CRL.

Two-component mixture model

In the unaffected pregnancies it was assumed that log(NT) arises from a mixture of two Gaussian distributions: firstly, a proportion $(1 - p)$ in which there is a quadratic relationship between mean log(NT) (μ_o) and CRL ($\mu_0 = \beta_0 + (\beta_1 \times \mathrm{CRL}) + (\beta_2 \times \mathrm{CRL}^2)$) with an SD that is constant (σ_0), and secondly, a proportion (p) in which NT is CRL-independent with a mean of μ_1 and SD of σ_1.

In each chromosomally abnormal pregnancy (trisomies 21, 18 and 13 and Turner syndrome) it was assumed that log(NT) also arises from a mixture of two Gaussian distributions: firstly, a proportion $(1 - p_{abnormal})$ with the same CRL-dependent distribution as in unaffected pregnancies, and secondly, a chromosomal abnormality-specific proportion ($p_{abnormal}$) in which NT is CRL-independent with a mean log(NT) of $\mu_{abnormal}$ and SD of $\sigma_{abnormal}$. The proportions $p_{abnormal}$ defining the mixture, and the mean and standard deviation of the CRL-independent component differ according to abnormality (trisomies 21, 18 and 13 and Turner syndrome).

For unaffected pregnancies the CRL-dependent component dominates and p is close to 0, while for the chromosomal abnormalities the CRL-dependent component is uncommon and p is close to 1. Allowing p in unaffected pregnancies to depend on CRL, according to a logistic regression model, improves the fit of the model and has a clinically meaningful interpretation that we shall discuss. In this model $p = 1/(1 + \exp(-\alpha_0 - \alpha_1 \mathrm{CRL}))$.

To complete the model we assumed that variation between operators is represented by random effects acting additively on log(NT) with mean 0 and standard deviation σ_{op}. The degree of heterogeneity between operators is reflected in the magnitude of σ_{op}. The mixture model was fitted within a Bayesian framework using Markov chain Monte Carlo (MCMC) implemented in WinBUGS[5]. Copies of the WinBUGS model specification are available on request from the authors.

Assessment of screening performance

Crude detection rates and false positive rates were calculated by taking the proportions with risks above a given risk threshold. Standardized rates were produced by first calculating age-specific detection and false positive rates and then weighting them according to the maternal age distributions of affected and unaffected pregnancies in England and Wales in 2000–2002[6]. These standardized rates were compared with detection and false positive rates estimated using Monte Carlo methods to sample from the modeled mixtures of Gaussian distributions.

RESULTS

The search of the database identified 38 791 singleton pregnancies but 1303 (3.4%) were excluded from further analysis because the fetal karyotype or pregnancy outcome was not available ($n = 1231$) or was due to a chromosomal abnormality other than trisomy 21, 18, 13

or Turner syndrome ($n = 72$). In the remaining 37 488 cases there were 37 078 pregnancies with a normal karyotype or delivery of a phenotypically normal baby (unaffected group), 264 with trisomy 21, 81 with trisomy 18, 38 with trisomy 13 and 27 with Turner syndrome. The characteristics of the women included in this study are shown in Table 1. According to the maternal age distribution of our population and the gestational age at the time of screening we would have expected 274 (95% prediction interval: 241–306) cases with trisomy 21[7–9].

Distribution of logMoM (NT)

Gaussian probability plots of logMoM (NT) in unaffected pregnancies at 11, 12 and 13 weeks' gestation are shown in Figure 1. Contrary to the assumptions of the MoM approach there are departures from the Gaussian form owing to the upper tail, especially at 11 weeks' gestation.

Non-parametric centile curves for NT by CRL

Non-parametric centile estimates for NT by CRL at 1%, 5%, 50%, 95% and 99% fitted to the data of unaffected pregnancies on a linear axis and on a logarithmic axis are shown in Figure 2. Under the assumptions of the delta NT approach the centiles in Figure 2a should be parallel, but instead the plot shows substantial deviations from parallelism. Most notably, the 99th centile is almost horizontal and increases with smaller CRLs, while the other centiles increase with CRL. This means that the distribution of delta NT is changing with gestation in a way that cannot be captured by a common non-parametric density estimate fitted to the data combined across all gestations.

Under the assumptions of the MoM approach, the centiles on the log scale in Figure 2a should be symmetric about the median according to a Gaussian distribution. Although they are reasonably symmetric for CRLs above 60 mm – corresponding to gestational ages above the middle of week 12 – there are marked departures from symmetry at lower CRLs.

Table 1 Characteristics of the study population

Parameter	*Median (range) or* n *(%)*
Maternal characteristics	
Age (years, median (range)	35.2 (16.0–52.0)
Weight (kg, median (range)	63.6 (39.0–150.0)
Spontaneous conception (*n* (%))	35 628 (95.0)
Smoker (*n* (%))	1458 (3.9)
Ethnicity (*n* (%))	
Caucasian	35 366 (94.3)
Afro-Caribbean	283 (0.8)
East Asian	378 (1.0)
South Asian	1191 (3.2)
Mixed	270 (0.7)
Gestational age (*n* (%))	
11 + 0 to 11 + 6 weeks	4413 (11.8)
12 + 0 to 12 + 6 weeks	20 602 (55.0)
13 + 0 to 13 + 6 weeks	12 473 (33.3)
Crown–rump length (mm, median (range))	62.6 (45.0–84.0)
Karyotype (*n* (%))	
Normal	37 078 (98.9)
Trisomy 21	264 (0.7)
Trisomy 18	81 (0.2)
Trisomy 13	38 (0.1)
Turner syndrome	27 (0.1)
Total	37 488

Mixture model

The fitted mixture model is described in Table 2. In the unaffected pregnancies the dominant part of the mixture is the CRL-dependent Gaussian distribution, which accounts for about 95% of cases. In contrast, in all chromosomally abnormal pregnancies the dominant part of the mixture is the CRL-independent Gaussian distribution, which accounts for about 95% of cases with trisomy 21, 70% of trisomy 18, 85% of trisomy 13 and 80% of Turner syndrome (Figure 3). The SD of logMoM (NT) from the fitted mixture model in unaffected pregnancies decreases with gestation (Figure 4). The SDs are substantially lower than in previous studies[10,11].

The estimated SD of the operator effects was 0.0289, which is small relative to the SD of the CRL-dependent distribution (0.079). Operator effects account for an estimated 12% [$0.0289^2/(0.079^2 + 0.0289^2) \times 100\%$] of the total variation from the CRL-dependent process with operator effects added.

In the mixture model, as in the MoM and delta NT methods, it is necessary to incorporate truncation limits to prevent misleading results at extremes and ensure that the likelihood ratio is a monotonic function of NT. The upper truncation limit in our model was 10 mm and the lower increased with CRL from 1.2 mm at 45 mm to 1.8 at 70 mm and then remained constant until 84 mm.

Detection rates and false positive rates

Crude, standardized and modeled detection rates for fixed false positive rates are shown in Table 3, and the accuracy of estimated risk for trisomy 21 by a combination of maternal age and fetal NT is shown in Table 4.

DISCUSSION

The findings of this study demonstrate that fetal NT follows two distributions, one of which is dependent on CRL while the other is independent of CRL. The distribution in which NT increases with CRL is the same for chromosomally abnormal and unaffected pregnancies but the proportion that follows this distribution is large in the unaffected group (about 95%) and small in the abnormal group, being about 5%, 30%, 15% and 10% for trisomies 21, 18, 13 and Turner syndrome, respectively. In contrast, the proportion of cases in which NT does not change with gestation is small

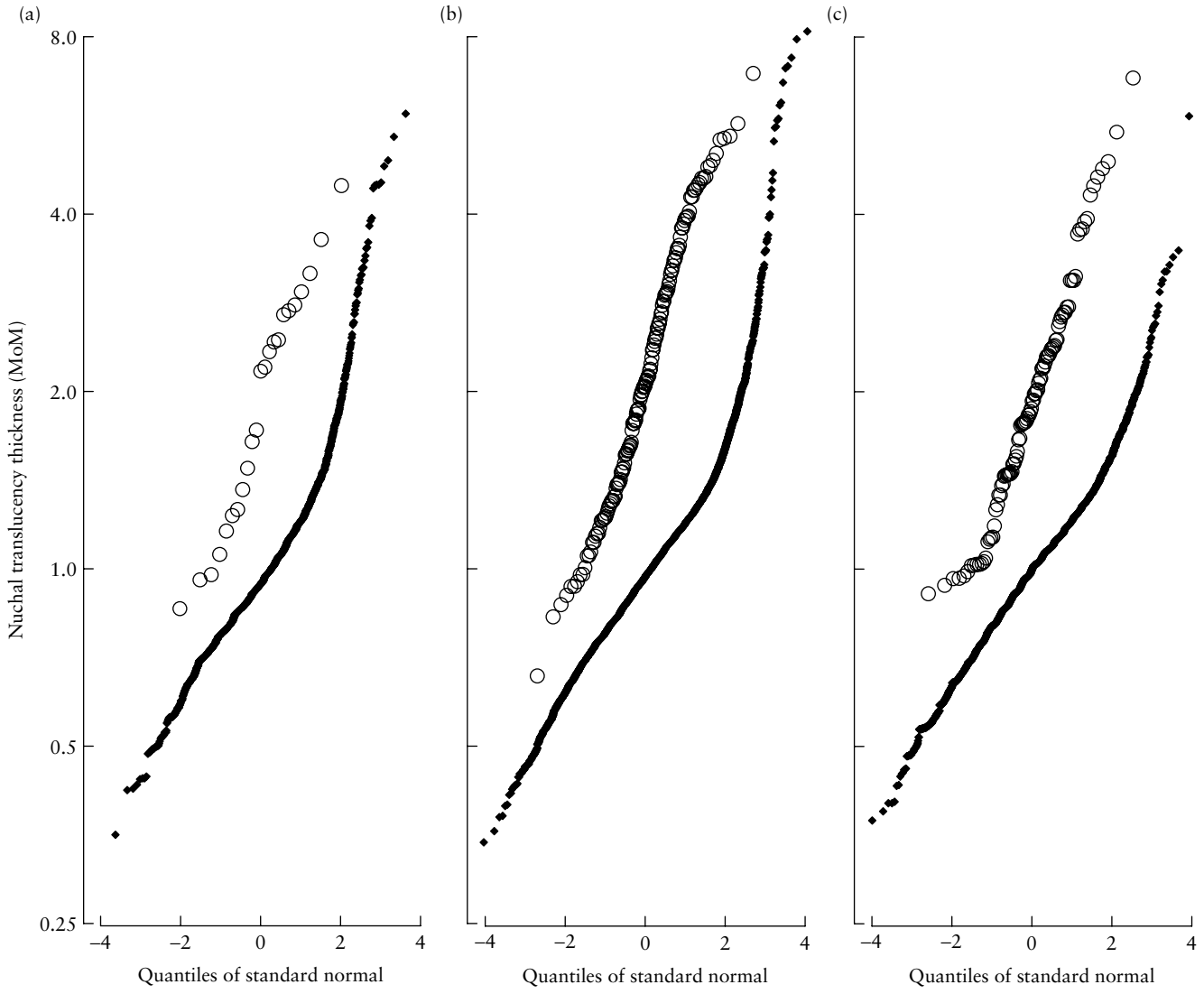

Figure 1 Gaussian probability plots of nuchal translucency thickness (multiples of the median (MoM)) in unaffected (♦) and trisomy 21 (○) pregnancies at 11 (a), 12 (b) and 13 (c) weeks of gestation. The vertical axis is a logarithmic scale.

for unaffected pregnancies and large for the abnormal group. Furthermore, the median NT is different, being 2.0 mm for the unaffected group and 3.4, 5.5, 4.0 and 7.8 mm for trisomies 21, 18, 13 and Turner syndrome, respectively.

The study has also highlighted the limitations of the two previous methods of assessing NT thickness. We found that, contrary to the assumption underlying the delta NT method, the non-parametric centile estimates for NT by CRL show that the distribution of delta NT changes with CRL. Similarly, the assumption of a Gaussian distribution that underpins the MoM method is not valid because there are departures from such a form in the logMoM (NT), and the centiles on the log scale are not symmetric about the median. The delta NT and MoM methods provide a measure of the deviation of an observed NT from its expected value. However, to produce accurate risks, the above assumptions need to be taken into account.

The mixture model of the form we propose is useful in situations where a single Gaussian or other distribution fails to provide an adequate fit. One of the earliest applications, published in 1894, was a mixture of two Gaussian distributions fitted by Karl Pearson on the ratio of forehead to body length in crabs sampled from the bay of Naples. This led to the conjecture that the crabs came from different species[12].

The mixture model of NT distributions is compatible with our understanding of the pathophysiology of increased NT in both chromosomally normal and abnormal fetuses[13–21]. The CRL-dependent NT distribution in unaffected pregnancies presumably reflects a physiological development of the fetal nuchal region during the gestational range of $11+0$ to $13+6$ weeks. The increased CRL-independent NT observed in the chromosomally normal fetuses could at least in some cases be a consequence of a wide range of well-reported non-chromosomal defects, such as cardiac, skeletal and other malformations, genetic syndromes and hematological disorders. The proportion of NT measurements arising from the CRL-independent process in the mixture model decreased with CRL from around 10% at a CRL of 45 mm to around 3%

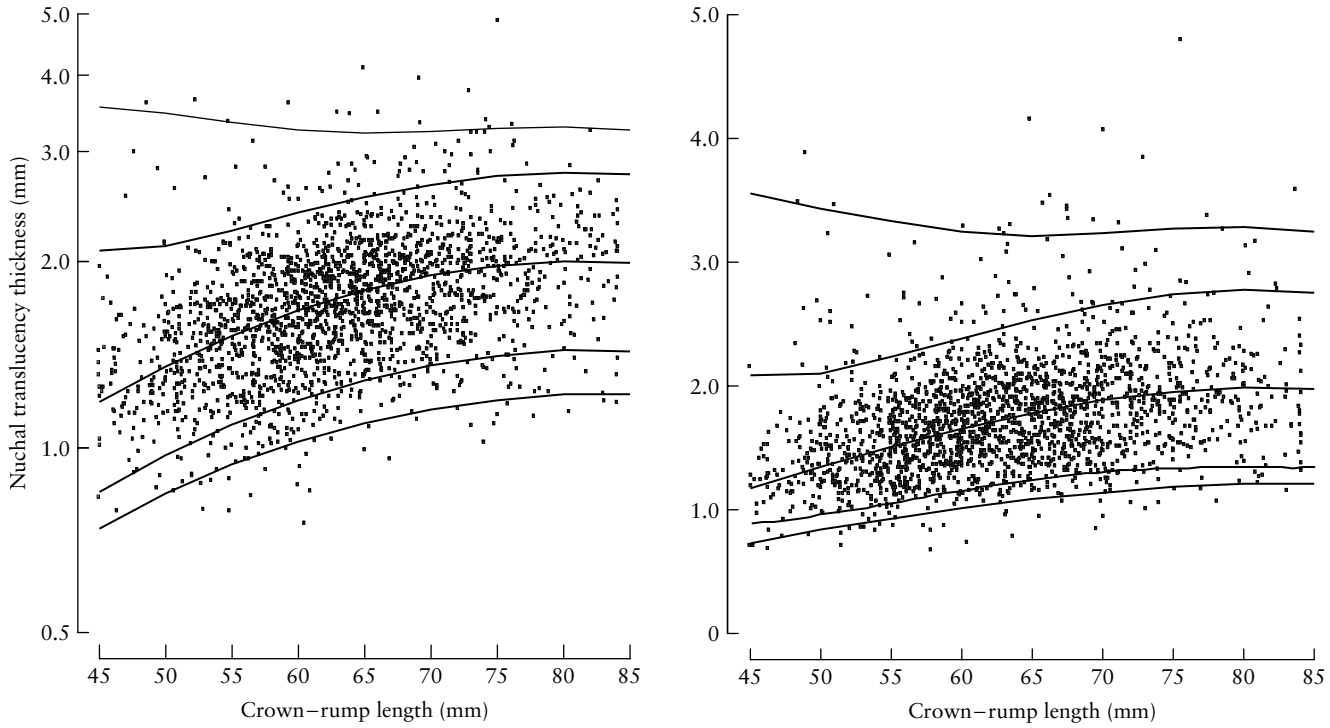

Figure 2 Distribution of nuchal translucency thickness with crown–rump length in unaffected pregnancies together with the modeled median and 1st, 5th, 50th, 95th and 99th centiles on a logarithmic scale (a) and on a linear scale (b).

Table 2 Fitted mixture model for nuchal translucency thickness

Parameter	*Estimate*	*90% CI*
CRL-dependent		
Intercept (β_0)	−0.8951	−0.9460 to −0.8423
Coefficient of CRL (β_1)	0.02940	0.02781 to 0.03101
Coefficient of CRL^2 (β_2)	−0.0001812	−0.0001935 to −0.0001686
Standard deviation (σ_0)	0.07900	0.07792 to 0.08008
CRL-independent: normal		
Logistic model intercept for mixture proportion		
Intercept (α_0)	−0.3319	−1.1220 to 0.4707
Coefficient of CRL (α_1)	−0.03790	−0.05208 to −0.02423
Mean (μ_1)	0.3019	0.2860 to 0.3195
Standard deviation (σ_1)	0.1945	0.1852 to 0.2045
CRL-independent: trisomy 21		
Proportion (p_{T21})	0.9406	0.0116 to 0.9913
Mean (μ_{T21})	0.5330	0.5052 to 0.5623
Standard deviation (σ_{T21})	0.2093	0.1925 to 0.2271
CRL-independent: trisomy 18		
Proportion (p_{T18})	0.7096	0.6188 to 0.7956
Mean (μ_{T18})	0.7439	0.6990 to 0.7875
Standard deviation (σ_{T18})	0.1658	0.1414 to 0.1972
CRL-independent: trisomy 13		
Proportion (p_{T13})	0.8376	0.6603 to 0.9804
Mean (μ_{T13})	0.6018	0.5100 to 0.6969
Standard deviation (σ_{T13})	0.2032	0.1414 to 0.2693
CRL-independent: Turner syndrome		
Proportion (p_{Turner})	0.8090	0.7793 to 0.9894
Mean (μ_{Turner})	0.9629	0.7624 to 1.0030
Standard deviation (σ_{Turner})	0.1316	0.1929 to 0.3905
Operator standard deviation (σ_{op})	0.02890	0.02337 to 0.3573

CRL, crown–rump length.

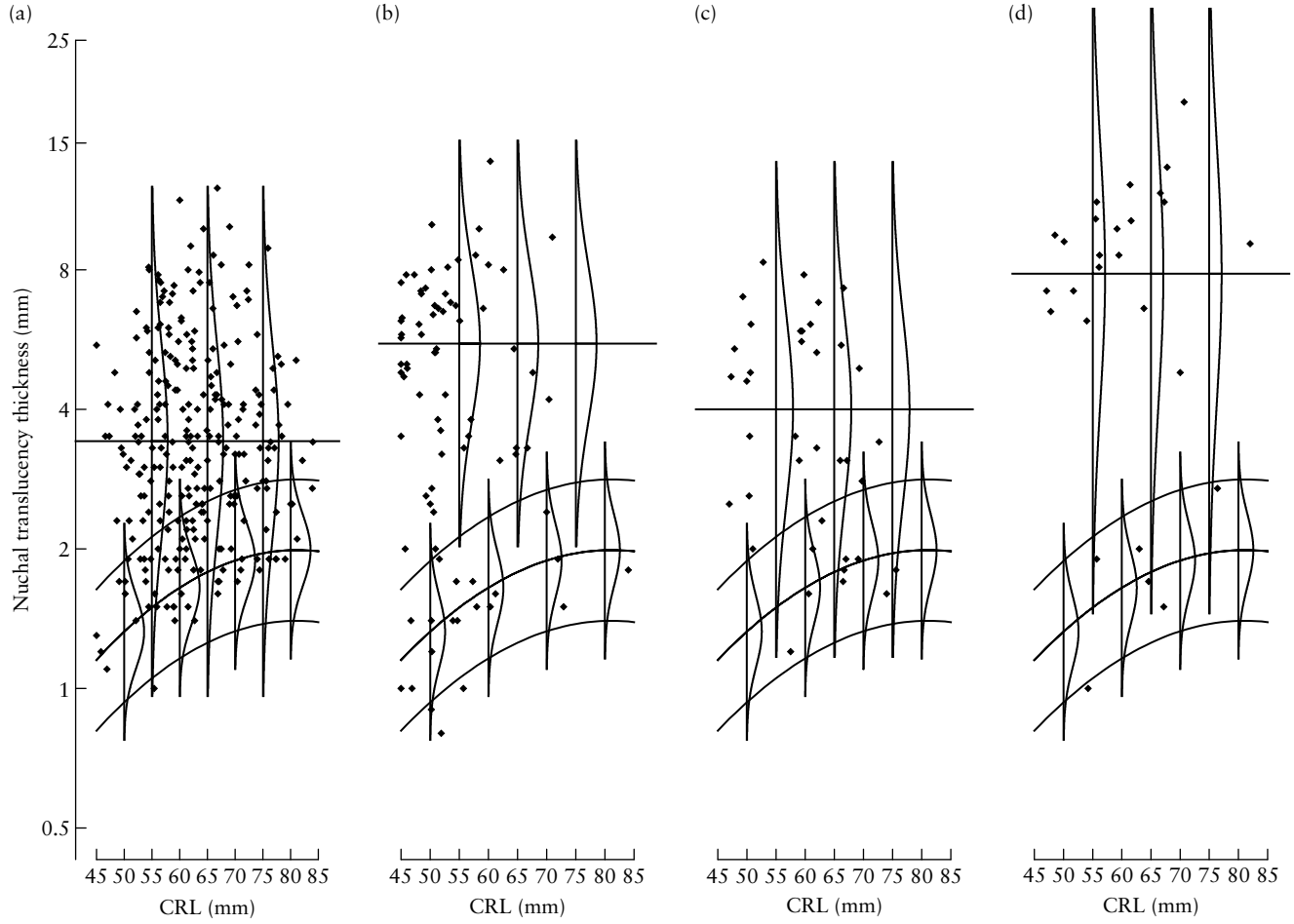

Figure 3 Mixture model with crown–rump length-independent (upper) and crown–rump length-dependent (lower) distribution in trisomies 21 (a), 18 (b) and 13 (c) and Turner syndrome (d).

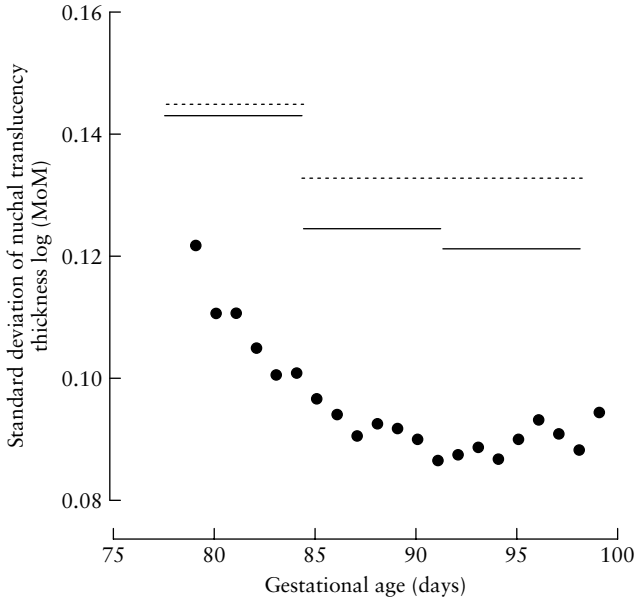

Figure 4 Relationship between the standard deviations of nuchal translucency thickness (log multiples of the median (MoM)) with gestational age in unaffected pregnancies in this study (●) and in two previous studies (SURUSS[10] (-------) and FASTER[11] (———)).

at a CRL of 85 mm. This most likely reflects the falling pregnancy loss rate with increasing gestational age.

The findings in the chromosomally abnormal fetuses are compatible with the wide range of phenotypic expression in these abnormalities. Presumably, in the 5–30% of cases with CRL-dependent NT distribution the development of the fetal nuchal region is normal. In the ones with increased CRL-independent NT there is abnormal nuchal development due either to chromosomal abnormality-specific primary alterations in the composition of the dermis and lymphatic channels or to secondary accumulation of subcutaneous fluid caused by associated cardiovascular, thoracic and other malformations.

The data confirm the high association between increased fetal NT and trisomy 21 as well as the other major chromosomal abnormalities. The detection rates for given false positive rates expected in population screening using the mixture model are similar to those observed in our cases after the appropriate adjustments to take into account the maternal age distribution of pregnancies in England and Wales (Table 3). Additionally, as shown in Table 4, the patient-specific risks derived from the new mixture model are accurate and valid for counseling. The high detection rates achieved by NT screening and the low SDs in this study re-emphasize the importance

Table 3 Detection rates of trisomy 21 for given false-positive rates

False-positive rate (%)	Detection rate (%)											
	Overall (n = 264)			*11 weeks* (n = 23)			*12 weeks* (n = 145)			*13 weeks* (n = 96)		
	Crude	*STD*	*Modeled*	*Crude*	*STD*	*Modeled*	*Crude*	*STD*	*Modeled*	*Crude*	*STD*	*Modeled*
1	58	54	55	44	36	56	61	60	56	61	61	53
2	64	65	64	48	48	68	66	71	66	66	68	61
3	69	72	70	52	51	74	72	76	71	71	70	65
4	76	77	73	57	63	78	79	83	75	75	74	68
5	77	80	75	57	63	81	81	84	77	78	76	70
10	83	87	83	70	89	89	87	88	84	82	86	77

The crude rates are the ones observed in our population with mean maternal age of 35 years, the standardized (STD) rates are the ones after adjustments to the maternal age distribution of pregnancies in England and Wales in 2000–2002[6] and the modeled rates are the standardized rates predicted from the mixture model in this study.

Table 4 Accuracy of estimated risk for trisomy 21 by a combination of maternal age and fetal nuchal translucency thickness

Estimated risk (range (median))	*Trisomy 21 (n (%))*	*Unaffected (n (%))*	*Observed risk*
≥ 1 in 10 (1 in 3)	129 (48.9)	218 (0.6)	1 in 3
1 in 10 to 1 in 100 (1 in 49)	66 (25.0)	1396 (3.8)	1 in 22
1 in 100 to 1 in 250 (1 in 185)	25 (9.5)	2684 (7.2)	1 in 108
1 in 250 to 1 in 1000 (1 in 583)	34 (12.9)	13 196 (35.6)	1 in 389
1 in 1000 to 1 in 5000 (1 in 1837)	10 (3.8)	17 636 (47.6)	1 in 1765
< 1 in 5000 (1 in 5200)	0	1948 (5.3)	—

of appropriate training and certification of competence of sonographers as well as regular audit of images and distributions of measurements[14].

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APPENDIX

Illustration of calculations

This paper describes a two-component mixture model for the distribution of log(NT) in chromosomally normal pregnancies and in pregnancies with trisomies 21, 18 and 13. We illustrate the calculations for a pregnancy with fetal CRL of 60 mm and NT of 2.5 mm (see Table 2).

CRL-dependent component (normal pregnancies)

- Estimated mean $= -0.8951 + (0.02940 \times 60) - (0.0001812 \times 60^2) = 0.2166$.
- Estimated standard deviation $= (0.07900^2 + 0.02890^2)^{0.5} = 0.08412$.
- The median NT for the CRL dependent process is $10^{0.2166} = 1.6466$
- The measured NT of 2.5 mm is equivalent to $2.5/1.6466 = 1.518$ MoM.
- The probability density at $\log(2.5) = 0.3979$ for the fitted Gaussian distribution is 0.4642.

CRL-independent component (normal pregnancies)

- Estimated mean = 0.3019
- Estimated standard deviation $= (0.1945^2 + 0.02890^2)^{0.5} = 0.1966$.
- The probability density at $\log(2.5) = 0.3979$ for the fitted Gaussian distribution is 1.8007.

Mixture model (normal pregnancies)

- According to the mixture for unaffected pregnancies, the fitted logit of the proportion arising from the CRL-independent process is given by $-0.3319 - (0.03790 \times 60) = -2.6059$. The fitted proportion is then given by $1/(1 + \exp(-(-2.6059))) = 0.06878$ (approximately 7% of observations of NT arise from the CRL-independent component).
- The probability density for unaffected pregnancies is given by a weighted average of two Gaussian densities: the CRL-independent process (weight = 0.06878) and the CRL-dependent process (weight $= 1 - 0.06878 = 0.93122$). This gives the fitted mixture model probability density of $(0.06878 \times 1.8007) + (0.93122 \times 0.4642) = 0.5561$.

CRL-independent component (trisomy 21 pregnancies)

- Estimated mean = 0.5330
- Estimated standard deviation $= (0.2093^2 + 0.02890^2)^{0.5} = 0.2113$.
- The probability density at $\log(2.5) = 0.3979$ for the fitted Gaussian distribution is 1.5393.

Mixture model (trisomy 21 pregnancies)

- According to the mixture model the estimated proportion of trisomy 21 pregnancies arising from the CRL-independent component is 0.9406. This gives the fitted mixture model density of $(0.9406 \times 1.5393) + (0.0594 \times 0.4642) = 1.4754$.

Likelihood ratio

The likelihood ratio of trisomy 21 to normal pregnancies is given by the probability density of trisomy 21 pregnancies divided by the probability density for normal pregnancies $= 1.4754/0.5561 = 2.653$.

Figure 5 shows the behavior of the likelihood ratio for the pregnancy with CRL = 60 mm and illustrates how with the mixture model the likelihood ratio rises steeply and then flattens as NT increases. This reflects the CRL independent component of the mixture model.

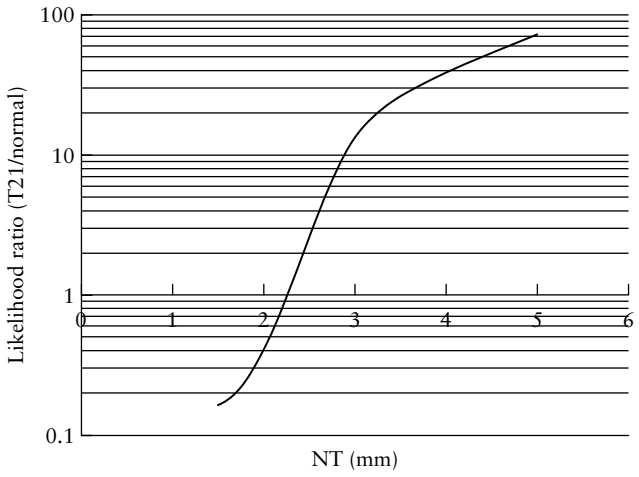

Figure 5 Relationship between likelihood ratio and nuchal translucency (NT) thickness for a crown–rump length of 60 mm.