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Delta-NT or NT MoM: which is the most appropriate method for calculating accurate patient-specific risks for trisomy 21 in the first trimester?

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KEYWORDS: chromosomal abnormalities; Down syndrome; nuchal translucency; prenatal screening; statistics

ABSTRACT

Objective *To assess whether in screening for trisomy 21 by nuchal translucency (NT) the delta or the multiples of the median (MoM) approach is the most appropriate method for calculating accurate individual patient-specific risks.*

Methods *Data on fetal NT and crown–rump length from 128 030 unaffected and 428 trisomy 21 pregnancies, measured by sonographers who had obtained The Fetal Medicine Foundation Certificate of Competence in the 11–14-Week Scan, were used. We examined first, if the distribution of NT MoM and log_{10}(NT MoM) was Gaussian; second, if the standard deviation of the distributions did not change with gestation; and third, if the median MoM in the affected population was a constant proportion of the median for unaffected pregnancies. All of these features are required to underpin the MoM approach. NT distributions and those of delta-NT were also analyzed. A non-parametric kernel density method was then used to assess the validity of both methods. Errors in the estimation of individual patient-specific risks using the MoM approach were assessed.*

Results *In the unaffected pregnancies, the distributions of NT MoM and log_{10}(NT MoM) were not Gaussian and the standard deviation of log_{10}(NT MoM) decreased with gestation. In the trisomy 21 pregnancies, the median NT MoM decreased significantly with gestation, whereas the median delta-NT did not change with gestation. The non-parametric density approach showed that contours of constant likelihood ratio were parallel to the gestational age-dependent median NT values, thus supporting the delta-NT approach. The NT MoM approach resulted in women being given an overestimate of risk for trisomy at 11 weeks and a considerable underestimate of risk at 13 weeks.*

Conclusion *In the calculation of risk for trisomy 21 by NT the NT MoM approach is inaccurate and inappropriate because the underlying assumptions are not valid. In contrast, the delta-NT approach gives accurate estimates of risks. Copyright © 2003 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

The most effective marker of trisomy 21 is fetal nuchal translucency (NT), measured ultrasonographically at 11–14 weeks of gestation using standardized conditions (www.fetalmedicine.com/nuchal.htm)[1]. In the first description of fetal NT in 1992 we used a fixed cut-off value of 3.0 mm but we subsequently established that in normal pregnancies fetal NT increases with gestation[2,3]. Consequently, in screening for trisomy 21 the use of a fixed cut-off approach is wrong because it provides inaccurate patient-specific risk estimates. To take account of this gestational variation in NT we expressed the measured fetal NT as the difference from the normal median NT at the measured crown–rump length (CRL), which is the delta-NT[3]. The median NT in unaffected pregnancies was derived by regressing log_{10}(NT) on gestational age, and likelihood ratios for trisomy 21 were calculated from the relative frequency of trisomy 21 and unaffected pregnancies at any one given delta-NT[1,3]. In the delta-NT approach patient-specific risks for trisomy 21 are calculated by multiplying the *a priori* maternal age risk with the likelihood ratio of the observed delta-NT[1,3,4].

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In screening using maternal serum biochemical markers, a different approach has been used to take account of gestational variation in marker levels. This method involves converting the measured concentration into a multiple of the median (MoM) of unaffected pregnancies of the same gestational age[5,6]. Essentially, the Gaussian distributions of $\log_{10}$MoMs in trisomy 21 and unaffected pregnancies are derived and the ratio of the heights of the distributions at a particular MoM, which is the likelihood ratio for trisomy 21, is used to modify the *a priori* maternal age-related risk to produce a patient-specific risk. When more than one marker is used account is taken of the correlation between markers in affected and unaffected pregnancies[6]. When first-trimester screening using fetal NT and maternal serum biochemistry became feasible it was suggested that fetal NT could be considered like any other biochemical variable, converted to a MoM and used in a multivariate Gaussian model[7].

For the Gaussian MoM approach to be valid and to provide accurate individual patient-specific risks for trisomy 21 across the 11–14-week window it is necessary to be able to demonstrate that:

(a) either NT MoM or some transformation of NT MoM has a Gaussian distribution;
(b) the standard deviation (SD) of the MoM in the transformed domain is constant; and
(c) the median MoM in trisomy 21 pregnancies is a constant proportion of the median for unaffected pregnancies.

The aim of this study was to assess whether in screening for trisomy 21 by fetal NT thickness the delta or the MoM approach is the most appropriate method for calculating accurate individual patient-specific risks.

METHODS

Study population

Fetal NT and CRL were measured using standardized techniques (www.fetalmedicine.com/nuchal) by sonographers who had obtained The Fetal Medicine Foundation Certificate of Competence in the 11–14-Week Scan. The study group comprised trisomy 21 and unaffected pregnancies from four prospective studies. The first data set included the 95 476 unaffected pregnancies and 326 trisomy 21-affected pregnancies in the UK multicenter study[1]. For the purposes of this study only the 95 476 unaffected and the 298 trisomy 21 cases with CRL values of 45–84 mm, which is equivalent to 77–98 days of gestation, were used. The second, third and fourth datasets were derived from prospective screening studies for trisomy 21 by a combination of fetal NT and maternal serum free beta-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A at 11–14 weeks and included 14 240 unaffected and 82 trisomy 21 pregnancies[8], 11 105 unaffected and 25 trisomy 21 pregnancies[9], and 7209 unaffected and 23 trisomy 21 pregnancies (K. Spencer, unpublished data), respectively. In total, the combined dataset included 128 030 unaffected and 428 trisomy 21 pregnancies.

Statistical analysis

All NT measurements were converted to both NT MoM and delta-NT using the regressed median NT from an analysis of unaffected cases in the UK multicenter study[1]. Statistical analyses were performed using SPSS (SPSS UK Ltd, Woking, UK), S-Plus (Insightful, Seattle, WA, USA) or Analyse-It (Smart Software, Leeds, UK) software.

Assessment of the performance of NT MoM and delta-NT as screening tools in combination with maternal age was examined using standard statistical modeling techniques[10]. For NT MoM, a series of 15 000 random MoM values were selected from within the distributions of the trisomy 21 and unaffected pregnancies, and these values were used to calculate likelihood ratios. For delta-NT, a series of 15 000 random delta-NT values were selected from the 128 030 normal datasets and these were used together with the delta-NT in the trisomy 21 cases to calculate likelihood ratios. The likelihood ratios from NT MoM and delta-NT were then combined with the age-related risk for trisomy 21 in the first trimester and the maternal age distribution of pregnancies in England and Wales in 2000 to calculate expected detection rates for trisomy 21 pregnancies at a fixed false-positive rate[4,11]. This simulation was repeated 10 times with new NT MoM and delta-NT values for each simulation.

The above assessments are based at the population level since detection rates and false-positive rates are population level statistics. In this study we wanted to investigate the quality of each approach to estimate the correct patient-specific risk, thereby aiding clinical assessment for the individual patient. To be able to achieve this objective some attempt at determining the 'true' patient-specific risk is required. When there are sufficient data non-parametric density estimates are ideal for this purpose since they are data-led and as such are not model-dependent[12]. Donovan[13] explored these approaches for the two second-trimester screening markers alpha-fetoprotein and hCG, and concluded that the MoM approach was appropriate for these two markers.

In essence with this approach one replaces each data point, specifying an individual's gestational age and NT value, by a bivariate Gaussian density (kernel) that is centered on the point itself. The smoothed density surface is then the average of the contributions from each Gaussian kernel[12,13].

RESULTS

In the unaffected pregnancies, the distribution of NT MoM and $\log_{10}$(NT MoM) was not Gaussian, whilst in the trisomy 21 pregnancies, probably because of small numbers, the distribution did not significantly depart from Gaussian form (Table 1). The median NT MoM was 1.00

Table 1 Tests for Gaussianarity of $\log_{10}$(NT MoM) in unaffected and trisomy 21 pregnancies

Statistic	*Unaffected cases* (n = *128 030*)	*Trisomy 21 cases* (n = *428*)
Mean $\log_{10}$(NT MoM)	− 0.0030	0.3281
SD $\log_{10}$(NT MoM)	0.1246	0.2292
Kolmogorov–Smirnov coefficient (probability)	0.033 (< 0.0005)	0.039 (0.130)

MoM, multiple of the median; NT, nuchal translucency; SD, standard deviation.

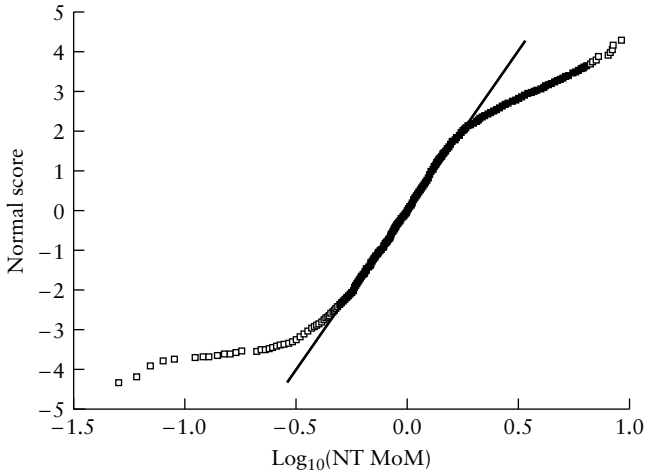

Figure 1 Individual cases (□) and probability plot of NT MoM in unaffected pregnancies showing clear deviation from a Gaussian distribution. The solid line is the expected fit if the distribution was Gaussian.

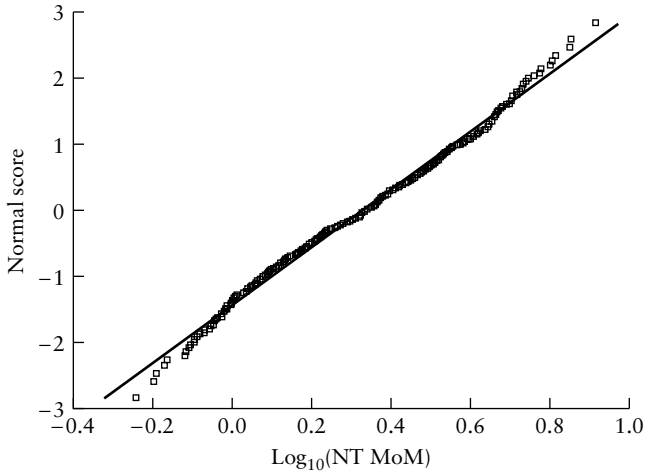

Figure 2 Individual cases (□) and probability plot of NT MoM in trisomy 21 pregnancies. The solid line is the expected fit if the distribution was Gaussian.

for the unaffected pregnancies and 2.18 for the trisomy 21 pregnancies. In the unaffected pregnancies, there was a clear deviation from linearity in the probability plot at MoM values of 2.25 or more and at 0.45 MoM or less (Figure 1). In the trisomy 21 pregnancies, there was an adequate linear fit with some departure at the tail ends (Figure 2).

There was a gestational age-dependent departure from a Gaussian distribution in $\log_{10}$(NT MoM) and this is illustrated by examining the ratio of the difference between the 97.5th and 2.5th percentiles of $\log_{10}$(NT MoM) and the difference between the 75th and 25th percentiles. If the distribution was Gaussian the ratio would have been constant (2.9) over the complete gestational age range, but as shown in Figure 3 there are systematic departures from this figure. Other ratios are also shown for completeness.

The within-gestational day SD of $\log_{10}$(NT MoM) in the unaffected pregnancies changed significantly with gestation (SD $\log_{10}$(NT MoM) = $1.198 - 0.0234 \times GA + 0.000126 \times GA^2$, where GA is the gestational age in days; $P < 0.0005$; Table 2, Figure 4). In the trisomy 21 pregnancies, there was no significant change in SD with gestation ($P = 0.248$), probably because of the small number of cases examined (Table 2).

In the trisomy 21 pregnancies, $\log_{10}$(NT MoM) decreased significantly with gestation ($\log_{10}$(NT MoM) =

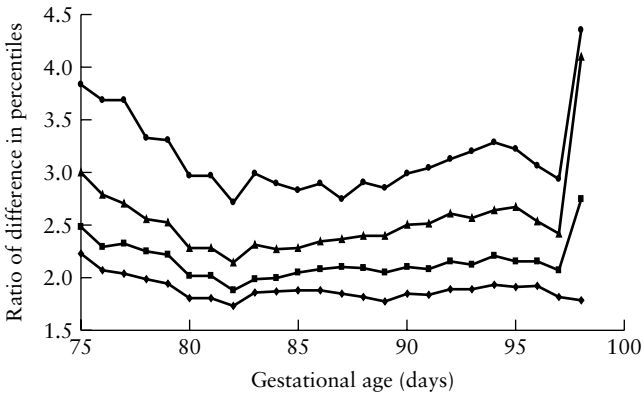

Figure 3 Ratio of difference in percentiles with gestational age showing inconsistency of ratio with gestational age in unaffected pregnancies. (●, ratio of 90–10 : 75–25; ▲, ratio of 92.5–7.5 : 75–25; ■, ratio of 95–5 : 75–25; ♦, ratio of 97.5-2.5 : 75–25).

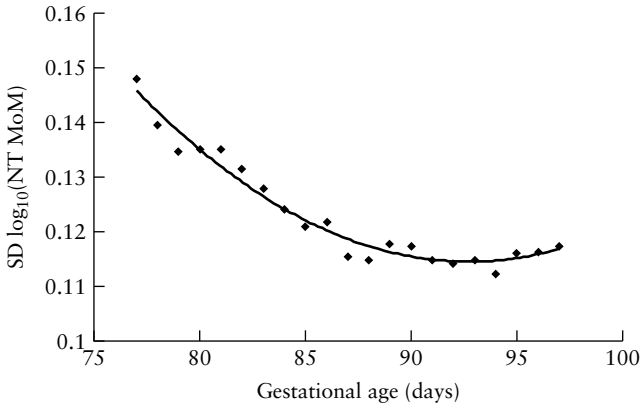

Figure 4 Variation of standard deviation of $\log_{10}$(NT MoM) with gestational age in unaffected pregnancies. Solid line is the second order polynomial fit to the data.

Table 2 Unaffected and trisomy 21 pregnancies at each gestational day and standard deviation of $\log_{10}$(NT MoM) by gestational day (unaffected) or by grouped day (trisomy 21)

Gestation	*Unaffected cases**		*Trisomy 21 cases*	
(days)	n	*SD*	n	*SD*
77	1729	0.1478		
78	3845	0.1390	9	
79	3029	0.1346	6	0.2500
80	5466	0.1353	21	
81	6460	0.1351	28	0.2137
82	7310	0.1314	27	
83	8365	0.1277	25	0.2239
84	9246	0.1240	34	
85	9675	0.1210	29	0.2377
86	9849	0.1217	47	
87	9312	0.1155	38	0.2519
88	8928	0.1147	33	
89	8108	0.1178	22	0.2133
90	6963	0.1173	28	
91	6244	0.1149	35	0.2238
92	6147	0.1142	16	
93	3827	0.1149	12	0.2172
94	3050	0.1122	10	
95	2390	0.1162	2	
96	2024	0.1164	1	
97	1287	0.1173	5	0.1859
98	21	0.1389		

*Excluding 4755 cases with gestations prior to 77 days. MoM, multiple of the median; NT, nuchal translucency; SD, standard deviation.

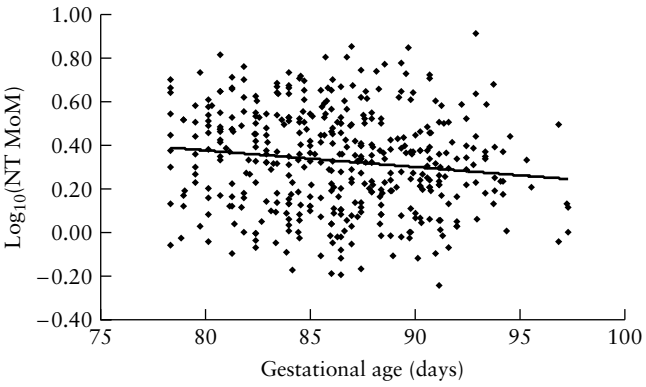

Figure 5 Variation of $\log_{10}$(NT MoM) with gestational age in trisomy 21 pregnancies. The solid line is the regression line.

$0.929 - 0.00696 * GA$, $P = 0.009$; Figure 5). The median NT MoM was 2.53 at 11 weeks, 2.12 at 12 weeks ($P = 0.043$) and 1.94 at 13 weeks ($P = 0.008$). In contrast, the delta-NT did not change significantly with gestation; $P = 0.224$; Figure 6). The median delta-NT in trisomy 21 was 1.89 mm.

The distribution of the $\log_{10}$(NT MoM) for the unaffected fetuses is shown in Figure 7; this is the distribution of values that produced the normal plot shown in Figure 1. As can be seen from the superimposed normal density, there are serious departures from a Gaussian distribution throughout the $\log_{10}$(NT MoM) range. A

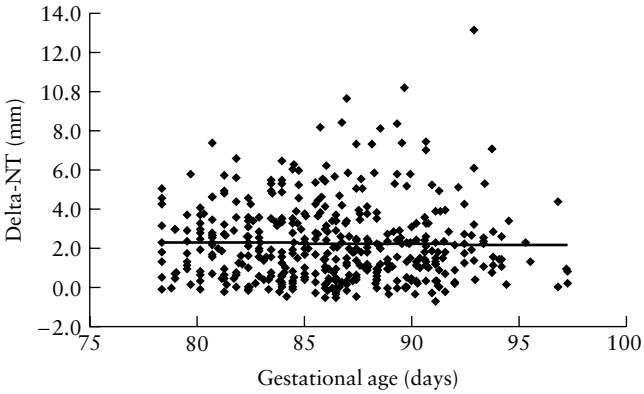

Figure 6 Variation of delta-NT with gestational age in trisomy 21 pregnancies. The solid line is the regression line.

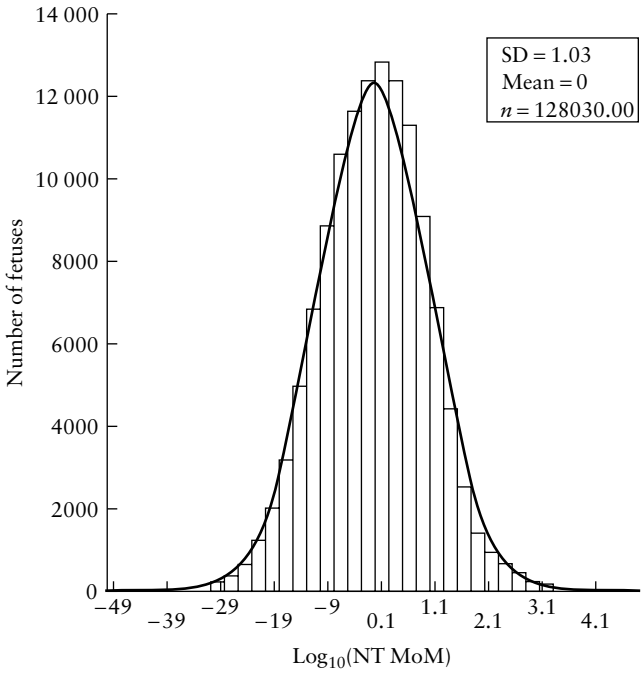

Figure 7 Histogram of the frequency distribution of $\log_{10}$(NT MoM) in unaffected pregnancies with a superimposed normal Gaussian density function (solid line).

one-dimensional non-parametric density estimate using the same data is shown in Figure 8 with the same Gaussian curve superimposed for comparison. The non-parametric density estimate is acceptably smooth and captures the distributional pattern of the data much more closely.

Using the non-parametric approach the contours of constant likelihood ratio were approximately parallel to the baseline (Figure 9), suggesting that a patient's risk is determined by the magnitude of the displacement of the NT measurement from the baseline. This is the approach used in The Fetal Medicine Foundation software for the calculation of risk[1,3]. Figure 10 shows the corresponding contours of constant likelihood ratio using the NT MoM approach and making the necessary Gaussian assumptions. These diverge from

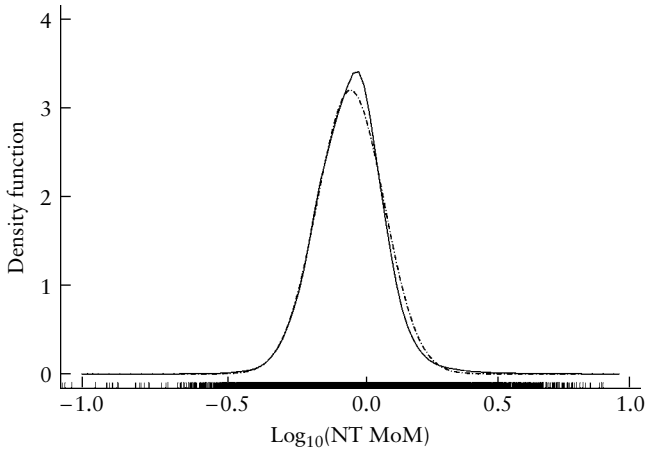

Figure 8 A one-dimensional non-parametric density estimate of $\log_{10}$(NT MoM) in unaffected pregnancies (solid line) with the same superimposed normal Gaussian density function as in Figure 7 (dotted line).

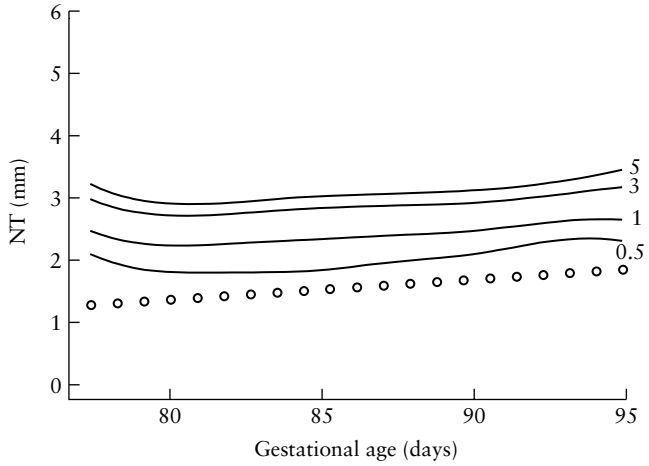

Figure 9 Likelihood ratio contours derived from the non-parametric density estimates of nuchal translucency (NT) at various gestational ages. The contours are shown as solid lines at likelihood ratios of 0.5, 1, 3 and 5 (reading from bottom to top). For reference, the baseline variation of NT with gestational age is indicated by open circles.

the baseline and therefore the NT MoM approach is not appropriate for risk estimates associated with NT measurements.

There is one further modification, in fact a simplification to the non-parametric approach, which can be made. This follows from the conclusion that contours of constant risk (likelihood ratio) are parallel to the baseline. This being the case, it follows that the delta-NT values, which are the residual NT values about the baseline, can be accumulated to determine the patient-specific risk. This is the conclusion that supports the delta-NT approach. The non-parametric likelihood ratio profile for delta-NT values is shown in Figure 11. The profile plotted is reasonably smooth for likelihood ratio values up to 50. From a practical point of view the range over which the non-parametric approach is reliable is adequate for clinical purposes.

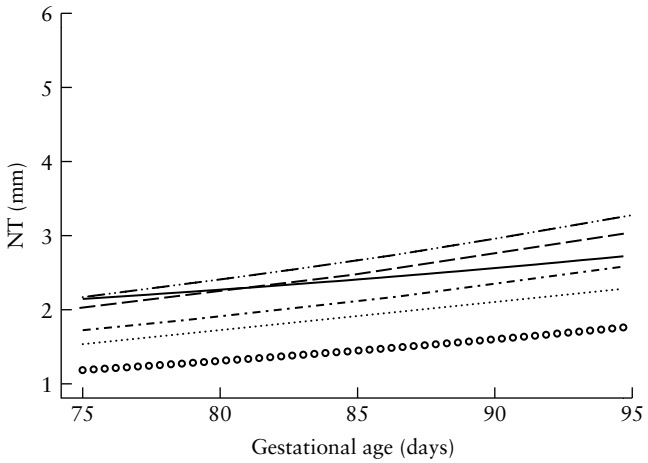

Figure 10 Corresponding contours of constant likelihood ratio using the Gaussian MoM approach plotted against nuchal translucency (NT) and gestational age. The contours are shown at 0.5 (· · · · ·), 1 (– · – · –), 3 (– – –) and 5 (· — · — ·). For reference, the baseline variation of NT with gestational age is indicated by open circles and displaced by 1 mm (solid line).

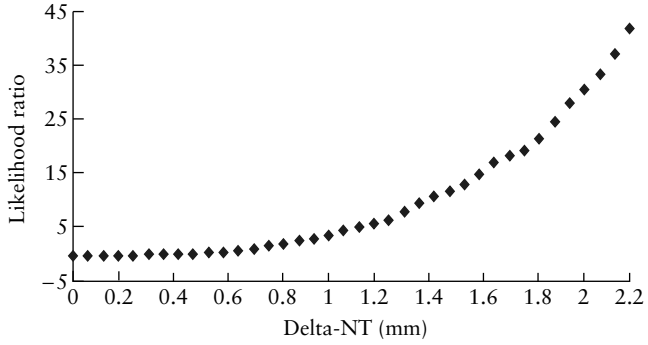

Figure 11 The non-parametric likelihood ratio profile for delta-NT.

Table 3 At a fixed delta-NT, risks of trisomy 21 at each gestational day calculated using the NT MoM approach and the delta-NT approach in a 30-year-old woman (*a priori* age-related risk of 1 in 626)

Gestation (days)	*NT (mm)*	*Delta-NT (mm)*	*NT MoM*	*Risk delta-NT*	*Risk NT MoM*
77	2.2	1.0	1.79	1 in 156	1 in 136
84	2.6	1.0	1.73	1 in 156	1 in 191
91	2.8	1.0	1.63	1 in 156	1 in 278

MoM, multiple of the median; NT, nuchal translucency.

The detection rate of trisomy 21, for a fixed 5% false-positive rate, using the NT MoM approach was 74% and with the delta-NT approach it was 76%. The difference between the two was not statistically significant. However, there were major differences between the two methods in the calculation of individual patient-specific risks for trisomy 21. Table 3 shows the estimated risks with the two methods in a 30-year-old woman (*a priori* age risk of 1 in 626) and an observed fetal delta-NT of 1.0 mm (solid line in Figure 10). The NT MoM approach

provides inaccurate risk assessments because at 11 weeks it overestimates the risk, whereas at 12 and 13 weeks it underestimates the risk.

DISCUSSION

The findings of this study demonstrate that in screening for trisomy 21 by fetal NT, calculation of risks by the NT MoM and delta-NT methods provide similar overall detection rates. This was also the case in the only previous comparison of NT MoM and delta-NT in 3180 unaffected and 32 trisomy 21 pregnancies[14]. However, we found that the NT MoM approach provides inaccurate individual patient-specific risks for trisomy 21 and therefore the use of this method is inappropriate. None of the three basic assumptions that underpin the NT MoM approach was valid. Thus in the unaffected population, the distributions of NT MoM and $\log_{10}$(NT MoM) were not Gaussian, the SDs did not remain constant with gestation, and the median MoM in the trisomy 21 pregnancies was not a constant proportion of the median for unaffected pregnancies. Although this is the largest dataset of trisomy 21 cases studied, the small number of cases at each gestational day was insufficient for us to confirm non-Gaussian fit or variation of SD with gestational day. However it is unlikely that these factors in trisomy 21 cases should behave differently from the large unaffected population studied.

The data in previous publications using the NT MoM approach also demonstrate a deviation from a Gaussian distribution. Thus, in the study of Wald and Hackshaw there was a clear deviation from a Gaussian distribution at 1.2 and 0.7 MoM in unaffected pregnancies[7]. Crossley *et al.* also showed a probability plot with clear deviation from Gaussianarity at 1.5 and 0.5 MoM in unaffected pregnancies[15]. The variation in SD of $\log_{10}$(NT MoM) with gestational age and the declining median NT MoM in trisomy 21 pregnancies clearly all add further evidence to the inappropriateness of the MoM approach, which ultimately leads to women being given inaccurate patient-specific risks. Such temporal variation of marker MoMs has also been observed with first- and second-trimester biochemical markers, but in general the distributions in the $\log_{10}$ domain are Gaussian[16]. Nevertheless, it was suggested that to produce accurate patient-specific risks the algorithms should no longer use the constant median separation model but they should be modified to a variable separation model in which each week of gestation has its own specific model parameters producing more accurate individual patient-specific risks[17]. In the cases of NT even this approach would be inaccurate because the $\log_{10}$(NT MoM) distribution is not Gaussian.

Non-parametric density estimates are ideal for determining the 'true' patient-specific risk, because they are data-led and as such are not model-dependent. Examination of NT measurements using this approach has clearly demonstrated that the contours of constant likelihood ratio are parallel to the baseline for unaffected pregnancies. This provides conclusive evidence that accurate patient-specific risks can be determined by the magnitude of the displacement of their NT measurements from the baseline, which is the delta-NT approach.

What happens in population terms is of little relevance to an individual mother who wishes to be given the best estimate of risk for her – for too long screening for chromosomal anomalies has focused on population detection rates rather than accurate risks for individuals. It is clear from our analysis that when using NT in the first trimester accurate patient-specific risks cannot be provided by the NT MoM approach and that the delta-NT approach is the best method available for ensuring accurate risks when using NT alone or in conjunction with maternal serum biochemistry[8,9].

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