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Frontomaxillary facial angle in screening for trisomy 21 at 11 + 0 to 13 + 6 weeks

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KEYWORDS: 3D ultrasonography; first-trimester screening; frontomaxillary facial angle; trisomy 21

ABSTRACT

Objective *Trisomy 21 is associated with a flat face, which can now be quantified by measurement of the frontomaxillary facial (FMF) angle. The aim of this study was to examine whether in trisomy 21 fetuses fetal nuchal translucency (NT) thickness and maternal serum free ß-human chorionic gonadotropin (ß-hCG) and pregnancy-associated plasma protein-A (PAPP-A) are independent of the FMF angle, and to estimate the performance of a first-trimester screening test for trisomy 21 that includes measurement of the FMF angle.*

Methods *This was a prospective study in singleton pregnancies at 11 + 0 to 13 + 6 weeks of gestation in which three-dimensional volumes of the fetal head were obtained and measurement of the FMF angle performed immediately before fetal karyotyping by chorionic villus sampling (CVS). The women chose to have CVS after risk assessment by a combination of maternal age, fetal NT thickness and maternal serum free ß-hCG and PAPP-A. Regression analysis was used to examine the significance of the association within the euploid and within the trisomy 21 fetuses between the deviation from the normal median in FMF angle and the deviation in NT, free ß-hCG and PAPP-A. We estimated the detection rate (DR) and false positive rate (FPR) of first-trimester screening for trisomy 21 by measuring the FMF angle in all cases and of an alternative policy in which first-stage screening is by fetal NT and maternal serum biochemistry in all patients, followed by second-stage assessment of FMF angle only in those with an intermediate risk (1 in 51 to 1 in 1000) after the first stage.*

Results *The FMF angle was measured in 782 euploid and 108 trisomy 21 fetuses. In the euploid fetuses the mean FMF angle decreased linearly with CRL from 83.5° at a crown–rump length (CRL) of 45 mm to 76.4° at a CRL of 84 mm. In the euploid fetuses the mean delta FMF angle was 0.0 (SD, 4.264)° and the respective values in the trisomy 21 fetuses were 7.172 (SD, 4.092)°. Incorporating the FMF angle in first-trimester combined screening increased the estimated DR from 90 to 94% at an FPR of 5% and from 85 to 92% at an FPR of 3%. In two-stage screening it would be necessary to measure the FMF angle in 12% of cases and the DRs would be 93 and 91% at FPRs of 5 and 3%, respectively.*

Conclusions *Measurement of the FMF angle improves the performance of first-trimester screening for trisomy 21.* *Copyright © 2008 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Effective screening for trisomy 21 is provided in the first trimester of pregnancy by a combination of maternal age, fetal nuchal translucency (NT) thickness and maternal serum free β-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A) with a detection rate of about 90% for a false positive rate of 5%[1–3]. Trisomy 21 is associated with a flat face, which can now be quantified by measurement of the frontomaxillary facial (FMF) angle. Prenatal ultrasonographic studies have reported that in trisomy 21 fetuses both in the first and second trimesters of pregnancy the FMF angle is wider than in euploid fetuses[4,5]. Furthermore, a study of euploid fetuses at 11 to 13 + 6 weeks of gestation reported that there was no significant association between the FMF angle and fetal NT thickness or maternal serum free β-hCG and PAPP-A[6].

The aim of this study was to examine whether in trisomy 21 fetuses NT thickness and maternal serum free

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β-hCG and PAPP-A are independent of the FMF angle and to estimate the performance of a screening test that integrates the two sonographic and two biochemical markers. We examined two screening strategies: firstly, integrated first-trimester screening in all patients, and secondly, first-stage screening of all patients using fetal NT and maternal serum free β-hCG and PAPP-A followed by second-stage assessment of the FMF angle only in those with an intermediate risk of 1 in 51 to 1 in 1000 after the first stage[3].

METHODS

This was a prospective study in singleton pregnancies at 11 to 13 + 6 weeks of gestation in which three-dimensional (3D) volumes of the fetal head were obtained and measurement of the FMF angle performed immediately before fetal karyotyping by chorionic villus sampling (CVS). The women chose to have CVS after risk assessment by a combination of maternal age, fetal NT thickness and levels of maternal serum free β-hCG and PAPP-A. Transabdominal ultrasound examination was performed to diagnose any major fetal defects and for measurement of crown–rump length (CRL) and fetal NT thickness[7]. Automated machines that provide reproducible results within 30 min were used to measure levels of PAPP-A and free β-hCG (Kryptor system, Brahms AG, Berlin, Germany or Delfia Express System, Perkin Elmer, Waltham, MA, USA). Maternal demographic characteristics, ultrasononographic measurements and biochemical results were recorded in a computer database. Karyotype results and details on pregnancy outcomes were added into the database as soon as they become available.

In each case, we attempted within a period of 15 min to obtain a 3D volume of the fetal head in the mid-sagittal plane of the face with the transducer being parallel to or within 30° of the long axis of the nose[8]. The 3D volumes were examined off-line using the multiplanar mode to identify the exact mid-sagittal plane and to make minor corrections from the original acquisition plane when necessary. The exact mid-sagittal plane was defined by the presence of the echogenic tip of the nose and rectangular shape of the palate anteriorly, the translucent diencephalon in the center and the nuchal membrane posteriorly. Minor deviations from the exact midline plane would cause non-visualization of the tip of the nose and visibility of the zygomatic process of the maxilla[8].

The FMF angle was measured between a line along the upper surface of the palate and a line that traversed the upper corner of the anterior aspect of the maxilla, extending to the external surface of the forehead, represented by the frontal bones or an echogenic line under the skin below the metopic suture that remains open (Figure 1)[8].

All examinations were carried out transabdominally (RAB 4-8L probe, Voluson 730 Expert, GE Healthcare Technologies, Milwaukee, WI, USA), by sonographers with extensive experience in first-trimester scanning and 3D ultrasound who were not aware of the fetal karyotype.

Statistical analysis

In each chromosomally normal and trisomy 21 pregnancy, the measured NT was transformed into a likelihood ratio using the mixture model of NT distributions[9]. The measured free β-hCG and PAPP-A were converted into a multiple of the median (MoM) for gestational age adjusted for maternal weight, ethnicity, smoking status, method of conception, parity and machine used for the measurements, and each MoM was converted

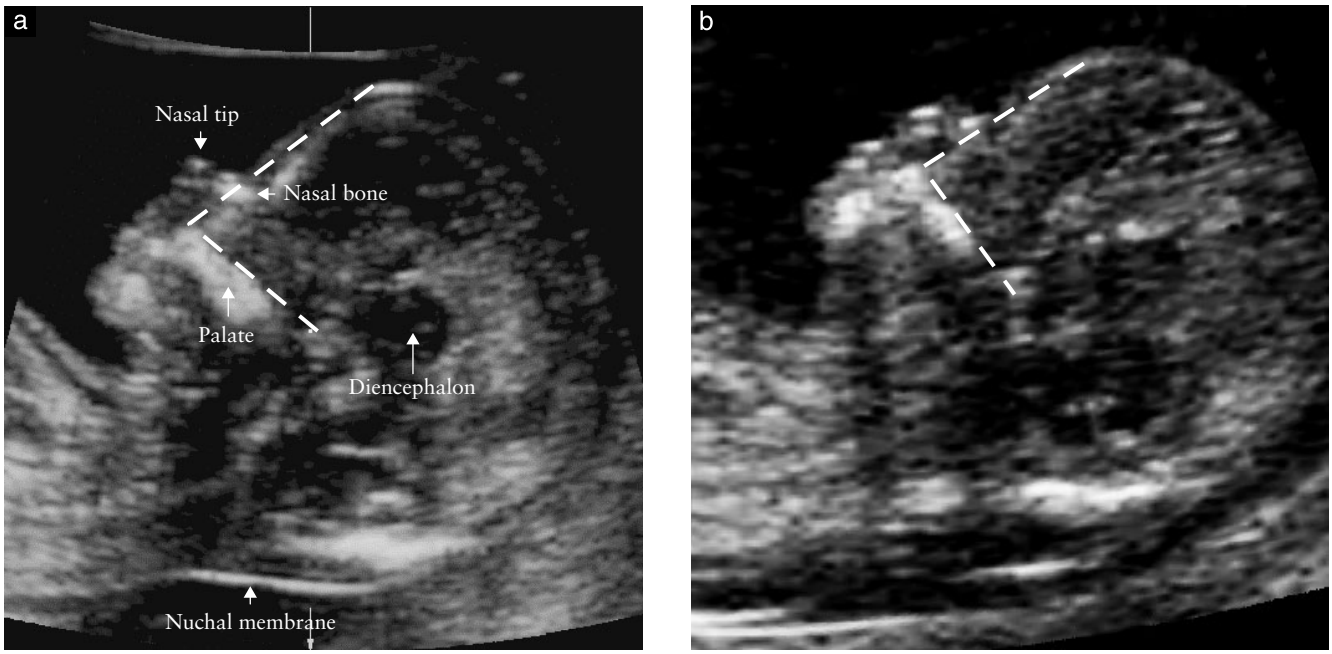

Figure 1 Ultrasound images showing measurement of the frontomaxillary facial angle in a chromosomally normal (a) and trisomy 21 (b) fetus. The angle is defined by a line along the upper surface of the palate and a line from the upper corner of the anterior aspect of the maxilla extending to the external surface of the frontal bone.

into a likelihood ratio[10]. Regression analysis was used to examine the significance of the association within the euploid and within the trisomy 21 fetuses between the delta FMF angle and delta NT, free β-hCG MoM and PAPP-A MoM.

In each case the maternal age-related risk for trisomy 21 at term was calculated and adjusted according to the gestational age at the time of screening[11,12]. The likelihood ratios for NT, the biochemical markers and facial angle were multiplied with the age-related risk in each case to derive the adjusted patient-specific risk.

In order to examine the screening performance of the facial angle in the general population we used a commonly used statistical modeling approach[13]. The population parameters for fetal NT and maternal serum free β-hCG and PAPP-A in the chromosomally normal and trisomy 21 pregnancies were analyzed as previously described by the mixture model for NT and the multiple regression approach for the biochemical markers[9,10].

We generated a database of 20 000 random cases of euploid fetuses and 20 000 random cases with trisomy 21. The maternal age distribution of the euploid group was the one from live births in England and Wales in 2000–2002[14]. The maternal age distribution of the trisomy 21 group was estimated by applying the maternal age-specific risk for trisomy 21 to the maternal age distribution of live births in England and Wales in 2000–2002[14]. In each dataset we randomly assigned firstly, a value of CRL for 12 weeks' gestation, secondly, a value of NT thickness for CRL according to the mixture model of NT[9], thirdly, a free β-hCG and PAPP-A MoM according to the distribution of values in our screening study – which included 491 cases of trisomy 21 and 96 803 unaffected pregnancies[10] – and fourthly, a value of delta FMF facial angle from the respective Gaussian distributions in the present study. We calculated the detection rates of trisomy 21 for fixed false positive rates between 1 and 5% in screening by maternal age alone; maternal age and fetal NT thickness; maternal age, fetal NT thickness and serum free β-hCG and PAPP-A; and by a combination of maternal age, fetal NT thickness, serum biochemistry and FMF angle. In terms of the FMF angle, we examined two screening strategies: firstly, assessment of the FMF angle in all patients and secondly, first-stage screening of all patients using fetal NT and maternal serum biochemistry followed by second-stage assessment of FMF angle only in those with an intermediate risk (1 in 51 to 1 in 1000) after the first stage[3].

RESULTS

Data description

Acquisition of a 3D volume of the fetal head in the appropriate mid-sagittal plane of the face was successfully performed in 939 (84.3%) of 1114 consecutively-examined

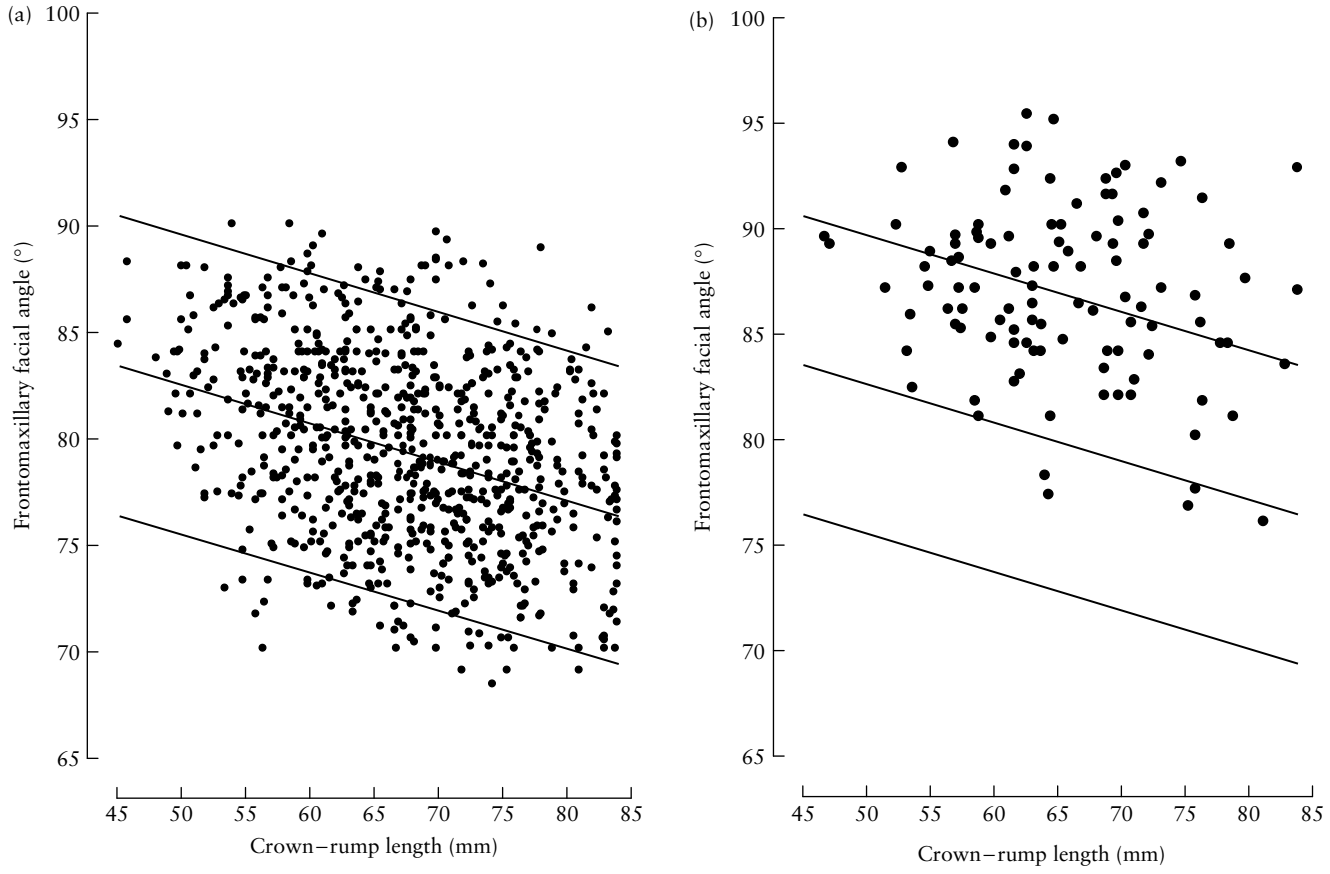

Figure 2 Frontomaxillary facial angle in euploid (a) and trisomy 21 (b) fetuses plotted on the reference range (mean, 95th and 5th percentiles) with crown–rump length of the euploid fetuses.

fetuses. In 175 cases the fetal position was such that within the allocated 15 min it was not possible to image the fetal profile and obtain the appropriate 3D volume. The 175 cases comprised 148 with normal karyotype, eight with trisomy 21 and 19 with other chromosomal defects. In the 939 cases with an FMF angle measurement there were 782 euploid fetuses, 108 with trisomy 21 and 49 with other chromosomal defects. The demographic characteristics of the euploid and trisomy 21 pregnancies are compared in Table 1.

Table 1 Characteristics of the study population

Characteristic	*Trisomy 21* (n = *108*)	*Normal* (n = *782*)
Maternal characteristics		
Age (years)	37 (19–46)	35 (17–49)
Weight (kg)	64.1 (42–101)	66.1 (41–130)
Spontaneous conception	101 (93.5)	757 (96.8)
Smoker	6 (5.6)	54 (6.9)
Ethnicity		
Caucasian	100 (92.6)	692 (88.5)
Afro-Caribbean	2 (1.9)	29 (3.7)
East Asian	1 (0.9)	5 (0.6)
South Asian	4 (3.7)	37 (4.7)
Mixed	1 (0.9)	19 (2.4)
Ultrasound characteristics		
11 + 0 to 11 + 6 weeks	5 (4.6)	37 (4.7)
12 + 0 to 12 + 6 weeks	56 (51.9)	303 (38.7)
13 + 0 to 13 + 6 weeks	47 (43.5)	442 (56.5)
Crown–rump length (mm)	65 (47–84)	67 (45–84)

Data are given as medium (range) or *n* (%).

Distribution of FMF angle

In the euploid fetuses the mean FMF angle decreased with CRL from 83.5° at a CRL of 45 mm to 76.4° at a CRL of 84 mm (FMF angle = 91.702 − (0.182 × CRL), $r = 0.342$, $P < 0.0001$; Figure 2a). The delta FMF angle was normally distributed and the mean was 0.0° with an SD of 4.264°. There was no significant association between delta FMF angle and fetal delta NT ($r = 0.038$, $P = 0.295$; Figure 3a), maternal serum PAPP-A MoM ($r = 0.021$, $P = 0.567$; Figure 4a) or maternal serum free β-hCG MoM ($r = 0.033$, $P = 0.351$; Figure 5a).

In the trisomy 21 fetuses delta FMF angle was normally distributed and the mean was 7.172° with an SD of 4.092°. There was no significant association between delta FMF angle and CRL ($r = 0.1777$, $P = 0.66$; Figure 2b), fetal delta NT ($r = 0.031$, $P = 0.751$; Figure 3b), maternal serum PAPP-A MoM ($r = 0.159$, $P = 0.0.99$; Figure 4b) or maternal serum free β-hCG MoM ($r = 0.042$, $P = 0.666$; Figure 5b).

The distribution of delta FMF in the euploid and trisomy 21 fetuses and likelihood ratio of delta FMF for trisomy 21 are shown in Figure 6.

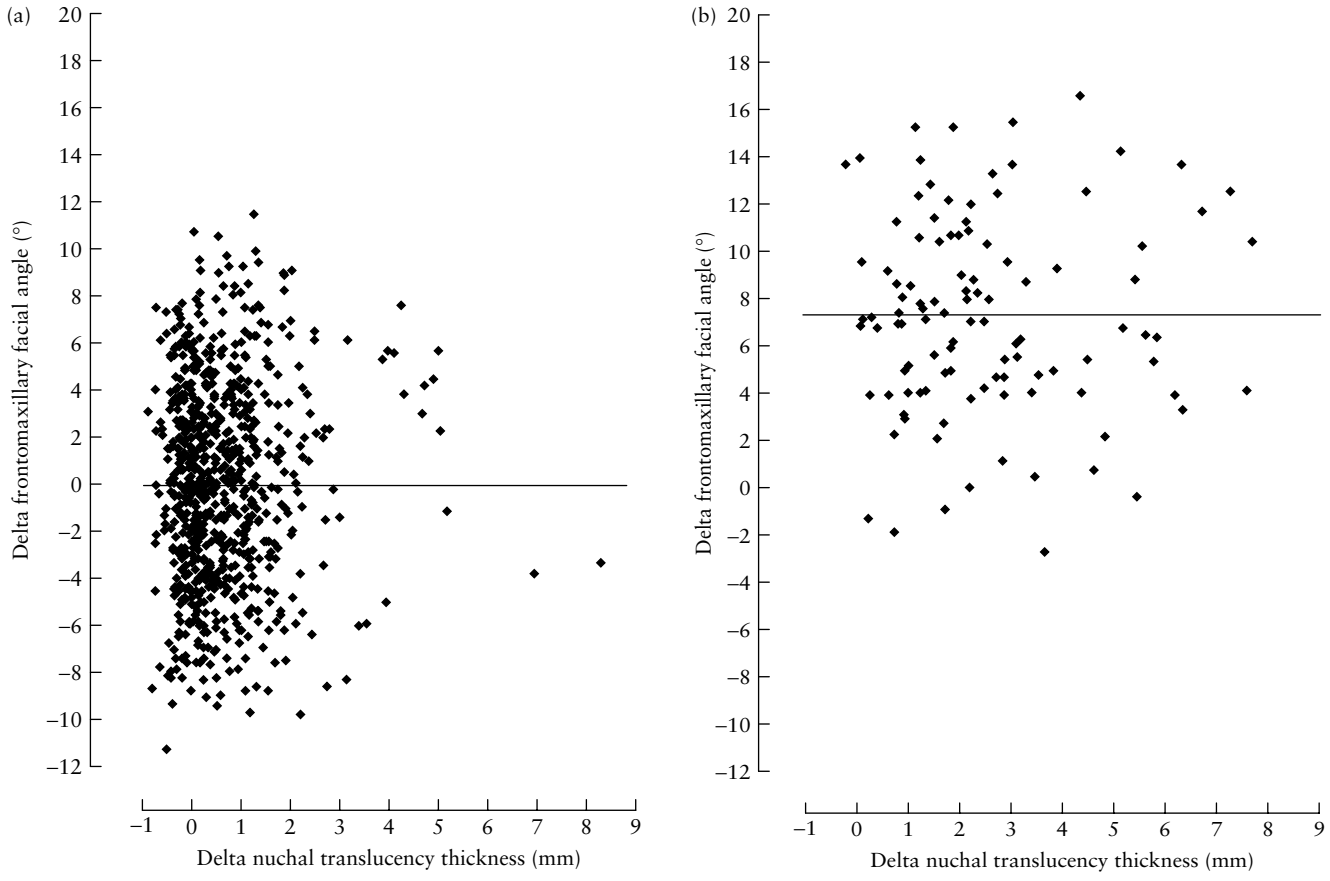

Figure 3 Relationship between delta frontomaxillary facial angle and fetal delta nuchal translucency thickness in euploid (a) and trisomy 21 (b) fetuses. Horizontal lines represent the mean.

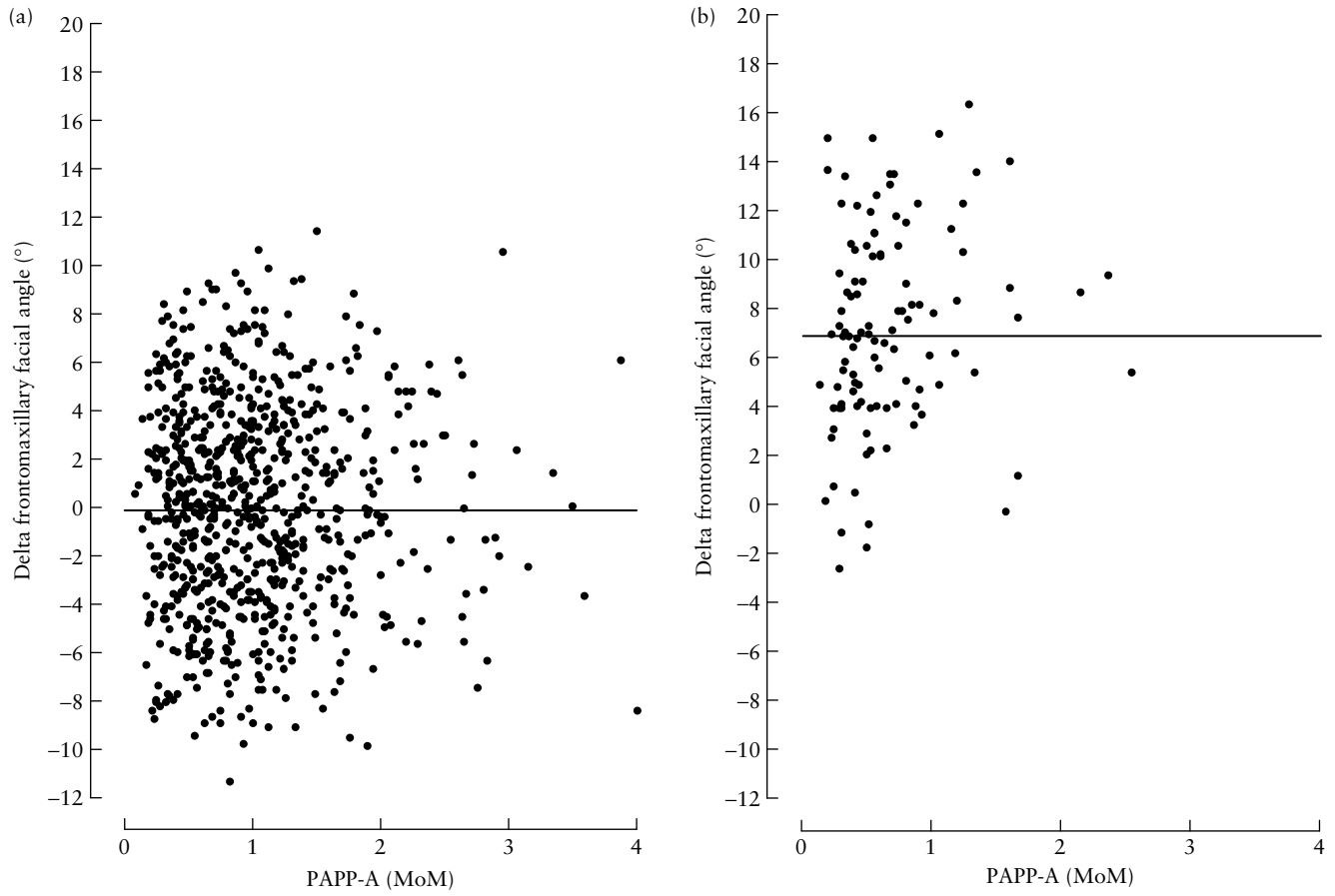

Figure 4 Relationship between delta frontomaxillary facial angle and maternal serum pregnancy-associated plasma protein-A (PAPP-A) multiples of the median (MoM) in euploid (a) and trisomy 21 (b) fetuses. Horizontal lines represent the mean.

Estimated performance of screening in the general population

The estimated detection rates of trisomy 21 for fixed false positive rates between 1 and 5% in screening by maternal age alone; maternal age and fetal NT thickness; maternal age and serum biochemistry; maternal age, fetal NT thickness and serum biochemistry; and by a combination of maternal age, fetal NT thickness, serum biochemistry and fetal FMF angle are shown in Table 2. With combined first-trimester NT thickness and serum screening, a detection rate of 90% was achieved at a false positive rate of 5%. Inclusion of the FMF angle in all cases was associated with detection rates of 92 and 94% at false positive rates of 3 and 5%, respectively.

The alternative policy of screening all patients by fetal NT thickness and maternal serum biochemistry followed by second-stage assessment of FMF angle only in those with an intermediate risk (1 in 51 to 1 in 1000) after the first stage would necessitate measurement of the FMF angle in 11.9% of cases for overall detection rates of 91 and 93% at false positive rates of 3 and 5%, respectively.

DISCUSSION

The findings of this study – that at 11 to 13 + 6 weeks of gestation the FMF angle in euploid fetuses decreases with gestation and that in trisomy 21 the angle is significantly wider than in chromosomally normal fetuses – are compatible with those of previous reports[4,6]. In addition, the data demonstrate that firstly, there is no significant association between the FMF angle and fetal NT thickness or maternal serum free β-hCG or PAPP-A, and secondly, measurement of the FMF angle improves the performance of first-trimester screening for trisomy 21.

The National Screening Committee in the UK recommended that a screening test for trisomy 21 should provide an overall detection rate of at least 75% for a false positive rate of 3% or less[15]. In our study at a false positive rate of 3% the estimated detection rate by combined screening by fetal NT thickness and maternal serum free β-hCG and PAPP-A was 85%, which is substantially higher than the respective 53 and 60% achieved by the triple and quadruple second-trimester biochemical tests[16]. Inclusion of the FMF angle in first-trimester screening improves the detection rate to 92% if the FMF angle is measured in all cases and to 91% if it is measured only in those with an intermediate risk (1 in 51 to 1 in 1000) after first-stage combined screening.

Accurate assessment of the FMF angle necessitates extensive experience in scanning and, as demonstrated in our study, it may not be possible to obtain the exact mid-sagittal plane of the fetal face within a period of 15 min in about 15% of cases. It is therefore unlikely that the

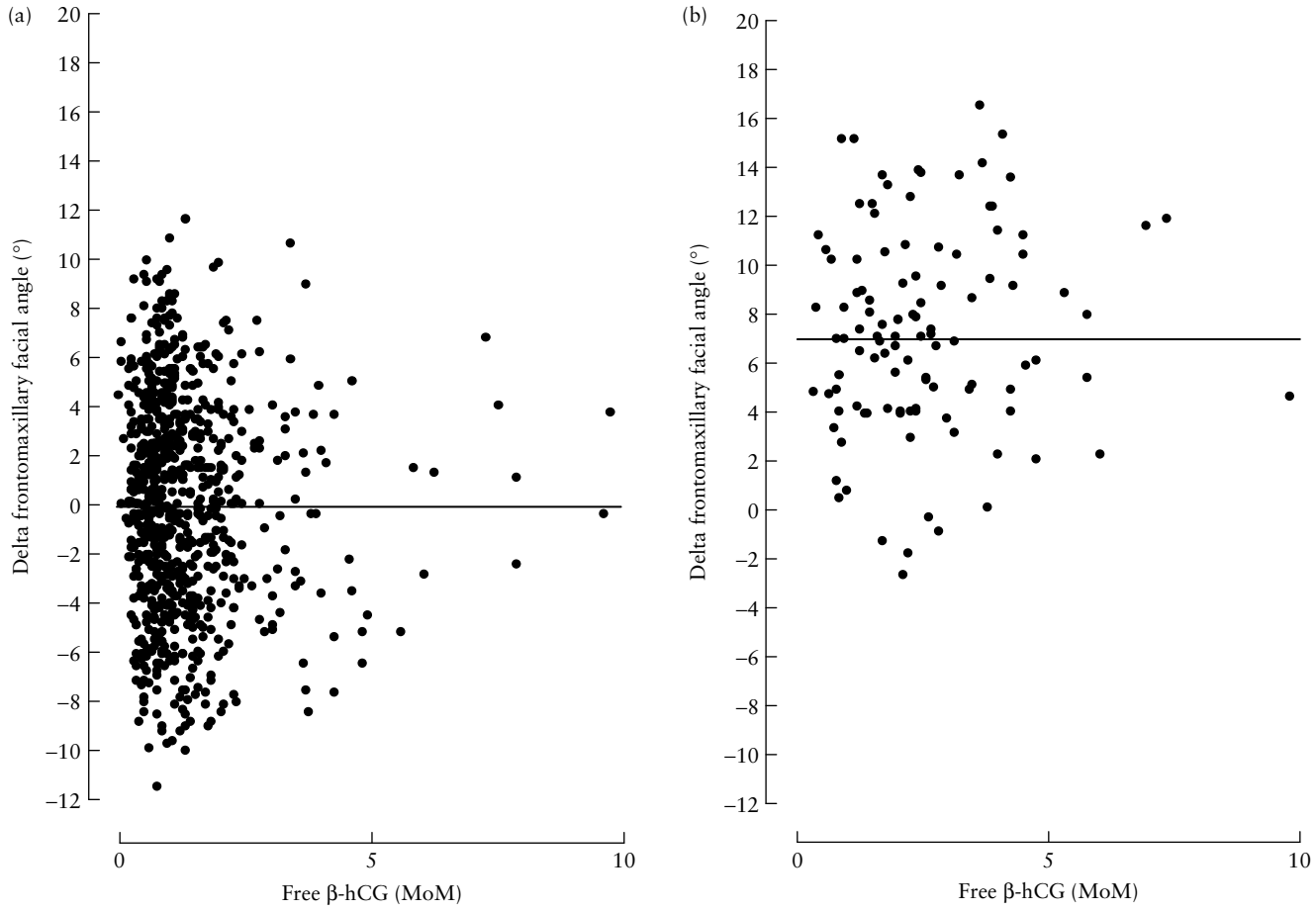

Figure 5 Relationship between delta frontomaxillary facial angle and maternal serum free β-human chorionic gonadotropin (β-hCG) multiples of the median (MoM) in euploid (a) and trisomy 21 (b) fetuses. Horizontal lines represent the mean.

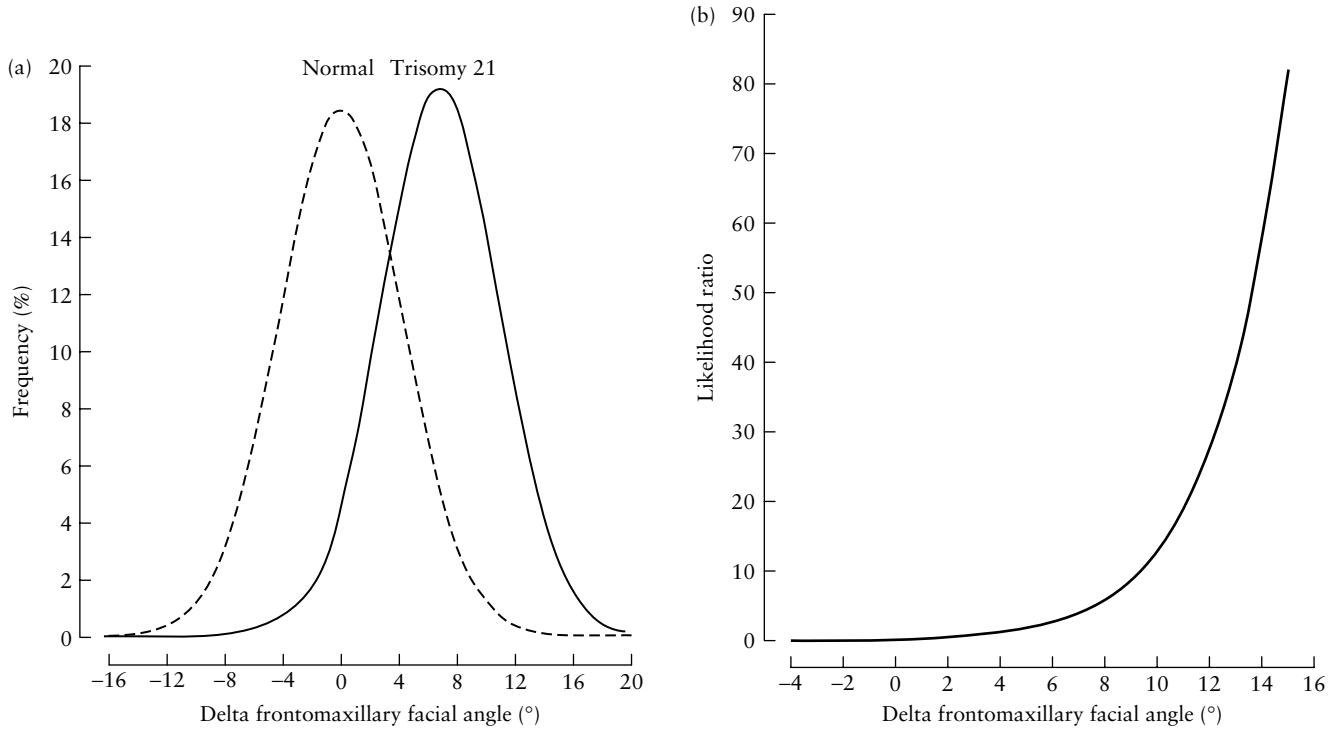

Figure 6 Distribution of delta frontomaxillary facial angle in the euploid and trisomy 21 fetuses (a) and likelihood ratio of delta frontomaxillary facial angle for trisomy 21 (b).

Table 2 Estimated performance of screening in a population with the maternal age distribution of live births in England and Wales in 2000–2002

	Detection rate (%) for given false-positive rate				
Screening policy	*1%*	*2%*	*3%*	*4%*	*5%*
Maternal age and fetal NT	55.4	65.9	70.2	74.3	76.4
Maternal age and serum biochemistry	46.4	54.9	61.1	65.4	68.3
Maternal age, NT and biochemistry	75.6	82.0	85.2	87.4	89.5
Combined screening and FMF angle in all	85.1	89.6	91.9	93.3	94.3
Combined screening and FMF angle in the intermediate-risk group	81.0	88.5	91.0	92.2	93.1

The frontomaxillary facial (FMF) angle can be measured in all cases or only in those with an intermediate risk (1 in 51 to 1 in 1000) after first-stage screening by the combined test of maternal age, fetal nuchal translucency thickness (NT) and maternal serum free β-human chorionic gonadotropin and pregnancy-associated plasma protein-A.

FMF angle will be incorporated into routine first-trimester combined screening for chromosomal abnormalities in all cases. However, the alternative approach of reserving measurement of the FMF angle to the subgroup of pregnancies with an intermediate risk after combined screening, which constitutes only 12% of the total population, is feasible and improves substantially the performance of screening[3].

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