The fetal frontomaxillary facial angle in normal and trisomy 21 ultrasounds at 11–13+6 weeks of gestation: findings among the ethnic Chinese compared with Caucasian

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ABSTRACT
Objective The aim of this research was to compare the fetal frontomaxillary facial (FMF) angle between normal and trisomy 21 fetuses at 11+0–13+6 weeks gestation in a Chinese population.

Methods A prospective observational study was performed that included 640 euploid and 45 trisomy 21 singleton pregnancies undergoing first trimester ultrasound screening between 11 and 13+6 weeks of gestation. The FMF angle was measured in the midsagittal plane using the standard technique.

Results The fetal mean FMF angle decreased with the increasing crown-rump length (CRL) from 88.6° at a CRL of 45 mm to 78.5° at a CRL of 84 mm (FMF angle = 100.212 + 0.258 CRL, R² = 0.222, p < 0.001). The overall mean FMF angle in the euploid population was 82.9° ± 4.1° and in trisomy 21 cases, 92.3° ± 5.2°.

Conclusions Fetal FMF angle is affected by gestational age in a Chinese population, although it remains a significant predictor of fetal trisomy 21. © 2013 John Wiley & Sons, Ltd.

INTRODUCTION
First trimester screening for trisomy 21 using a combination of fetal nuchal translucency (NT) thickness, maternal free beta-human chorionic gonadotropin (β-hCG), and pregnancy-associated plasma protein-A (PAPP-A), at 11–14 weeks of gestation is now established as an effective screening program for main fetal aneuploidies, with a reported detection rate of approximately 90% at a 5% false positive rate.1–3 This method is also highly effective among Chinese subjects,3 in which it was first introduced in 2002.

The flat face characteristic of Down syndrome is a consequence of underdevelopment of the maxilla, which has been described in affected fetuses during both the first and second trimesters of pregnancy.4–7 Borenstein M. was the first to use ultrasound for prenatal measurement of the frontomaxillary facial (FMF) angle and he reported that it was likely to be a useful adjunct in the screening for trisomy 21 at 11–13th weeks gestation.8,9

When incorporating the FMF angle into fetal screening for chromosome abnormalities, ethnic differences in the facial profile should be considered.9,10 In a retrospective study in a Chinese population, the fetal FMF angle was reported to be useful for screening of trisomy 21.11,12 The goal of our study was to study the fetal FMF angle prospectively during 11–13th weeks gestation in a Chinese population.

MATERIALS AND METHODS
In this prospective study, first trimester screening was performed from March 2007 to December 2010. The screening was performed between 11th and 13th weeks gestation and it included measurement of the fetal crown-rump length (CRL), NT, FMF angle, nasal bone evaluation, maternal serum biochemistries (free β-hCG and PAPP-A). Screening for chromosomal abnormalities was evaluated using a fetal scan performed by sonographers that were accredited by the Fetal Medicine Foundation. Using Fetal Medicine Foundation software, individual Down syndrome risks were calculated, and high-risk cases (risk greater than 1/300) were offered invasive testing using chorionic villus sampling or amniocentesis.
The total scanning time was more than 25 min. Overall, there was an 8% failure rate for measurement of the FMF angle due to fetal position or maternal obesity. FMF angle was measured in the midsagittal plane of the fetal profile using both two-dimensional (2D) and three-dimensional (3D) volumes. The measurement of the FMF angle was performed according to Sonek:13 the angle was defined between the facial line transverse to the upper corner of the anterior aspect of the maxilla extending to the external surface of the frontal bone at the point of its greatest anterior excursion and a horizontal line along the upper surface of the upper palate (Figure 1). All 2D and 3D examinations were carried out transabdominally (A-B 2-7L 2D/AB 4-8L curved array 3D transducer, Voluson 730 Pro GE Medical Systems, WI, USA). All examinations were performed off-line using 4D-view software (version 4.1 GE Medical Systems Kretztechnik GmbH). In a subgroup of 60 euploid cases, the fetal FMF angle was measured using 2D ultrasound prior to 3D ultrasound, and then the 3D volumes were used to measure the FMF angle by the same examiner twice and by another examiner once to test repeatability of the measurement. These intra-observer and inter-observer measurements of the FMF angle were performed as described previously.14–16 The Institutional Review Board of the institution approved this study and informed consent was obtained from all patients.

Statistical methods
The Klmogorov–Smirnov test confirmed that the delta value in both groups was normally distributed. The Student t-test was used to examine the mean differences between continuous variables. A regression model was used to assess the relationship between the delta FMF angle and delta NT, free β-hCG MoM, and PAPP-A MoM. Multiple logistic regression models were used to evaluate the FMF angle incorporated into the first trimester screening. Statistical analysis was performed using the IBM version of spss 19.0 (IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.) and Excel for Windows 2007. A *p*-value < 0.05 was considered to represent statistical significance.

RESULTS
From the cohort population of the study period, 19 750 singleton pregnancies, 640 euploid, and 45 trisomy 21 cases documented at chorionic villus sampling or amniocentesis were selected for analysis. Table 1 displays demographic, ultrasonographic, and maternal serum characteristics of the study population in relation to fetal karyotype results. In all cases, the mother was an ethnic Chinese.

In those cases with paired measurements, there was no statistical difference between the measurements that were performed either by the same or by two different sonographers (*p* > 0.05) or between the 2D and 3D ultrasound measurements according to the Bland Altman plot (Figure 2). This finding demonstrates that the measurements obtained had a high internal and external reliability.

Table 1 Characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal</th>
<th>Trisomy 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>30.2(20–46)</td>
<td>33.1(23–43)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>53.8(31–97)</td>
<td>54.7(40–76)</td>
</tr>
<tr>
<td>Spontaneous conception</td>
<td>622(97.2)</td>
<td>45</td>
</tr>
<tr>
<td>Smoker</td>
<td>18(2.8)</td>
<td>0</td>
</tr>
<tr>
<td>Ultrasound characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 + 0 to 11 + 6 weeks</td>
<td>25(3.9%)</td>
<td>7(15.6%)</td>
</tr>
<tr>
<td>12 + 0 to 12 + 6 weeks</td>
<td>308(48.1%)</td>
<td>21(46.6%)</td>
</tr>
<tr>
<td>13 + 0 to 13 + 6 weeks</td>
<td>307(48.0%)</td>
<td>17(37.8%)</td>
</tr>
<tr>
<td>Crown-rump length (mm)</td>
<td>67.3(45–84)</td>
<td>66.9(48–82)</td>
</tr>
<tr>
<td>Biochemistry characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free β-hCG (MoM)</td>
<td>1.09</td>
<td>1.67</td>
</tr>
<tr>
<td>PAPP-A (MoM)</td>
<td>1.09</td>
<td>0.51</td>
</tr>
<tr>
<td>Nuchal translucency (mm)</td>
<td>1.66</td>
<td>3.95</td>
</tr>
</tbody>
</table>

*p* *n* (%)

Figure 1 Ultrasound midsagittal plane view, the frontomaxillary facial 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, euploid fetus (left), and trisomy 21 (right)
Among the euploid fetuses, the mean FMF angle decreased with increasing CRL from 88.6° at CRL of 45 mm to 78.5° at CRL of 84 mm, and the overall mean was 82.9°. (FMF angle = \(100.22 - 0.26 \times \text{CRL}, R^2 = 0.222, p < 0.001\); Figure 3). The mean delta FMF was \(-0.02, 95\% \text{ CI} -0.30 to 0.25\). There was no significant association between the delta FMF angle and the delta NT (\(r = 0.007, p = 0.875\)), maternal serum PAPP-A MoM (\(r = 0.012, p = 0.793\)) or maternal serum \(\beta\)-hCG MoM (\(r = 0.100, p = 0.832\)) in euploid fetuses. Among the 45 trisomy 21 fetuses, the mean FMF angle was 92.3°. The FMF angle was above the 95th percentile in 60.0% (27/45) of the trisomy 21 fetuses; 66.7% (30/45) had an FMF angle over 89.0°. The difference in the delta FMF angle between fetuses with trisomy 21 and euploid controls was 8.9° (Figure 4). The FMF angle had no significant correlation with the fetal NT, serum PAPP-A or \(\beta\)-hCG, or maternal body weight.

A stepwise logistic regression model was used to assess the relative contribution of the fetal FMF angle as part of the first trimester screening, and the NT, FMF, free \(\beta\)-hCG, and MoM were retained in the final model. These four markers explained 34.6% of the variance between the euploid and trisomy 21 fetuses. NT was the first variable used in the model and the NT itself accounted for 26.8% of the difference between euploid and trisomy 21 fetuses, whereas the FMF angle added 5.4% to the variance. Both the free \(\beta\)-hCG and PAPP-A were retained in the final model but only accounted for 2.5% of the variance (Table 2).

Table 2 Final model: multiple logistic regression analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>LB</th>
<th>UB</th>
<th>R-square</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT</td>
<td>75.642</td>
<td>11.635</td>
<td>491.778</td>
<td>0.2681</td>
</tr>
<tr>
<td>FMF</td>
<td>1.669</td>
<td>1.267</td>
<td>2.200</td>
<td>0.3223</td>
</tr>
<tr>
<td>Free (\beta)-hCG</td>
<td>0.103</td>
<td>0.011</td>
<td>0.999</td>
<td>0.3414</td>
</tr>
<tr>
<td>PAPP-A</td>
<td>1.017</td>
<td>1.008</td>
<td>1.026</td>
<td>0.3460</td>
</tr>
</tbody>
</table>

OR, odds ratio; LB, lower bound for 95% confidence interval of OR; UB, upper bound for 95% confidence interval of OR; NT, nuchal translucency; FMF, frontomaxillary angle; hCG, human chorionic gonadotropin; PAPP-A, pregnancy associated plasma protein A.
Prenatal Diagnosis

Data regarding the normal distribution of the fetal FMF angle in the Chinese population have been published previously.\(^1,2\) In our prospective study of a Chinese population, the mean FMF angle significantly decreased with increasing CRL. This finding suggests that correction for CRL should be used for FMF, as it is performed for NT.

An additional novel observation of our study is that the FMF angle that we measured in a Chinese population of euploid and trisomy 21 fetuses is different from that reported in a Caucasian population\(^3\), with a difference of 7.17 and 9.42\(^\circ\), respectively. The mean (SD) difference between the fetal FMF angle derived from the Chinese formula and that from the published Caucasian equation was 4.8 (0.61) (95% CI 1.37–1.58) (p < 0.0001). In previous studies, the mean FMF angle in normal Caucasian, Chinese and Korean fetuses was 78.1, 82.8 and 88.6\(^\circ\), respectively.\(^4,5\) Therefore, the ethnic differences in FMF angle measurements of the facial profile should be considered when incorporating the FMF angle in a fetal screening algorithm for chromosome abnormalities. Including the fetal FMF angle in the first trimester screening requires further study that includes consideration of ethnic differences.

Preliminary results previously reported that the FMF angle with trisomy 21 is different from that in euploid cases.\(^6\) Although in trisomy 21 cases, the fetal FMF angle had a more variable delta NT than did euploid group, the results of our logistic regression analysis confirm that FMF angle is an independent predictor of fetal Down syndrome.

In the combined screening test, serum PAPP-A and free \(\beta\)-hCG levels require adjustment for ethnicity, smoking, method of conception, diabetic mellitus, and body weight.\(^7,8\) Our results show no significant correlation of the FMF angle with maternal body weight, suggesting that adjustment for this variable is not necessary.

In a reproducibility study of the fetal FMF angle, the differences between measurements by the same observer or by two different observers were within 3\(\circ\) of each other in about 95% of the cases.\(^9,10\) Another study used a novel technique measuring the angle between the upper palate and the frontal bone on images generated by 3D ultrasonography to identify the true midsagittal plane.\(^11\) A prospective study reported that the normal range of the fetal FMF angle at 11\(^–\)13\(^+\)6 weeks of gestation was similar and reproducible using 3D or 2D ultrasound.\(^12\) The results of this study confirm that using the standard midsagittal view for measurement of the fetal FMF angle is highly reproducible (Figure 2).

CONCLUSION

The results of this study show that at 11–13\(^+\)6 weeks gestation, the FMF angle decreases with increasing CRL and trisomy 21 screening; however, correction for CRL and ethnicity should be considered.

WHAT’S ALREADY KNOWN ABOUT THIS TOPIC?

- The fetal frontomaxillary facial (FMF) angle has been used to improve detection of Down syndrome in the first trimester screening. The normal fetal FMF angle is dependent on the ethnic background. A previous retrospective study has shown that the fetal FMF angle remains constant across the crown-rump lengths at 11–13\(^+\)6 weeks gestation and that there is no significant difference in FMF angles between Chinese and Caucasian populations.

WHAT DOES THIS STUDY ADD?

- The results of this prospective study show that the fetal FMF angle decreases with the crown-rump length at 11–13\(^+\)6 weeks gestation. The mean fetal FMF angle is significantly different between euploid and trisomy 21 fetuses in a Chinese population.

REFERENCES