Frontomaxillary Facial Angle Measurements in Euploid Korean Fetuses at 11 Weeks' to 13 Weeks 6 Days' Gestation

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Objective. The purpose of this study was to evaluate the distribution of fetal frontomaxillary facial angles in a euploid Korean population at 11 weeks' to 13 weeks 6 days' gestation. ***Methods.*** Three-dimensional volumes of the fetal head were obtained from women with low-risk singleton pregnancies at 11 weeks' to 13 weeks 6 days' gestation who consented to this prospective study. Only fetuses with either a normal karyotype confirmed by amniocentesis or no abnormalities after delivery were considered eligible for analysis and were characterized as euploid for the purposes of this study. Women with multiple pregnancies and those who were lost to follow-up and fetuses with abnormal karyotypes or anomalies diagnosed in utero or postnatally were excluded. The frontomaxillary facial angle was measured twice offline by a single examiner. Cases were categorized by crown-rump length (CRL) in 10-mm intervals for analysis of the frontomaxillary facial angle. ***Results.*** Among 375 enrolled cases, 158 were eligible for frontomaxillary facial angle analysis. The overall mean frontomaxillary facial angle ± SD was 88.6° ± 9.7°. The mean frontomaxillary facial angle for fetuses with a CRL of 40 to 49 mm (n = 35) was 93.7°; 50 to 59 mm (n = 53), 92.6°; 60 to 69 mm (n = 36), 85.3°; and 70 to 79 mm (n = 34), 81.0°, showing an inverse relationship between the mean frontomaxillary facial angle and CRL ($r = -0.5334$; $P < .0001$). The proportion of cases with frontomaxillary facial angles of 85° or greater was 60.8%, and that of cases with angles of 90° or greater was 37.3%. ***Conclusions.*** Ethnic differences in frontomaxillary facial angle measurements should be considered when incorporating the frontomaxillary facial angle in fetal aneuploidy screening in the Korean population.
Key words: ethnic differences; euploid fetuses; first trimester; frontomaxillary facial angle; Korean population.

Abbreviations
CRL, crown-rump length; 3D, 3-dimensional

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The frontomaxillary facial angle measured at the time of nuchal translucency measurement is substantially different between euploid fetuses and fetuses with trisomy 21; therefore, it has been suggested as a feasible early screening sonographic marker to be used in conjunction with other markers.[1,2] According to Sonek et al,[2] the mean frontomaxillary facial angle in fetuses with trisomy 21 between 11 weeks' and 13 weeks 6 days' gestation was 88.7°, significantly larger than 78.1° in euploid fetuses, suggesting more dorsal displacement of the maxilla in relation to the forehead in fetuses with trisomy 21.

In the past, trisomy 21 was misnamed "mongolism" owing to its phenotypic characteristics such as a flat face, a flat nose, and upslanting palpebral fissures that resembled East Asian facial features.[3] We are aware of differences in the facial profile across ethnicities; nonetheless, this has not been considered in developing fetuses. So far, many studies pertaining to the frontomaxillary facial angle in trisomy screening either did not verify ethnicity or included no or too few Asian fetuses. Therefore, norms based on data from white study populations may not be applicable to Asian populations with different facial profiles.

In light of these matters, this study was conducted to determine the distribution of frontomaxillary facial angle measurements and to determine its normal value in euploid Korean fetuses at 11 weeks' to 13 weeks 6 days' gestation.

Materials and Methods

The study was conducted prospectively in 2 tertiary referral centers from November 2007 through December 2008 in low-risk singleton pregnancies at 11 weeks' to 13 weeks 6 days' gestation. This study was approved by the Institutional Review Board, and all patients consented to participation. Patients were enrolled immediately before nuchal translucency screening after being interviewed for exclusion criteria, including unconfirmed dating of gestational age by sonography before 10 weeks' gestation, advanced maternal age, family history or obstetric history of trisomy or skeletal dysplasia, and higher-order pregnancy. Nuchal translucency and crown-rump length (CRL) measurements were obtained by sonography. If a fetal anomaly (including absence of the nasal bone), higher-order pregnancy, or missed abortion was diagnosed, the case was excluded. On completion of the pregnancies, medical records were reviewed to only include cases that had a normal karyotype confirmed by genetic screening or had no abnormalities after delivery, which were characterized as euploid for the purposes of this study. In addition, we censored retrospective occurrences of fetal aneuploidy, fetal anomalies, termination of pregnancy due to medical reasons, preterm delivery of a nonviable neonate, and loss to follow-up before volume analysis.

Eligible cases underwent 3-dimensional (3D) volume acquisition of the fetal head and upper thorax in the midsagittal plane as defined previously.[4,5] If the 3D volume acquisition was unsuccessful within 15 minutes because of an unsatisfactory fetal position or excessive fetal movement, the case was considered a failure. All examinations were performed transabdominally (Accuvix XQ, Medison Co, Ltd, Seoul, Korea; and Voluson 730 Expert, GE Healthcare, Zipf, Austria) by 1 of 3 ultrasound specialists experienced in first-trimester scanning and 3D sonography.

Analysis of the 3D volumes was performed using external software (SonoView Pro version 1.4, Medison Co, Ltd; and 4D View version 5.0, GE Healthcare) by a single examiner to measure the frontomaxillary facial angle twice within a 1-week interval blinded to the first measurement to assess intraobserver variability. The 3D volume was manipulated in the 3 axes to obtain the correct midsagittal plane defined by Plasencia et al[4,5] to simultaneously depict the nasal bone, diencephalon, rectangular maxilla, and nuchal membrane. The frontomaxillary facial angle was measured between a line drawn on the upper margin of the maxilla and a line drawn from the upper anterior corner of the maxilla to the frontal bone, as previously described (Figure 1).[4,5] To assess interobserver variability, another specialist with extensive experience in first-trimester scanning and blinded to the first measurements repeated the frontomaxillary facial angle measurement in 30 cases.

The Kolmogorov-Smirnov test was used to confirm the normal distribution of the frontomaxillary facial angle measurements. Eligible cases were categorized by the CRL in 10-mm intervals for statistical analysis of the frontomaxillary facial angle. Continuous variables were expressed as mean ± SD or median and range. Data analysis was performed using SPSS version 12.0 software (SPSS Inc, Chicago, IL) and Excel for Windows 2007 (Microsoft Corporation, Redmond, WA). $P < .05$ was considered statistically significant. The relationship for the frontomaxillary facial angle and CRL was evaluated by the Pearson correlation coefficient. Interobserver and intraobserver bias and agreement in frontomaxillary facial angle measurements were evaluated using a Bland-Altman plot, and the statistical difference was evaluated by a Student *t* test.

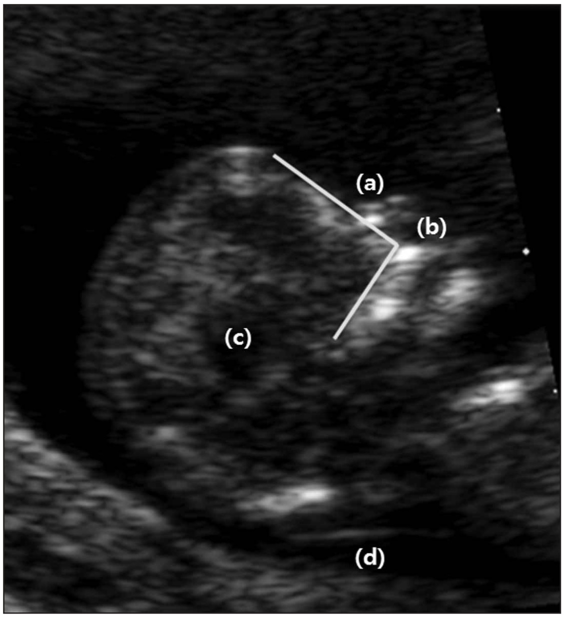


Figure 1. Sonogram showing measurement of the frontomaxillary facial angle. On an image simultaneously depicting the nasal bone (a), diencephalon (b), rectangular maxilla (c), and nuchal membrane (d), the frontomaxillary facial angle was measured between a line drawn on the upper margin of the maxilla and a line drawn from the upper anterior corner of the maxilla to the frontal bone.

Results

Among 375 cases initially enrolled in the study, volume acquisition in the midsagittal view was successful in 303 (80.8%). Of these 303 cases, 104 were excluded from analysis because the pregnancy resulted in termination (n = 1), fetal death with an unknown karyotype (n = 2), or loss to follow-up (n = 101). Unclear delineation of the anterior margin of the maxilla at the time of retrospective analysis of the 3D volume excluded 41 cases (20.6%), leaving 158 cases for frontomaxillary facial angle measurement (Table 1). As shown in Table 1, the proportion of cases with unsuccessful measurements was the highest in the group with a CRL of 40 to 49 mm.

In the 158 cases evaluated, the median maternal age was 32 years (range, 25–44 years); the median CRL at volume acquisition was 58.5 mm (range, 40.0–79.0 mm); and the mean frontomaxillary facial angle was 88.6° ± 9.7°, which did not show a statistical difference when compared with that of cases lost to follow-up (Table 2). An inverse relationship was found between the mean frontomaxillary facial angle and CRL (r = –0.5334; P < .0001; Figure 2 and Table 1), where the mean frontomaxillary facial angle decreased from 93.7° ± 9.5° at a CRL of 40 to 49 mm to 81.0° ± 6.1° at 70 to 79 mm.

Intraobserver agreement in 158 cases and interobserver agreement in 30 randomly selected cases were assessed. The mean difference and the 95% limits of agreement are showed in Figure 3 and Table 3.

Of the 158 cases, 60.8% and 37.3% had frontomaxillary facial angles of 85° or greater and 90° or greater, respectively (Table 4). The proportion of cases increased significantly in relation to the CRL, presenting an inverse relationship (P < .001).

Discussion

The effect of ethnic differences on nuchal translucency and nasal bone evaluation has been previously reported.[6,7] Thilaganathan et al[6] showed a small but significant difference in nuchal translucency measurements between fetuses of different ethnic origins, emphasizing the need to take ethnicity into account in the interpretation of such sonographic markers and the need to develop race-specific normative data. In Korea, normative data for fetal nuchal translucency thickness formulated by Chung et

Table 1. Frontomaxillary Facial Angle Values in 158 Euploid Korean Fetuses Successfully Measured by 3D Volume Analysis in Relation to CRL

CRL, mm	Total Cases, n	Successfully Measured, n (%) No	Successfully Measured, n (%) Yes	FMF, ° Mean ± SD	FMF, ° Minimum	FMF, ° Maximum
40–49	55	20 (36.4)	35 (63.6)	93.7 ± 9.5	68.0	120.1
50–59	61	8 (13.1)	53 (86.9)	92.6 ± 9.4	68.0	109.7
60–69	44	8 (18.2)	36 (81.8)	85.3 ± 7.4	70.2	105.7
70–79	39	5 (12.8)	34 (87.2)	81.0 ± 6.1	65.5	95.5
Total	199	41 (20.6)	158 (79.4)	88.6 ± 9.7	65.5	120.1

FMF indicates frontomaxillary facial angle.

Table 2. Comparison Between Included Cases and Cases Lost to Follow-up

Variable	Included (n = 158)	Lost to Follow up (n = 101)	*P*
Maternal age, y, median (range)	32 (25–44)	32 (23–36)	NS
CRL, mm, median (range)	58.5 (40.0–79.0)	55.3 (40.0–78.7)	NS
FMF, °, mean ± SD	88.6 ± 9.7	84.4 ± 6.6	NS

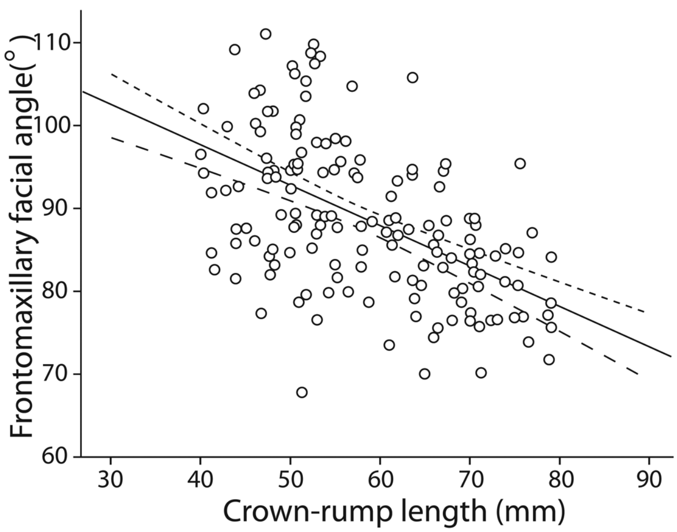
FMF indicates frontomaxillary facial angle; and NS, not significant.

al[8] are widely used as Korean-specific references. In addition, ethnic differences are present for the rates of visualization of the fetal nasal bone and its length.[7,9–13]

To date, data on the frontomaxillary facial angle in the first trimester have been limited, and to our knowledge, a potential racial difference in the frontomaxillary facial angle has not been formally evaluated (Table 5). The initial report of mean frontomaxillary facial angle values of 78.1° in euploid fetuses and 88.7° in fetuses with trisomy 21 and a 95th percentile cutoff of 85° did not specify the ethnic distribution of the study population.[1] In a recent study on the normal range of frontomaxillary facial angle measurements at 11 weeks' to 13 weeks 6 days' gestation, white patients constituted greater than 90% of the study population.[14]

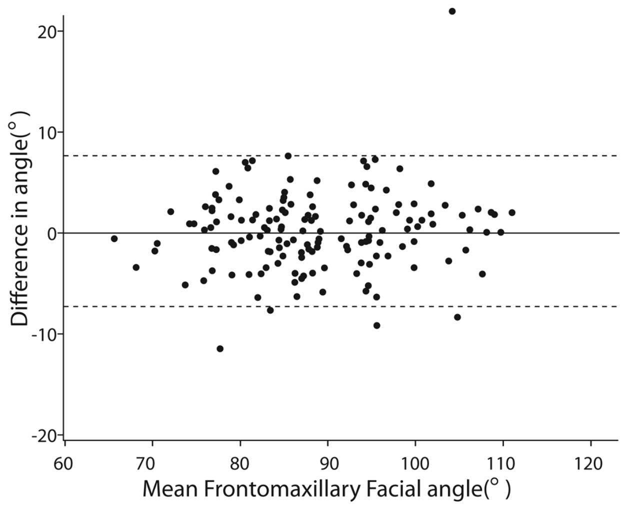
We found that the mean frontomaxillary facial angle measured in the first trimester was 88.6°, comparatively greater than the 78.1° in euploid fetuses reported by Borenstein et al.[14] In addition, measurements of the frontomaxillary facial angle at different CRLs were also higher. For example, the angle in our study was 93.7° at a CRL of 40 to 49 mm, compared with 84.3° at 45 mm and 81.0° at 70 to 79 mm, compared with 75° at 84 mm in the study by Borenstein et al.[14] Although a statistical comparison cannot be made between the two studies because of differences in populations and stratification, it is interesting to note that the mean frontomaxillary facial angle value of euploid Korean fetuses in our study (88.6°) was similar to that of fetuses with trisomy 21 (88.7°) in the study by Borenstein et al.[14] More importantly, we found that the proportion of Korean fetuses having a frontomaxillary facial angle above the previously proposed cutoff value of 85° for trisomy 21 screening was 60.8%, and for 90° it was 37.3%, which showed a negative correlation with the CRL (Table 4). This suggests that when the 95th percentile cutoff for euploid fetuses in white populations is to applied to Korean fetuses, almost two-thirds of the euploid fetuses would be falsely screened as having trisomy 21, and the percentage would become even higher with a decreasing CRL.

Figure 2. Frontomaxillary facial angle in 158 euploid Korean fetuses in relation to the CRL. Pearson correlation coefficient: $r = -0.5334$; $P < .0001$.



In this study, about one-third of cases in the group with a CRL of 40 to 49 mm had unsuccessful frontomaxillary facial angle measurements because of an unclear anterior margin of the maxilla and thus were excluded from the study. Specifically, the success rates of satisfactory visualization of the anterior margin of the maxilla in cases with a CRL of less than 50 mm and 50 mm or greater were 20 of 55 (36.4%) and 123 of 144 (85.4%), respectively. This may imply that frontomaxillary facial angle screening should be avoided at a CRL of 40 to 49 mm and postponed to a later gestation to attain optimal volume data for offline angle analysis.

Although others have failed to show a significant relationship between the CRL and frontomaxillary facial angle,[2,15] a significant negative correlation between the frontomaxillary facial



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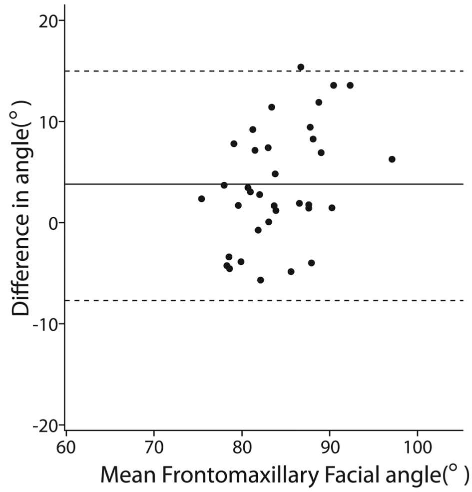

B

Figure 3. Intraobserver (**A**) and Interobserver (**B**) bias and agreement in measuring the frontomaxillary facial angle.

angle and CRL was observed in our results, which was consistent with recent observations made by Borenstein et al.[1,14] In addition, because the mean frontomaxillary facial angle significantly decreased with an increasing CRL, individualized 95th percentile cutoffs according to CRL may be more applicable rather than a single fixed cutoff. However, our sample size was not large enough to support the development of such cutoffs; therefore, validation should be made on the basis of larger number of cases.

Recently, Chen et al[15] reported frontomaxillary facial angle measurements in the first trimester in fetuses with trisomy 21 in the Chinese population. The mean frontomaxillary facial angles were 82.8° in euploid fetuses and 89.7° in fetuses with trisomy 21, showing a significant difference. It is not possible to directly compare their mean value in euploid fetuses with the value in white fetuses because their study setting was different; nonetheless, the mean angle of the Chinese population was relatively larger than that of the white population. Our mean frontomaxillary facial value was greater than that found in the Chinese population.[15] Of note, the median CRL in the study conducted by Chen et al[15] was greater compared with our data (64.4 versus 58.5 mm). Because the frontomaxillary facial angle and CRL are inversely related, the difference in the CRLs between the two studies may have contributed to the difference in the frontomaxillary facial angles.

There were potential limitations in this study. First, we were unable to obtain frontomaxillary facial angles in 20.6% of the enrolled cases compared with 100% success in other studies (Table 5). However, this difference may have been ascribable to the prospective nature of this study because another prospective study had a similar failure rate of 18.2%.[10] Second, a potential impact of a selection bias may have existed because one-third of the initially enrolled cases were retrospectively excluded from the final analysis

Table 3. Comparison of Paired Measurements of Frontomaxillary Facial Angle

	Intraobserver Variability			Interobserver Variability		
CRL, mm	Mean Difference ± SD, °	95% Limits of Agreement, °	*P*	Mean Difference ± SD, °	95% Limits of Agreement, °	*P*
40–79	0.32 ± 3.87	–7.26, 7.89	NS	3.63 ± 5.75	–7.64, 14.89	NS
<50	0.39 ± 5.32	–10.03, 10.82	NS	5.61 ± 4.57	–3.35, 14.58	.004[a]
≥50	0.29 ± 3.37	–6.31, 6.90	NS	2.13 ± 6.18	–9.98, 14.26	NS

NS indicates not significant.
[a]Bland-Altman analysis: $P < .05$, Student *t* test.

Table 4. Distribution of Frontomaxillary Facial Angles Above Proposed Cutoff Values by CRL in Euploid Korean Fetuses

CRL, mm	Cases, n	FMF ≥85° n	FMF ≥85° %	FMF ≥90° n	FMF ≥90° %
40–49	35	28	80.0	21	60.0
50–59	53	41	77.4	29	54.7
60–69	36	18	50.0	8	22.2
70–79	34	9	26.5	1	2.9
Total	158	96	60.8	59	37.3

FMF indicates frontomaxillary facial angle. $P < .0001$ for frontomaxillary facial angles of 85° or greater and 90° or greater, χ^2 test.

because of loss to follow-up. Because this was a prospective study to evaluate the frontomaxillary facial angle in euploid fetuses, we needed a precise delivery outcome to confirm that the neonates had no abnormalities. Thus, we meticulously censored cases that did not deliver at our institute, which resulted in large number of excluded cases. Nonetheless, we did not find a significant difference in the median maternal age, median CRL, and frontomaxillary angle measurements between the included cases and those lost to follow-up (Table 2). Third, our data delineated an increased interobserver variation compared with prior studies. This may have been due to the relatively higher inclusion of fetuses with a CRL of less than 50 mm in this study because a CRL of less than 50 mm was shown to effect the interobserver variation (Table 5). Fourth, our cases did not include Korean fetuses with trisomy 21, which might have provided more practical data with regard to the applicability of frontomaxillary angle measurements in the Korean population.

In conclusion, the mean frontomaxillary facial angle in euploid Korean fetuses measured at 11 weeks' to 13 weeks 6 days' gestation was larger than those reported previously in white fetuses, which highlights the necessity to consider ethnic differences when incorporating frontomaxillary facial angle measurements into first-trimester trisomy 21 screening protocols. Furthermore, because of an increased failure rate in obtaining a clear anterior margin of the maxilla for frontomaxillary facial angle measurement and higher intervariability observed in fetuses with a CRL of less than 50 mm, we suggest that frontomaxillary facial angle analysis using 3D sonography should be deferred until the CRL is greater than 50 mm. However, we strongly encourage further large-scale studies to verify our findings.

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Table 5. Comparison of Frontomaxillary Facial Angles Between Study Groups

Reference (Type of Study)	Status of Fetus	n	Successfully Obtained FMF, n (%)	Median CRL (Range), mm	Mean FMF angle, °	Ethnicity, %
Borenstein et al[14] (prospective)	E	611	500 (81.8)	68.2 (46–84)	85 (CRL 45 mm) 75 (CRL 84 mm)	91.2 white, 4.6 African Caribbean, 4.2 Indian or Pakistani
Sonek et al[2]	E	300	300 (100)	68 (45–84)	78.1	Not specified
(retrospective)	T21	100	100 (100)		88.7	
Chen et al[15]	E	220	220 (100)	64.7 (47.9–84.0)	82.8	100 Chinese
(retrospective)	T21	22	22 (100)	64.4 (48.5–82.4)	89.7	
This study (prospective)	E	199	158 (79.4)	58.5 (10.0–79.0)	88.6	100 Korean

E indicates euploid; FMF, frontomaxillary facial angle; and T21, trisomy 21.

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