Ultrasonographic Study of Fetal Facial Profile Markers During First Trimester

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Abstract

Background: To establish normal reference ranges of fetal facial profile markers, and to study their correlation with crown-rump length (CRL) during first trimester (11~13^{+6} weeks' gestation) in a Han Chinese population.

Methods: Ultrasonographic images of measuring fetal nuchal translucency (NT) were retrospectively selected randomly in normal pregnancies where both parents were of Han Chinese ethnicity. The facial markers included inferior facial angle (IFA), maxilla-nasion-mandible (MNM) angle, facial maxillary angle (FMA) and profile line (PL) distance. These markers were measured through ViewPoint 6 software by two experienced sonographers.

Results: Three hundred and eighty fetuses were selected. The ICCs (95% CI) of intra-operator 1 reproducibility of IFA, MNM angle, FMA, PL distance were 0.944 (0.886~0.973), 0.804 (0.629~0.902), 0.834 (0.68~0.918) and 0.935 (0.868~0.969), respectively. The ICCs (95% CI) of intra-operator 2 reproducibility of IFA, MNM angle, FMA, PL distance were 0.931 (0.857~0.967), 0.809 (0.637~0.904), 0.786 (0.600~0.892) and 0.906 (0.813~0.954), respectively. The ICCs (95% CI) of inter-operator reproducibility of IFA, MNM angle, FMA, PL distance were 0.885 (0.663~0.953), 0.829 (0.672~0.915), 0.77 (0.511~0.891) and 0.844 (0.68~0.925), respectively. The average±SD of IFA, MNM angle, FMA and PL distance were 80.2°±7.25°, 4.17°±1.19°, 75.36°±5.31°, 2.78±0.54 mm, respectively. IFA and PL distance significantly decreased with CRL, while MNM angle and FMA significantly increased with CRL.

Conclusion: It was feasible to measure fetal facial markers during first trimester. The normal range of each marker was obtained through large sample data, and the measurements were found to correlate with CRL.

Background

Fetal facial malformations mainly include cleft lip and palate (CLP), micrognathia, maxillary dysplasia, and absence of nasal bone, which are closely related to some chromosomal abnormalities or genetic syndrome [1, 2]. With the rapid development of ultrasound technology and the continuous accumulation of sonographers' experience in recent years, the majority of CLP can be diagnosed mainly during second and third trimester. Severe micrognathia can be subjectively judged based on the shape of fetal facial profile and also be assessed by measuring the mandible length [3]. However, if fetal facial malformations could be diagnosed during first trimester (11 ~ 13^{+6} weeks' gestation), healthcare providers and parents would have enough time to evaluate fetal prognosis, such as performing chorionic villus sampling (CVS) or early anatomic survey. It will have great clinical importance. Actually most facial structures of the fetus have been differentiated during first trimester [4]. It is feasible to evaluate fetal facial structure during first trimester [5]. The guideline issued in 2013 by International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) [6] pointed out that it was crucial to observe the fetal facial profile. However, prenatal diagnosis of fetal facial abnormalities is currently subjective in the first trimester, and a series of simple, reliable and reproducible objective parameters are still lacking. In this study, fetal facial markers including inferior facial angle (IFA), maxilla-nasion-mandible (MNM) angle, facial maxillary angle (FMA) and profile line (PL) distance, were measured in fetal facial mid-sagittal section during first trimester. The aim of the present study was to establish the normal range for each marker in the Chinese population and analyze their correlation with CRL during first trimester.

Methods

Study subjects

Ultrasound examinations where first trimester ultrasound screening were done at the Affiliated Suzhou Hospital of Nanjing Medical University between August 2017 and July 2019 were retrospectively selected. The pregnancy outcome was followed-up by the Suzhou Maternal-children health care system.

The inclusion criteria were as followings: (1) both parents of the fetus were the Han nationality; (2) pregnancies with significant maternal co-morbidities were excluded; (3) singleton pregnancy; (4) fetuses with normal ultrasound and normal follow-up outcomes; (5) the selected two-dimensional ultrasound (2D-US) images were the standard mid-sagittal section for measuring nuchal translucency (NT) thickness, which met the standardized protocol at 11–13 weeks' gestation of the Fetal Medicine Foundation (FMF). The forehead, nasal bone, palate, mandible, upper lip, lower lip and other structures should be clearly displayed in this section.

The study was approved by the Ethics Committee of Suzhou Municipal Hospital.

Equipment And Software

A Philips Affiniti70 and a GE Voluson E10 four-dimensional (4D) color ultrasound machines were utilized in this study; each was equipped with a convex probe of C9-2 and C5-1, with the frequency of 2 ~ 9 MHz and 1 ~ 5 MHz, respectively. The images obtained by transabdominal ultrasound examination were imported into the ultrasound workstation software, ViewPoint 6 in DICOM (Digital Imaging and Communications in Medicine) format.

Definition Of The Markers

IFA[7] was defined as the angle between the line orthogonal to the vertical part of the forehead at the level of the synostosis of the nasal bone and the line joining the tip of the mentum to the most anterior point of the more protruding lip (Fig. 1). MNM angle[8] was defined as the angle between maxilla-nasion line and mandible-nasion line in the mid-sagittal section (Fig. 2), and the nasion[9] was defined as the most anterior point at the intersection of the frontal and nasal bone. FMA[10] was the angle between the line overlying the maxilla and the line across mentum tip and upper lip (Fig. 3). The FPL[9] was defined as the line that passed through the middle point of the anterior border of the mandible and the nasion. PL distance[9] was the perpendicular distance from the facial profile line (FPL) to the outer border of the forehead (Fig. 4).

Measurement of the markers

Fetal facial markers (IFA, MNM angle, FMA, PL distance) were measured through ViewPoint 6 software by two experienced sonographers, who had obtained the FMF certification for NT scan. The average value of each marker was taken after three measurements.

Statistical analysis

The analysis was performed by SPSS21.0 (Chicago, IL, USA) and Graphpad Prism8.0. The intraclass correlation coefficient (ICC) and Bland-Altman analysis[11] were used to assess intra-operator and inter-operator reproducibility. Bland-Altman mean and 95% limits of agreement (LOA) were constructed. The reference range of the data with a Gaussian distribution was expressed by mean ± 1.96standard deviation (SD). Pearson correlation analysis and univariate regression analysis investigated the correlation between fetal facial markers and CRL.

Results

Eventually 380 fetuses that met the inclusion criteria were selected. The average age of pregnant women was 28.86 ± 3.70 (range18 ~ 43) years old. The average CRL was 67.08 ± 6.14 (50 ~ 84) mm, and the average NT thickness was 1.80 ± 0.43 (0.7 ~ 2.8) mm. The distribution of cases of fetuses in each gestational week is shown in Fig. 5.

Evaluation Of Intra-operator And Inter-operator Agreement

Thirty ultrasonographic images in fetal facial mid-sagittal section were selected to evaluate the reproducibility and feasibility of the measurement. The ICCs (95% CI) of intra-operator 1 reproducibility of IFA, MNM angle, FMA, PL distance were 0.944 (0.886 ~ 0.973), 0.804 (0.629 ~ 0.902), 0.834 (0.68 ~ 0.918) and 0.935 (0.868 ~ 0.969), respectively. The ICCs (95% CI) of intra-operator 2 reproducibility of IFA, MNM angle, FMA, PL distance were 0.931 (0.857 ~ 0.967), 0.809 (0.637 ~ 0.904), 0.786 (0.600 ~ 0.892) and 0.906 (0.813 ~ 0.954), respectively. The ICCs (95% CI) of inter-operator reproducibility of IFA, MNM angle, FMA, PL distance were 0.885 (0.663 ~ 0.953), 0.829 (0.672 ~ 0.915), 0.77 (0.511 ~ 0.891) and 0.844 (0.68 ~ 0.925), respectively.

Table 1 and Fig. 6a-d, Fig. 7a-d, Fig. 8a-d showed the Bland-Altman analysis evaluating intra-operator and inter-operator the agreement of measurement of IFA, MNM angle, FMA and PL distance. The reproducibility of these markers for intra-operator and inter-operator was good.

Table 1
Intra-operator and inter-operator agreement of IFA, MNM angle, FMA and PL distance

	operator 1		**operator 2**		**operator 1 and 2**	
	mean	95%LoA	mean	95%LoA	mean	95%LoA
IFA	-0.02	-6.10 ~ 6.05	-0.95	-6.75 ~ 4.85	2.34	-4.57 ~ 9.25
MNM angle	-0.08	-1.71 ~ 1.55	0.24	-1.39 ~ 1.87	-0.068	-1.53 ~ 1.39
FMA	0.11	-5.14 ~ 5.36	-0.43	-6.11 ~ 5.26	-1.49	-6.94 ~ 3.97
PL distance	0.003	-0.47 ~ 0.48	-0.05	-0.58 ~ 0.48	0.14	-0.51 ~ 0.79

Correlation Between Fetal Facial Markers And Crl

The measurement range of IFA was 55.9°~107.89° (80.2°±7.25°). IFA had significant negative correlation to CRL during first trimester (IFA = 127.601−0.707*CRL,r=-0.598；$p < 0.001$). IFA was Gaussian distributed, and its reference range was 65.99°~94.41° (mean ± 1.96SD).

The measurement range of MNM angle was 1.66°~9.21° (4.17°±1.19°). The MNM angle had significant positive correlation to CRL during first trimester (MNM angle=-4.112 + 0.123*CRL,r = 0.547；$p < 0.001$). The MNM angle was Gaussian distributed, and the reference range of the MNM angle was 1.84°~6.50° (mean ± 1.96SD).

The measurement range of FMA was 56.29°~89.59° (75.36°±5.31°). FMA depended significantly on CRL (FMA = 55.683 + 0.293*CRL,r = 0.339；$p < 0.001$). FMA was Gaussian distributed, and the reference range was 64.95°~85.77° (mean ± 1.96SD).

The measurement range of PL distance was 1.53 ~ 4.37 mm (2.78 ± 0.54 mm). The PL distance decreased with CRL (PL distance = 5.136 − 0.035*CRL,r=-0.399；$p < 0.001$). The PL distance was Gaussian distributed, and its reference range was 1.72 ~ 3.84 mm (mean ± 1.96SD).

Discussion

Trisomy 21, also known as Down Syndrome (DS), was the most common chromosomal abnormality, which were accompanied by different degrees of mid-facial hypoplasia and skin edema[12, 13]. DS fetuses had typical facial features compared to euploid fetuses, including hypoplastic or absent nasal bones, thickened prenasal skin, shortening and dorsal displacement of the maxilla, et al[14]. Most fetuses with trisomy 18, the second most common chromosomal abnormality, had micrognathia[15] and CLP. The diagnosis of micrognathia was mainly subjective during second and third trimester. In the meanwhile, CLP was the most common facial malformation. Although it was not fatal, it had great adverse impact on children and families involved. Moreover, 54% of CLP may associated with other anomalies or genetic syndromes [16], affecting about 1 ~ 2/1000 live births[17]. In this study, multiple facial markers that reflected the relative position of the forehead, maxilla, and mandible were analyzed to establish their normal reference ranges, and these markers could further provide objective and quantitative criteria for the early detection of fetal facial anomalies and underlying genetic abnormalities.

The embryonic development of facial bones has its main characteristics. The maxilla and mandible begin to ossify from 8 weeks onward[18]. The maxilla is anatomically fused with the skull and grows forward with the development of brain tissue, while the mandible is connected to the skull through the temporomandibular joint. Therefore, the mandibular forward growth rate during first trimester is slower than that of the maxilla[19]. From 20 weeks onward, the maxilla ossification has almost completed, and the developing fetal swallowing function accelerates the growth of mandible. After that, the position of facial bones is relatively constant, then fetal facial profile is basically formed [20].

In 2002, Rotten et al. [7] first introduced the IFA to detect micrognathia. They found that the mean IFA of normal fetuses was 65.5°±8.13° at 18 ~ 28 weeks' gestation, and it was constant during pregnancy. Using 49.2° (average-2SD) as a cut-off point, the IFA had a sensitivity of 1.0, a specificity of 0.989 to predict micrognathia. IFA could reflect the anterior and posterior position between the mandible and frontal bone to evaluate micrognathia, which was often associated with some genetic anomalies, such as Pierre-Robin syndrome, Stickler syndrome, trisomy 18 and trisomy 13[1, 21, 22]. During first trimester, we found that the mean IFA of normal fetuses was 80.2 (SD 7.25) °, and it decreased with CRL. This value was larger than Rotten et al. [7]. The reason might be that the mandibular forward growth rate during first trimester is slower than that of the forehead. While during second trimester, the position of facial bones is relatively constant. In our study, the reference range of IFA was 65.99°~94.41°. When IFA was less than 65.7° (average-2SD), the possibility of micrognathia should be considered, which was helpful for the early detection of certain genetic syndromes. However, the clinical significance of this cutoff value needed to be confirmed by large abnormal sample from multi-centers.

The MNM angle could reflect the relative position of the maxilla and mandible, further to evaluate fetal facial profile. De Jong-Pleij et al. [8] reported that the mean MNM angle was 13.5° and did not change in second and third trimester, which was a sensitive indicator for evaluating micrognathia and CLP. Vos et al. [23, 24] reported that the MNM angle had a definite implication for trisomy 21 and trisomy 18. In our study, the mean MNM angle was 4.17 (SD 1.19) °, which increased with CRL. It was close to Ko et al. [25] study (4.7°±3.3°) but smaller than the Lu et al. [10] study (12.4°±2.2°). The reason might be racial differences. During first trimester, the maxilla and frontal bone are directly connected with the skull, the mandible grows forward more slowly than the maxilla and frontal bone, which may cause the MNM angle to increase with CRL. While during the second trimester, the ossification of the maxilla completes, and the development of fetal swallowing function accelerates the growth of the mandible and the formation of fetal facial profile, so the MNM angle does not change with gestational age. Further studies are necessary to investigate the relationship between the MNM angle and fetal facial abnormalities or chromosomal abnormalities.

In order to avoid the influence of the curvature of the vomer, Lu et al. [10] used the surface of anterior half of the maxilla as a reference line. FMA could directly reflect the relative position of the maxilla and mandible and be independent of other facial structures. Their research showed that FMA was related to gestational week, which increased with gestation slightly (1°~ 2°/week) from 16 weeks till 28 ~ 31 weeks and decreased minimally thereafter. It might be consistent with the allometric growth relationship between different parts of fetal face. We found that FMA increased with CRL, with the reference range of 64.95°~85.77°. Lu et al. [10] reported the cut-off value of FMA in detecting micrognathia was 66°, with the detection rate of 100% and false positive rate of 2.5%, which was similar to our study (64.95°). A large prospective cohort was needed to determine the diagnostic accuracy of FMA for micrognathia during first trimester.

De Jong-Pleij et al. [26] showed that the mean PL distance at 27 ~ 36 weeks' gestation was 2.8 (range 2.1 ~ 3.6) mm, and 4 mm could be used as the upper limit of the normal for judging frontal bossing. The PL distance was the first objective quantitative indicator to assess frontal bossing, which was affected by the position of the mandible, nasion and frontal bone. In our study, the mean PL distance was 2.78 ± 0.54 mm, and it decreased with CRL, which was consistent with Bakker et al. [9]. It might be caused by a forward movement of the maxilla and a decrease in convexity of the forehead during first trimester. Bakker et al. [9] also pointed out that the PL distance was not the best ultrasound marker for aneuploidies.

There were some limitations in our study. Firstly, static image randomly selected from first trimester ultrasound screening was to measure the NT thickness, not specifically to observe facial abnormalities. Secondly, all parameters were measured on 2D images, without the use of 3D reconstructed techniques. Some research [7, 14] showed that 3D technique could better obtain the true mid-sagittal section, but it took a long time. On the other hand, 2D ultrasound was the basis of 3D ultrasound. 2D measurements were reported to be the same reliable and accurate as 3D measurements in the measurement of facial marker[27, 28].

Conclusions

Intra-operator and inter-operator reproducibility for facial profile markers (IFA, MNM angle, FMA, PL distance) were good during first trimester (11 ~ 13^{+6} weeks' gestation). It's feasible to measure these markers during first trimester. The normal range of each marker was obtained through large sample data, and these markers were significantly related to CRL, which can provide objective and quantitative criteria for the early detection of fetal facial anomalies and chromosomal abnormalities.

Abbreviations

CLP	**cleft lip and palate**
CRL	**crown-rump length**
CVS	chorionic villus sampling
DICOM	Digital Imaging and Communications in Medicine
DS	Down Syndrome
FMA	facial maxillary angle
FMF	Fetal Medicine Foundation
FPL	facial profile line
ICC	intraclass correlation coefficient
IFA	inferior facial angle
ISUOG	International Society of Ultrasound in Obstetrics and Gynecology
LOA	Limits of agreement
MNM	maxilla-nasion-mandible angle
NT	nuchal translucency
PL	profile line distance
SD	standard deviation
2D-US	two-dimensional ultrasound
4D	four-dimensional

Declarations

The study was approved by the Ethics Committee of Suzhou Municipal Hospital (K2016038). Informed consents were obtained from all pregnant women. All authors of this paper have read and approved the final version submitted. The data used or analyzed during the current study are available from the corresponding author on reasonable request. The authors declare that there were no conflicts of interest in the drafting of this article.

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Figures

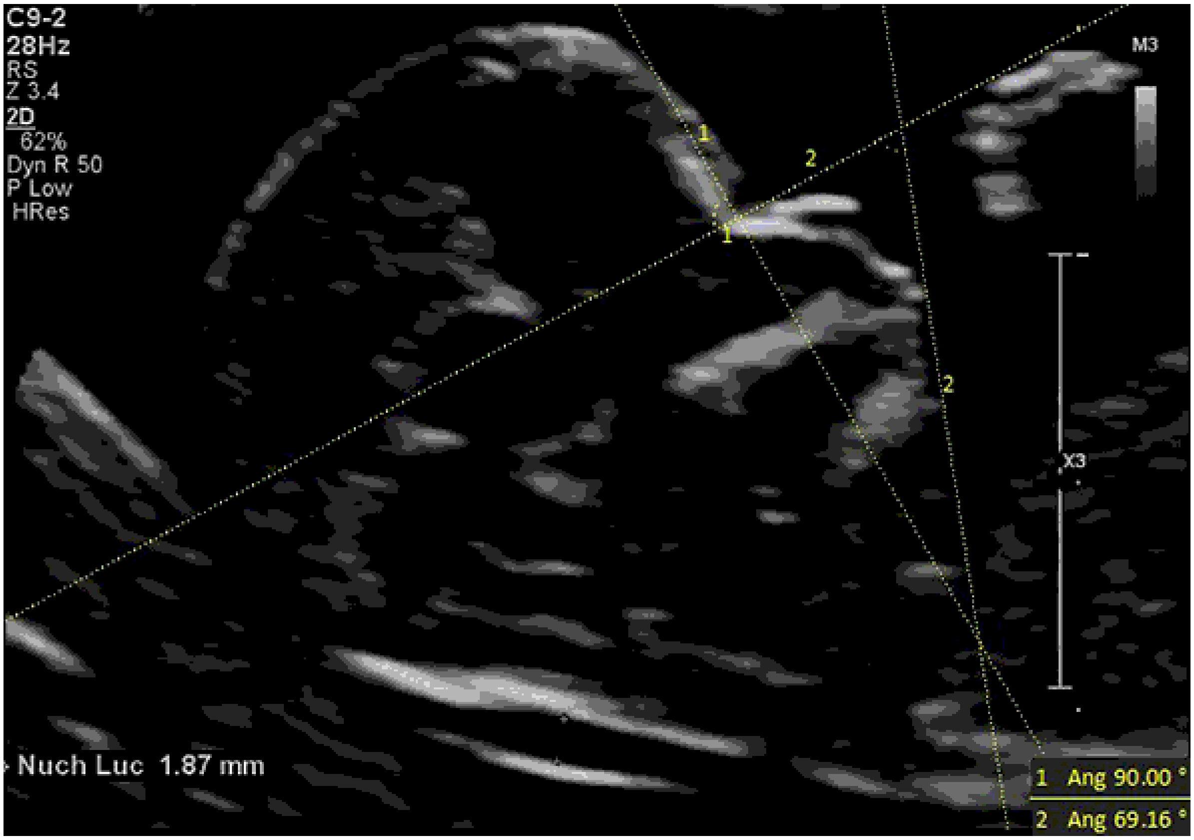

Figure 1

The measurement of IFA (69.16°)

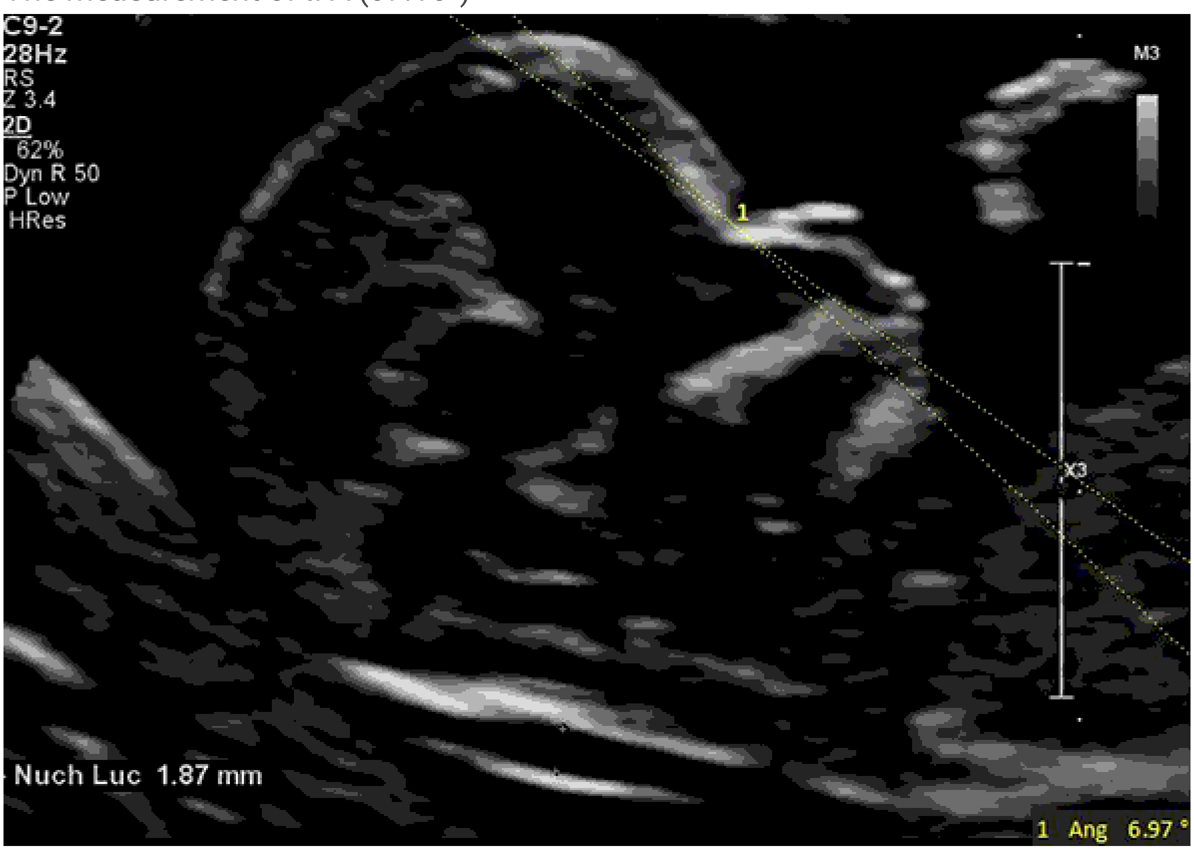

Figure 2

The measurement of MNM angle (6.97°)

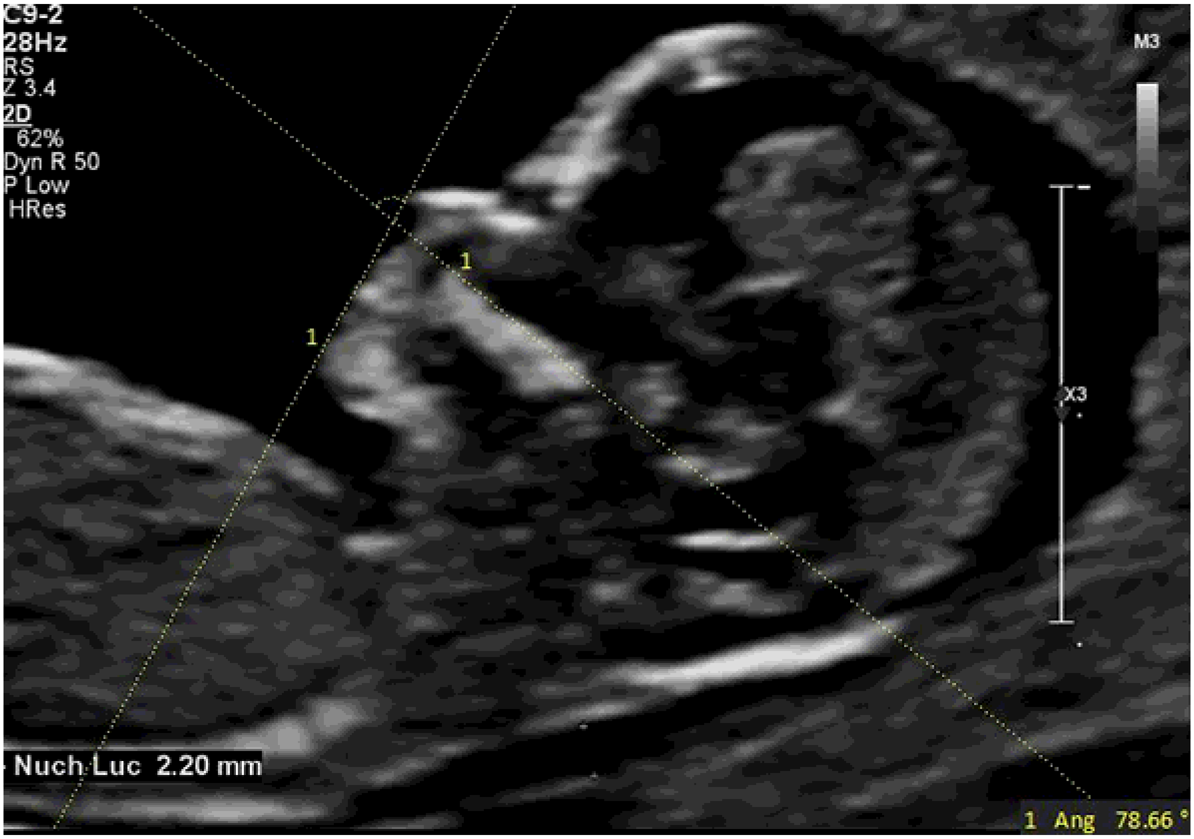

Figure 3

The measurement of FMA (78.66°)

Figure 4

The measurement of PL distance (3.3mm)

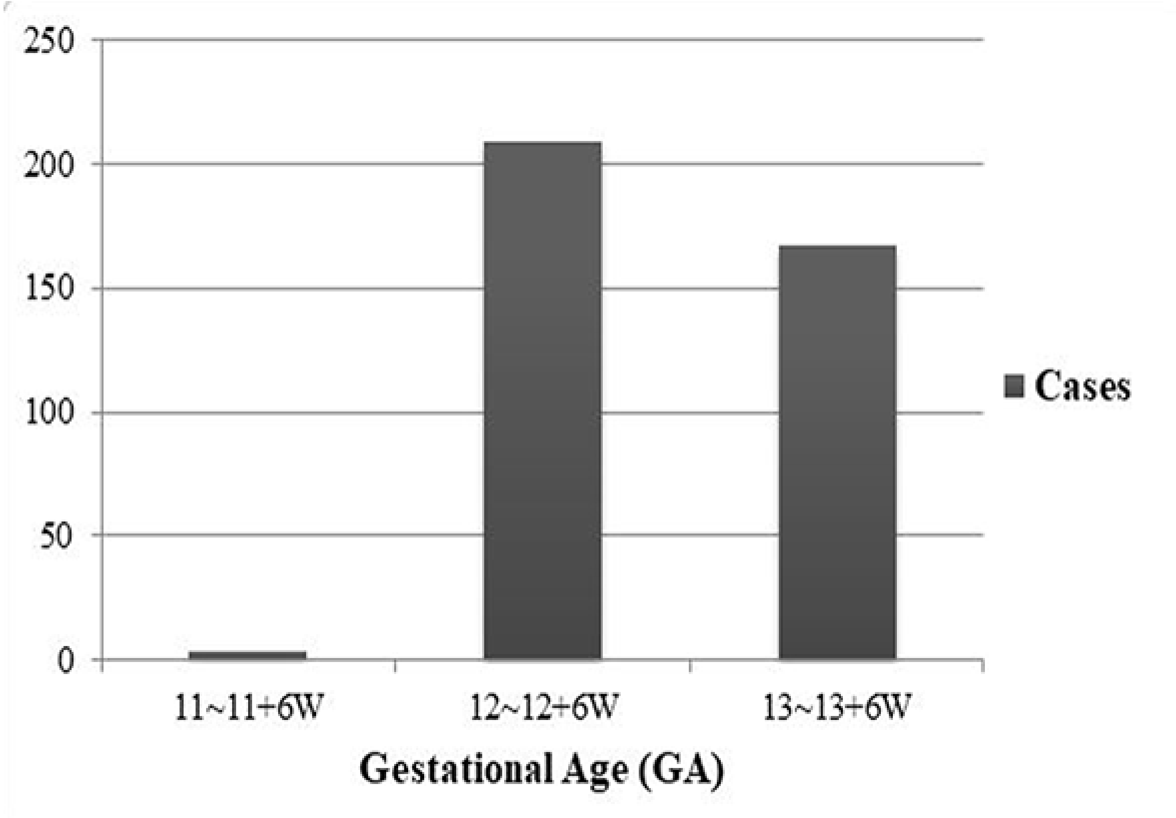

Figure 5

The distribution of the cases of fetuses in each gestational week

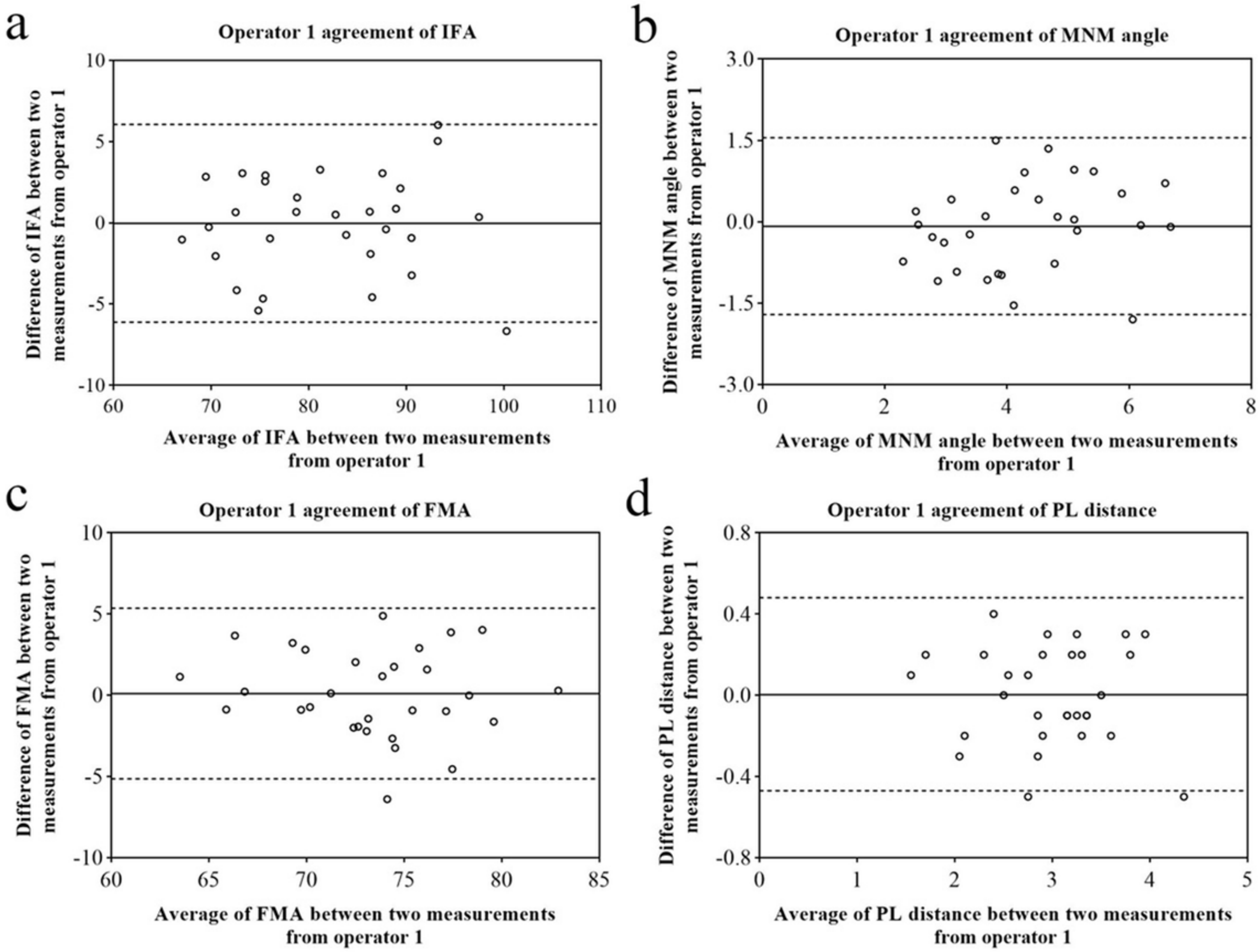

Figure 6

Operator 1 agreement in the measurement of IFA (a), MNM angle (b), FMA (c) and PL distance (d) solid line: the mean of the difference of the paired measurements; dotted line: 95%LOA of the difference

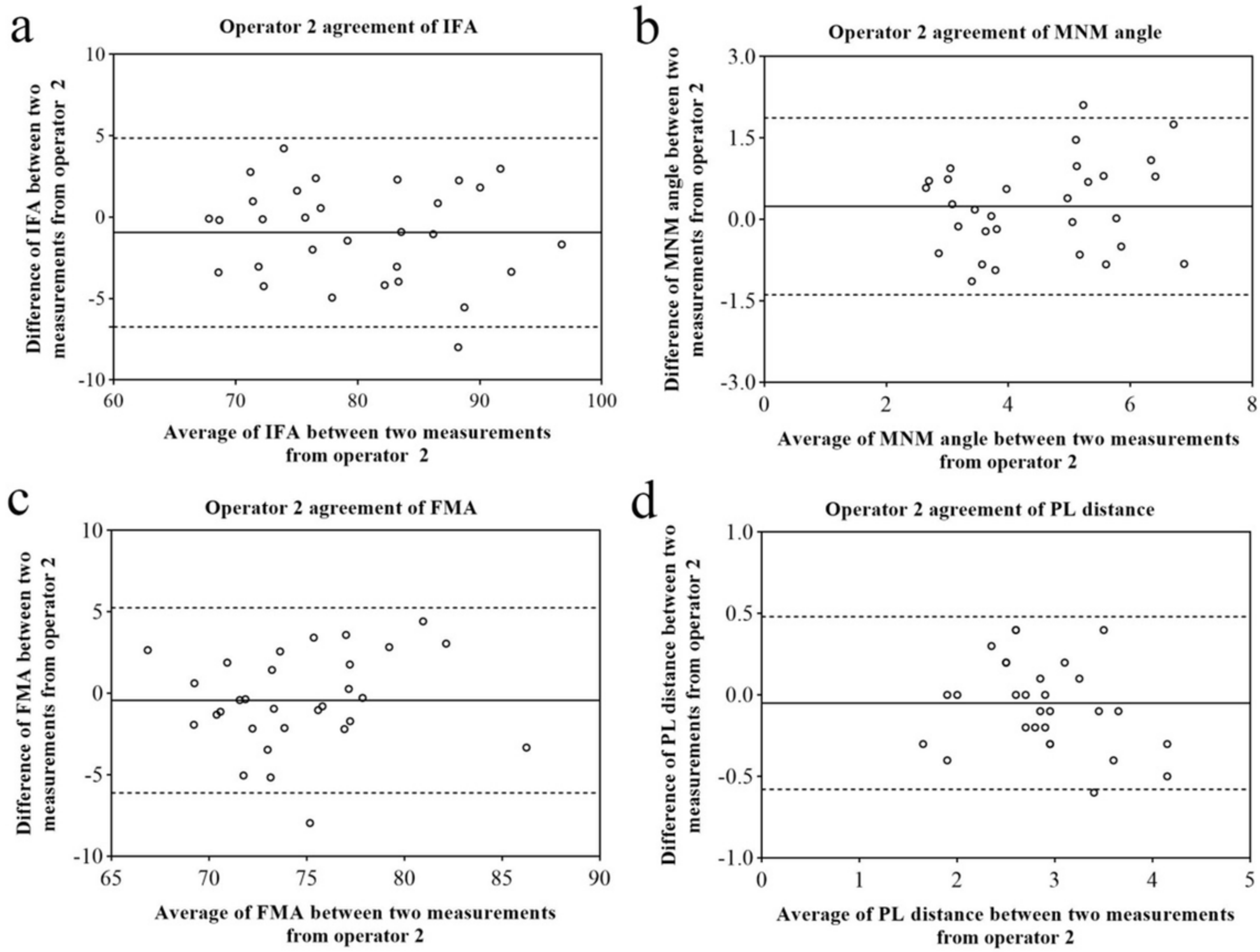

Figure 7

Operator 2 agreement in the measurement of IFA (a), MNM angle (b), FMA (c) and PL distance (d) solid line: the mean of the difference of the paired measurements; dotted line: 95%LOA of the difference

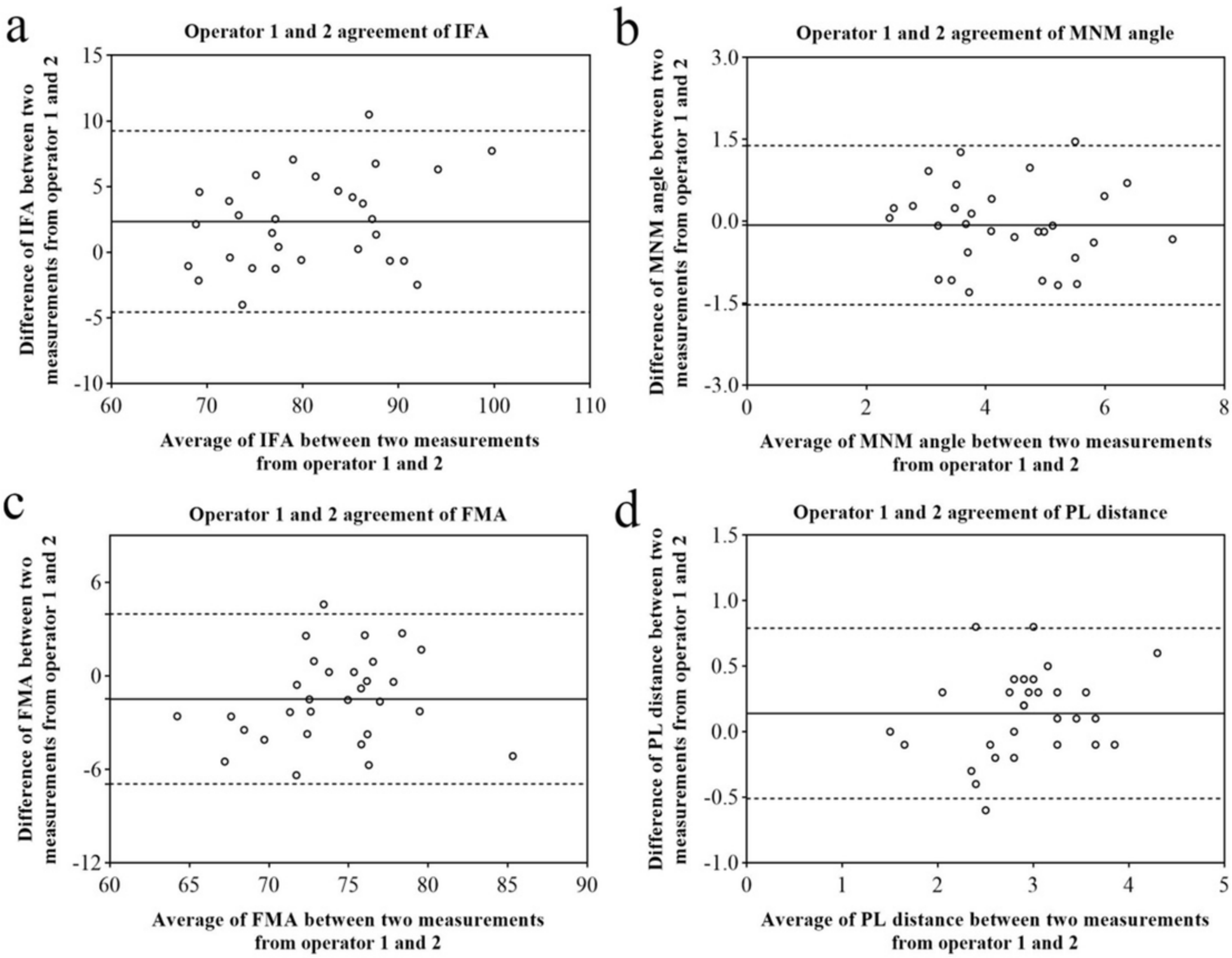

Figure 8

Operator 1 and 2 agreement in the measurement of IFA (a), MNM angle (b), FMA (c) and PL distance (d) solid line: the mean of the difference of the paired measurements; dotted line: 95%LOA of the difference