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Ultrasonography of fetal cleft lip and palate in first-trimester

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Summary

Purpose of Investigation: To explore the ultrasonographic methods towards cleft lip and palate (CLP) in first-trimester. *Materials and Methods:* 3,795 fetuses were scanned for facial structures including cross section of upper alveolar process, oblique coronal section of upper lip, and postnasal triangle section when measuring nuchal translucency (NT). The abnormal cases underwent ultrasonography for clear diagnosis at 17-18 gestational weeks (GWs), while the negative cases underwent systemic ultrasonography at 20-26 GWs, and followed up until birth. *Results:* Among the 3795 fetuses, 16 cases had CLP, with an incidence rate as 4.2%; 12 were detected in first-trimester, with a detection rate of 75%, and the detection rate of bilateral CLP was 100%, four were missed, with a misdiagnosis rate of 25%, and 12 cases examined at 17-18 GWs met first-trimester diagnosis. Among the four missed cases, two were diagnosed with systemic ultrasonography, and two were diagnosed postnatally. All cases were confirmed after induction of labor or after birth. *Conclusions:* Ultrasonography in first-trimester could diagnose severe case of CLP.

Key words: Cleft lip and palate; First-trimester; Congenital; Fetus; Ultrasonography.

Introduction

Fetal major organs would have been developed and formed before 12 gestational weeks (GWs), and more than 80% of fetal malformation would also be developed at this stage. With continuously improved resolution of ultrasonographic equipment and widely used nuchal translucency (NT) measurement technology, more and more fetal structural abnormalities could be diagnosed in first-trimester [1-3]. Fetal orofacial structures such as primary palate and others would be fully developed at nine GWs [4]. However, because fetal facial area is smaller in first-trimester, which could cause more difficulties towards ultrasonography, hence the related literature regarding ultrasound diagnosis of fetal cleft lip and palate (CLP) in this period were less [5-14]. In first-trimester, applying mandibular arch cross-section head side shifting method could obtain the images of cross section of upper alveolar process, oblique coronal section of upper lip, and postnasal triangle section.The present study aimed to investigate the values of this method towards fetal CLP screening in first-trimester.

Materials and Methods

3,672 pregnant women underwent NT examination in the present hospital from September 2012 to September 2013, with 123 cases of twin and a total of 3,795 fetuses, the oldest pregnant woman was 42 years of age, and the youngest pregnant woman was 23 years of age, with a mean age of 29 years, the GWs ranged from $11-13^{+6}$ weeks, with an average gestational weeks of 12^{+6} weeks, crown-rump length was 4.5−8.4 cm, with the average of 6.5 cm.

Color Doppler ultrasonic diagnostic apparatus were used, the probe frequencies were 3.5−5 MHz, and the NT examination condition in first-trimester were applied. The examination was performed by two experienced radiologists, with NT screening accreditation issued by Fetal Medicine Foundation (FMF), and in accordance with the standard methods developed by British Fetal Foundation. All abnormal cases were diagnosed by the co-examination of these two radiologists and the images captured were retained in the instruments for future comparative analysis. The pregnant women were placed in the supine position, underwent routine medical examination and measurement of whole fetal body. After measuring NT from fetal central sagittal standard section, the probe was rotated 90° clockwise or counterclockwise to obtain fetal mandibular arch cross-sectional image, the image was enlarged to make the target clear, in which the lower alveolar process was displayed as continuous complete arch with strong echo; parallelly shifted from this plane towards head side to obtain the cross-section of upper alveolar process, which was shown as upward continuous complete arch strong echo, while the arch angle was larger than the lower alveolar process, and the parallel hyperechoic line above it was the upper lip skin line. The probe was slightly shifted obliquely from this section towards fetal head side in order to obtain oblique coronal section of upper lip; upper alveolar process, upper lip skin line, and nose-tip skin line (with short stripped strong echo) were sequentially displayed from bottom to top. The probe was obliquely shifted from this plane again towards fetal head to obtain postnasal triangle section, which displayed left and right hyperechoic maxillary frontal process lines as the two sides of triangle, together with hard palate hyperechoic line as the bottom. Observations were made whether the echogenic lines in the above sections, lower alveolar process, upper lip and hard palate were continuously complete. As for the pregnant women with excessive anteflexion of uterus, they were asked to appropriately retain urine for the correction. As for the

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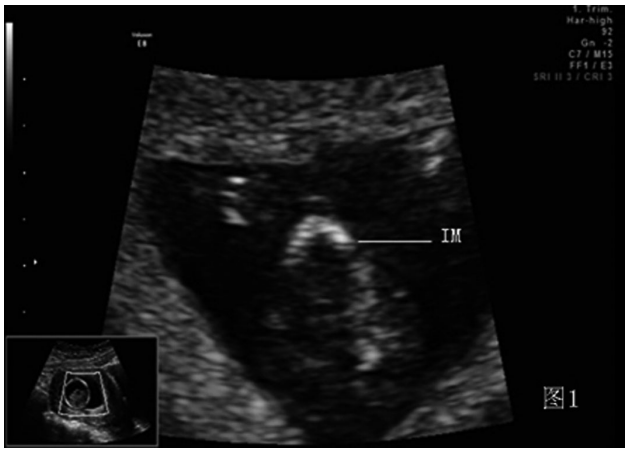

Figure 1. — Normal mandibular arch cross section.

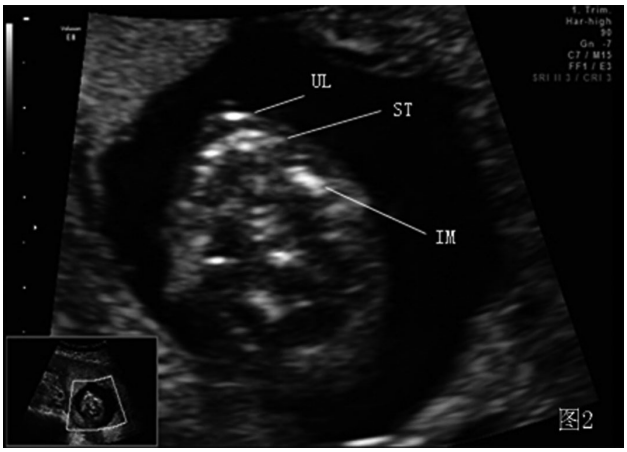

Figure 2. — Normal cross section of upper alveolar process.

patients unable to obtain standard sections, they were asked to rest for 20-30 minutes before repeating the examination; three-time unsuccessful examination was regarded failure. The examination time was control within 20 minutes.

Results

Among the 3,795 cases in this study, 3,732 cases displayed central facial structures, accounting for 98.3% (3,732/3,795), and among these 3,732 cases, displaying rate of fetal mandibular arch cross-section was 100% (3,732/3,732), while those of upper alveolar process cross section, upper lip oblique coronal section, and postnasal triangle were all 96.8% (3,613/3,732).

Among the 3,795 cases in this study, a total of 16 cases had CLP, with the incidence rate as 4.2%, including 13 cases of cleft lip and upper alveolar process or (and) palate, 81.2% (six cases were bilateral and six cases were unilateral), one case of central CLP, two cases of cleft lip alone, accounting for 12.5%, one case of cleft soft palate alone, accounting for 6.3%.

First-trimester examination detected out 12 cases of cleft lip and alveolar process or (and) palate, with the detection rate as 75% (12/16); six cases were bilateral (one case was associated with nasal bone deficiency, and one case was associated with multiple malformations), the detection rate was 100% (6/6); five cases were unilateral (one case was associated with nasal bone deficiency), the detection rate was 80% (5/6), one case of median lip and palate (full forebrain), the detection rate was 100% (1/1). Twelve cases were repeated ultrasonography at 17-18 GWs and in line with first-trimester diagnosis, all patients selected to terminate pregnancy, and all case were confirmed as cleft lip and upper alveolar process or (and) palate after abortion.

Four cases were missed, without other associated structural abnormality. Two cases were diagnosed with systemic ultrasonography in mid-pregnancy period (one case of II° cleft lip, one case of II° cleft lip and upper alveolar process), and confirmed after birth; two cases were diagnosed after birth (one case of I° unilateral cleft lip, one case of cleft soft palate alone). Twelve out of 16 cases of CLP were not associated with other structural abnormality, accounted for 75% (12/16).

The detection sensitivity and specificity of CLP in first-trimester were 75% and 100%, respectively, with positive predictive value of 100%, and negative predictive value of 99.8%. The detection rate of CLP in first-trimester was 75%, with missed-diagnosis rate as 25%.

Discussion

CLP is the most common facial abnormality, with the incidence rate in Chinese newborns of about 1.67% [15], ranking third among all kinds of congenital malformations following congenital heart disease and multi-finger (toe) malformation. In this group, the fetal incidence rate was 4.2%, higher than that in newborns. Kraus *et al.* [16] described the incidence of CLP accounted for 11.5% of spontaneously aborted fetuses before eight GWs, and 1.8% in 6~19 GW fetuses; about 0.16% live infants had CLP at birth. The above information showed that the incidence of CLP in fetuses was higher than in newborns. CLP might occur alone, or coexist with other malformations; currently, it had been found that CLP might appear in more than 180 genetic syndromes [17]. Lip and palate would be formed at 5-12 GWs of embryo, if spherical process, bilateral maxillary processes, and median nasal process could not fuse mutually in this period, it might lead to the occurrence of CLP, which would not only affect the appearance, but also cause dysfunctions in sucking, chewing, swallowing, and language, therefore, prenatal diagnosis of CLP has great importance.

Currently, diagnosing fetal CLP mainly relies on 2D ultrasonography to scan lip coronal section, upper alveolar

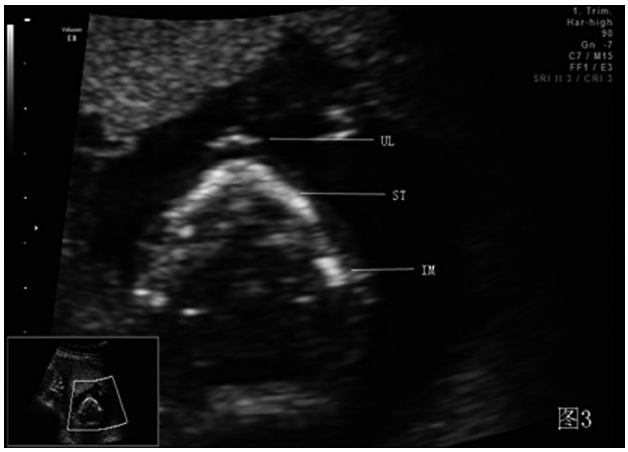

Figure 3. — Normal oblique coronal section of upper lip.

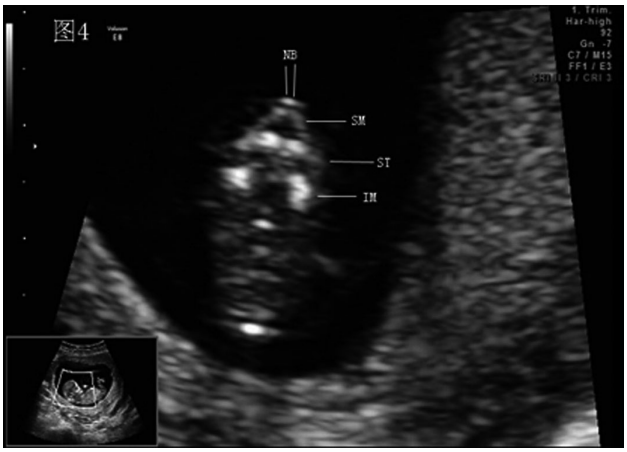

Figure 4. — Normal postnasal triangular section.

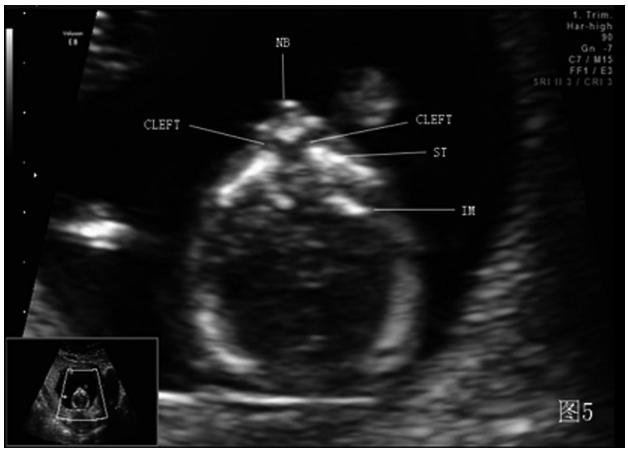

Figure 5. — Discontinuity of alveolar process displayed in the cross section of bilateral CLP alveolar process.

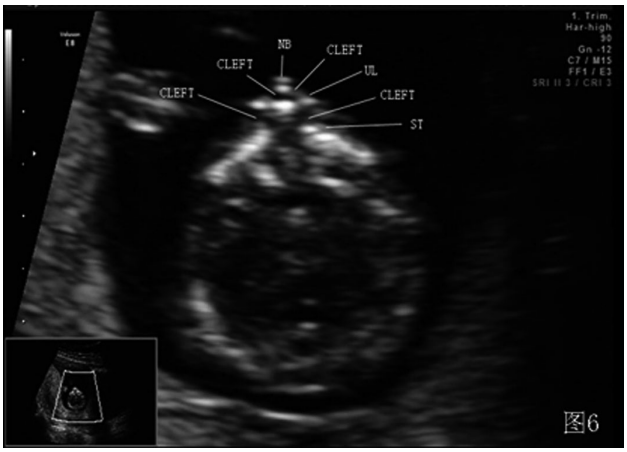

Figure 6. — Upper lip and upper alveolar process displayed in the oblique coronal section of bilateral CLP.

process cross-section, and facial median sagittal section in middle and advanced pregnancy [18]. Because fetal facial area is smaller in first-trimester, which could cause more difficulties towards ultrasonography, hence the related literature regarding ultrasound diagnosis of fetal CLP in this period were less. Picone *et al.* [5] reported the application of prenatal ultrasonographic specific signs in diagnosing two cases of fetal bilateral CLP, with the gestational ages as 10 and 12.5 GWs. Gullino *et al.* [7] performed transvaginal ultrasonography to diagnose one case of fetal bilateral CLP (11+5 GWs). Ghi *et al.* [8] used 3D ultrasonography and diagnosed one case of fetal bilateral CLP with 64-mm crown-rump length. Borenstein *et al.* [19] showed that among 23 cases of fetal 13 trisomy, nine were detected with CLP in first-trimester. Martinez-Ten *et al.* [11] used facial 3D volumetric data acquired to screen 240 fetuses in first-trimester, and diagnosed nine cases of primary cleft palate (false-positive rate as 0.9%), six cases of secondary cleft palate (one case was missed). In 2010, Sepulveda *et al.* [10] firstly proposed that postnasal triangle (hyperechoic triangle formed by bilateral maxillary frontal process and palate displayed in postnasal coronal section) could be used to effectively screen fetal cleft palate in first-trimester, and the ultrasound displaying rate of this postnasal triangle could reach 98.0%. Thereafter, the roles of postnasal triangle in screening fetal facial abnormalities in first-trimester had been increasingly considered [12-14, 20].

In the present study, the mandibular arch cross-section head side shifting method was used to sequentially display the cross section of upper alveolar process, oblique coronal section of upper lip, and postnasal triangle to screen CLP in first-trimester. The displaying rate of mandibular arch cross-section was 100%, and those of cross section of upper alveolar process, oblique coronal section of upper lip, and postnasal triangle were 96.8% (each normal section is shown in Figures 1-4). It was previously reported that 50%

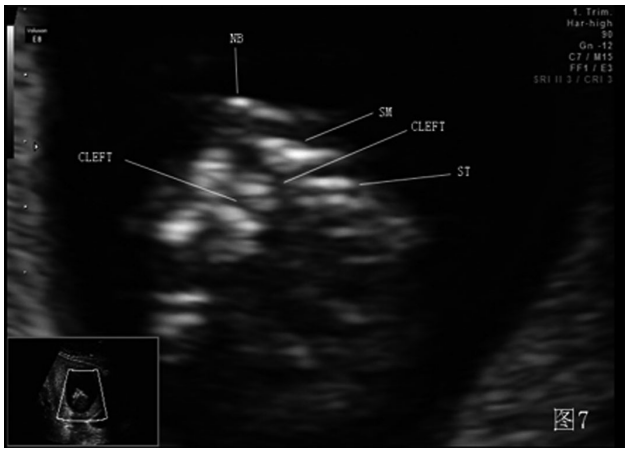

Figure 7. — Discontinuity of hyperechoic line displayed in the postnasal triangular section of bilateral CLP.

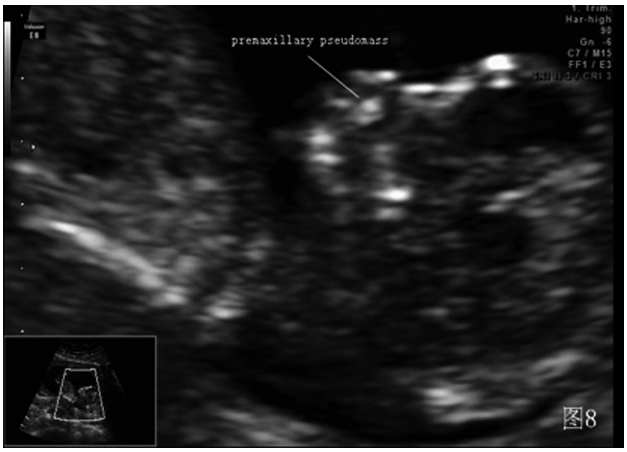

Figure 8. — Premaxillary pseudomass displayed in the median sagittal section of bilateral CLP. NB: nasal bone; SM: supermaxilla (maxilla); IM: inferior maxilla (mandible); ST: superior teeth (inferior alveolar); UL: upper lip (upper lip); CLEFT: cleft; premaxillary pseudomass: premaxillary pseudomass.

of CLP was cleft lip associated with cleft palate: about 25% was cleft lip alone and about 25% was cleft palate alone. In the present study, 81.2% was cleft lip and upper alveolar process or (and) palate, 12.5% was cleft lip alone, and 6.3% was cleft palate alone, which might be related to the small sample size. The ultrasonographic manifestations of CLP in first-trimester were upper alveolar process cross section, upper lip oblique coronal section, and postnasal triangle exhibited the discontinuity of hyperechoic lines in upper alveolar process, upper lip, and primary palate (Figures 5-7), respectively. This study showed that the detection rate of CLP in first-trimester was 75%, while those of bilateral and median CLP were both 100%. Bilateral CLP would exhibit the discontinuity of bilateral hyperechoic lines in upper alveolar process, upper lip, and hard palate from all the above three sections, while the central part of upper lip and palate protruded forward and formed premaxillary pseudomass. Maxillary pseudomass is a more reliable and better manifestation than cleft, and all cross and sagittal sections could display maxillary pseudomass (Figure 8). Bilateral CLP had greater facial anatomic structural abnormalities, therefore, it might be easily diagnosed in first-trimester. Median cleft lip accounted for about 0.5% of all cases, and often related with anterior whole brain or mouth-face-finger syndrome, with lip and upper middle palate deficiency, and larger split, therefore, it would be difficult to be diagnosed in first-trimester. Bilateral CLP and median CLP are more serious types, so early diagnosis would be of greater importance.

Analysis of missed cases. One case was II° cleft lip and upper alveolar process, while the cleft upper alveolar process purely exhibited as irregular upper alveolar process line (oblique cleft), while the continuity of upper alveolar process was not interrupted, therefore, this case was missed in first-trimester. One case was II° cleft lip alone, due to small fetus in first-trimester, lip soft tissues were thin, and the displaying difficulty led to missed-diagnosis. One case of I° cleft lip alone only showed lip pressure trace, therefore it was diagnosed after birth. One case of cleft soft palate alone was missed because all sections in this study could not display soft palate.

In conventional 2D ultrasonography in late pregnancy, since secondary palate would exhibit as a concave and would be occluded by the acoustic shadow of upper jaw; the detection rate of cleft palate alone, especially secondary cleft palate would be very low [21]. Campbell [22] proposed that because ossification of fetal maxillary bone in first-trimester is still poor, it would not block the palate, and at this time, the secondary palate is a plane; the characteristics might facilitate observers using 3D multi-plane ultrasonography to acquire the axial section of the palate, thereby improving the detection rate of secondary cleft palate. The present authors would also further evaluate this plane in future studies.

The facial displaying rate in the present study was 98.3%, and the main reasons of unclear facial displaying were poor fetal position, active fetal actions, hyperextension of fetal head, and maternal obesity.

The present study proposed the mandibular arch cross section head side shifting method for the first time in China and abroad to sequentially display the cross section of upper alveolar process, oblique coronal section of upper lip and postnasal triangle to screen CLP. The structures were displayed from simple to complex, and beginners could have a good gradual understanding process, so it would simple for them to grasp. Cleft inferior lip and alveolar process is rare, so alveolar process would usually be displayed as one normal section, hence the suspected cases of cleft upper alveolar process could be used as references for repeated comparison until obtaining correct diagnosis. In

this study, the screening method of CLP in first-trimester was simple, fast, effective and simple to master, so it should be widely applied.

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