Evaluation of the Accuracy of Prenatal Ultrasound Assessment of Facial Clefts

Yuki YK LAM, MBBS, MRCOG
Department of Obstetrics and Gynaecology, United Christian Hospital, Kwun Tong, Hong Kong
William WK TO, MBBS, MPhil, MD, Dip Med, FRCOG, FHKAM (O&G)
Department of Obstetrics and Gynaecology, United Christian Hospital, Kwun Tong, Hong Kong

Objective: To evaluate the accuracy of two-dimensional and three-dimensional ultrasound in the diagnosis of facial clefts, and particularly in predicting the presence or absence of associated alveolar cleft / cleft palate in the presence of cleft lip.
Methods: All cases of facial clefts diagnosed before 24 weeks over a 5-year period from 2009 to 2013 in a single obstetric unit were reviewed. The findings from conventional two-dimensional ultrasound scanning and three-dimensional ultrasound imaging, using the reverse face view, oblique face view, or other modified techniques were compared with the findings at postnatal examination of the babies or at pathological examination of the fetuses after termination of pregnancy. The degree of accuracy of prenatal diagnosis of cleft lip alone, or cleft lip with alveolar cleft / cleft palate was determined.
Results: A total of 42 cases were analysed. There were 35 unilateral, six bilateral, and one median cleft lips. Three cases involved a fetus of a monochorionic twin pair, and one case involved a fetus of a dichorionic twin pair. Associated structural abnormalities were detected by antenatal ultrasound in five cases, and significant karyotype abnormalities were detected in four cases. Termination of pregnancy was performed in 13 cases. There were 12 cases with cleft lip only, six cases with cleft lip with associated alveolar cleft, and 24 cases with cleft lip and palate. There were five cases where antenatal ultrasound overdiagnosed the severity of the cleft, while in three cases the extent of the cleft was underdiagnosed, giving an overall accuracy of 81%. The most common discrepancy was in the overdiagnosis or underdiagnosis of alveolar clefts, whereas there were no errors concerning the side of the cleft. When only the antenatal diagnostic accuracy of presence or absence of palate clefts was calculated, the overall accuracy was 95% (40/42; Phi value, 0.91).
Conclusion: The accuracy of prediction of the presence or absence of cleft palate in the presence of cleft lip was high, but the prediction of alveolar clefts was most prone to error. The limitations of such ultrasound predictions should be explained to parents at the time of antenatal counselling.
Hong Kong J Gynaecol Obstet Midwifery 2015; 15(1):46-52

Keywords: Cleft lip; Cleft palate; Imaging, three-dimensional; Ultrasonography

Introduction

Facial clefts are among the most common congenital fetal abnormalities. The overall prevalence of facial clefts has been reported to be between 1:500 and 1:1000 live births in various studies[1,2]. Facial clefts, or orofacial clefts, refer to cleft lip (CL), cleft lip with associated alveolar cleft (CLA), cleft lip and palate (CLP), and cleft palate (CP). The prevalence of these different types of clefts has been reported to be 0.29/1000 (CL), 0.48/1000 (CLP), and 0.31/1000 (CP)[3,4]. Mid-trimester ultrasound (USG) screening for facial clefts has been instituted in many different countries, and different authorities have also established guidelines for fetal morphology USG to detect these abnormalities[5,6]. However, screening of isolated CP has not been included in such protocols and the assessment of CP or alveolar clefts in the presence of other facial clefts is not detailed in such guidance.

Antenatal USG imaging of the fetal palate has improved in recent years with the use of advanced techniques using two-dimensional (2D) or three- or four-dimensional (3D / 4D) USG[7-12]. The improved detection and assessment of CP is mainly focused on those fetuses with associated CL, while in general, the detection of isolated CP without CL is still a rare event[13,14]. In addition, errors of varying degrees in the reporting of these facial clefts are not uncommon[15,16] and may influence the counselling given to the prospective parents.

This retrospective study in a local regional obstetric unit aimed to determine accuracy in predicting clefting of the alveolar bone or hard palate in the presence of CL

Correspondence to: Dr William WK To
Email: towkw@ha.org.hk

using current 2D and 3D / 4D USG techniques, as well as to assess performance against that reported in the literature.

Methods

A retrospective review of all cases of facial clefts diagnosed before 24 weeks' gestation over a 5-year period from 2009 to 2013 in a single obstetric unit were reviewed, based on the prenatal diagnosis registry of the department and a comprehensive obstetric database currently in use in all public obstetric units in Hong Kong. Within the study period, all patients detected to have facial clefts were referred to the prenatal diagnosis clinic for assessment by an accredited maternal-fetal-medicine subspecialist. The subspecialist routinely performed detailed USG to look for associated structural abnormalities, and also used conventional 2D USG and other 3D USG techniques, such as the reverse face view[7], flipped face view[8], oblique face view[9,10], or other modified views as appropriate or feasible, in an attempt to verify the extent and type of facial cleft. All USG examinations were carried out using either the Voluson 730 Expert or the Voluson E6 system (GE Healthcare, Wisconsin, US) and image volumes were obtained with a 4-8 MHz RealTime 4D curved array abdominal probe (GE Healthcare, Wisconsin, US), via a parasagittal section of the fetal head. Multi-slice techniques were not used in this series. Stored image volumes were processed with 4D View PC software (GE Healthcare, Wisconsin, US). The patient was counselled on the need for karyotyping by amniocentesis according to the findings, and in regard to their decisions on the subsequent management of the pregnancy. A joint 'cleft clinic' consultation, with the presence of the obstetric team, the neonatal team, the paediatric surgical team, and the maxillofacial and dental team was available for patients who wished to have more information and discussion on postnatal management plans and the long-term outcome for these babies.

The case notes, USG reports and stored images and volumes, if any, of each of the identified cases were reviewed in detail. The antenatal findings and provisional diagnosis that was given to the patient / couple at that stage for counselling were compared with the findings at the postnatal examination after birth, or at pathological examination of the fetus after termination of pregnancy. The degree of accuracy of antenatal predictions was determined, and the original diagnoses were then classified into either correct diagnosis, underdiagnosis, or overdiagnosis.

Results

Within the study period, there were a total of 24,978 deliveries. The overall incidence of facial clefts was 0.2% (n = 50). Of these cases, two did not have antenatal USG assessment and the clefts were diagnosed only after birth, while for one case, the antenatal routine morphology scan failed to detect a left CL, which was subsequently only detected on a repeat scan in the third trimester. Another two cases underwent antenatal assessment by their own obstetricians and were referred to our unit for delivery care only after 24 weeks. In addition, three had isolated CP without associated CL and were not diagnosed during the antenatal period; of these, one had associated congenital cardiac malformation and another had gastroschisis. The six undetected cases and the two referred cases were excluded from our analysis. The overall antenatal detection rate of facial clefts before 24 weeks in this cohort, including the two referred cases, was 88% (44/50).

The final cohort for analysis consisted of 42 cases, including 35 unilateral and six bilateral CLs as well as one median cleft. Three cases involved a fetus of a monochorionic-diamniotic twin pair, and one case involved a fetus of a dichorionic-diamniotic twin pair. Associated structural abnormalities were detected by antenatal USG in five cases, and significant karyotype abnormalities were detected in four cases. Termination of pregnancy was performed in 13 (31%) of the cases, and there was one case of stillbirth at around 35 weeks (case 14). There were 12 (29%) cases with CL only, six (14%) with CLA, and 24 (57%) with CLP (Tables 1 and 2). There were five cases where antenatal USG overdiagnosed the severity of the cleft, while three cases were underdiagnosed, giving an overall accuracy of 81% (34/42) [Table 2]. The most common discrepancy was in the overdiagnosis or underdiagnosis of CLA, with four of eight errors in diagnosis having a final diagnosis of cleft alveolar bone. There were no errors in diagnosing the side of the cleft. While all true palatal clefts were diagnosed on antenatal assessment, there were two false-positive diagnoses (cases 25 and 30). In a fetus with a unilateral CLP, the initial USG assessment showed an obvious left CL with associated CLP and a suspicious dimple CL on the right side (case 36). However, repeat USG at the time of amniocentesis within 1 week was able to exclude bilateral clefts, and so the USG diagnosis was considered correct. When only the antenatal diagnostic accuracy of presence or absence of CP was calculated, the overall accuracy was 95% (40/42, Phi, 0.91), giving a specificity of 88.8% and a sensitivity of 100% for the detection of CPs in the presence of CLs in this cohort (Table 3[13]).

Table 1. Clinical characteristics of the cohort (n=42)

	Antenatal diagnosis	Definitive diagnosis	Associated abnormalities	Karyotype abnormalities	Outcome	Diagnostic accuracy
1	Right CL	Right CL	Partial absence of corpus callosum	46,XY,del7q31.3-q34	TOP	
2	Left CLP	Left CLP	One of DCDA twins	Normal	LB	
3	Right CLP	Right CLP		Normal	LB	
4	Right CLP	Right CLP		Normal	LB	
5	Left CLP	Left CLP		Normal	LB	
6	Left CLA	Left CL		Normal	LB	Overdiagnosis
7	Right CLP	Right CLP		Normal	LB	
8	Left CL	Left CLA		Normal	LB	Underdiagnosis
9	Bilateral CLP	Bilateral CLP	One of MCDA twins; stillbirth of co-twin	Normal	LB	
10	Left CLP	Left CLP		Normal	LB	
11	Left CLP	Left CLP		Normal	TOP	
12	Left CLP	Left CLP		Normal	LB	
13	Left CL	Left CLA		Normal	LB	Underdiagnosis
14	Left CLP	Left CLP	One of MCDA twins	Normal	SB	
15	Left CL	Left CL		Normal	LB	
16	Left CLP	Left CLP		Normal	TOP	
17	Right CLP	Right CLP		Normal	LB	
18	Left CLA	Left CLA		Normal	TOP	
19	Right CL	Right CL		Normal	LB	
20	Right CLP	Right CLP		Normal	TOP	
21	Right CL	Right CL		Normal	LB	
22	Left CLA	Left CLA		Normal	LB	
23	Bilateral CLP	Bilateral CLP	Multiple malformations	46,XX,18q-	TOP	
24	Bilateral CLP	Bilateral CLP		Normal	LB	
25	Left CLP	Left CL		Normal	TOP	Overdiagnosis
26	Bilateral CLP	Bilateral CLP		Normal	LB	
27	Right CLA	Right CL		Normal	LB	Overdiagnosis
28	Right CL	Right CL		Normal	LB	
29	Left CLP	Left CLP		Normal	LB	
30	Left CLP	Left CL	Tetralogy of Fallot	Normal	TOP	Overdiagnosis
31	Left CL	Left CL		Normal	TOP	
32	Median CLP	Median CLP	Omphalocoele, limb deformities	Trisomy 18	TOP	
33	Right CLP	Right CLP	One of MCDA twins; hydropic co-twin	Normal	LB	
34	Right CL	Right CL		Normal	LB	
35	Left CLP	Left CLA		Normal	LB	Overdiagnosis
36	Left CLP	Left CLP		Normal	LB	
37	Left CLP	Left CLP		Normal	TOP	
38	Left CL	Left CLA		Normal	LB	Underdiagnosis
39	Bilateral CLP	Bilateral CLP		Normal	TOP	
40	Left CL	Left CL		Normal	LB	
41	Left CLP	Left CLP		Normal	LB	
42	Bilateral CLP	Bilateral CLP	Overlapping fingers, CPC	Trisomy 18	TOP	

Abbreviations: CL = cleft lip; CLA = cleft lip with associated alveolar cleft; CLP = cleft lip and palate; CPC = choroid plexus cyst; DCDA = dichorionic-diamniotic; LB = live birth; MCDA = monochorionic-diamniotic; SB = stillbirth; TOP = termination of pregnancy

Table 2. Characteristics of facial clefts and antenatal ultrasound prediction

Characteristic	Cleft lip (n=12)	Cleft lip with associated alveolar cleft (n=6)	Cleft lip and palate (n=24)
Type of cleft			
Unilateral	12	6	17
Bilateral	0	0	6
Median	0	0	1
Outcome of pregnancy			
Termination of pregnancy	4	1	8
Stillbirth	0	0	1
Live birth	8	5	15
Twin pregnancy	0	0	4
Associated structural abnormalities	2	0	3
Chromosomal abnormalities	1	0	3
Antenatal ultrasound diagnosis			
Lip cleft	8	3	0
Lip cleft with alveolus	2	2	0
Lip cleft with palate	2	1	24
Accuracy of antenatal ultrasound diagnosis			
Correct	8	2	24
Overdiagnosis	4	1	0
Underdiagnosis	0	3	0

Table 3. Antenatal ultrasound prediction of presence or absence of associated palate clefts*

	Antenatal ultrasound diagnosis		
	CLP	No palate cleft (CL and CLA)	Total
CLP	24[a]	0[b]	24
No palate cleft (CL and CLA)	2[c]	16[d]	18
Total	26	16	42

Abbreviations: CL = cleft lip; CLA = cleft lip with associated alveolar cleft; CLP = cleft lip and palate

* Degree of association (Phi) between antenatal and postnatal diagnosis of CLP versus no CLP[13]: (ad–bc) / √(a+b)(a+c)(d+b)(d+c), i.e. (24 x 16 – 0) / √(24 x 26 x 16 x 18) = 384 / 423.9 = 90.5%, p<0.001

Discussion

The overall detection rate of facial clefts by mid-trimester USG in this series was comparable to that reported in the literature[1,2,13]. There were apparently no false-positives and the specificity for detection of cleft lip approached 100%. The accuracy of detection of CP in the presence of CL was also comparable to results reported in the literature[13,15,17], with an overall accuracy of around 95%. Half of the cases of underdiagnosis or overdiagnosis related to the diagnosis of alveolar ridge clefts.

The performance of screening USG in the detection of facial clefts has been observed to progressively improve over the years in several studies. This improvement has been associated with improvements in USG techniques and training of sonographers. In a survey of all orofacial clefts referred to a specialist centre in Glasgow, it was reported that the antenatal detection rate had increased from 11% in 1999 to over 50% in 2008. The increased use of routine USG for anomaly screening was shown to significantly improve the detection rates when compared with scanning high-risk pregnancies only[18]. In another Norwegian study, the detection rate was observed to increase from 34% in 1987-1995, to 58% in 1996-2004[13]. In a recent prospective

screening study of 35,000 low-risk women and 2800 high-risk women in the Netherlands, the overall detection rate of facial clefts was 88%[19]. Our calculated detection rate of facial clefts of 88% in this retrospective cohort was in line with the high detection rates reported in the literature[17,19,20]. However, where the fetal lip is normal, midline CP is almost never diagnosed on antenatal assessment unless there is clinical suspicion arising from the family history, and expert USG is carried out specifically to look for hard and soft palate clefts. Our experience concurs with various studies that have reported very low or zero detection rates of isolated CPs in the absence of lip clefts, even in the presence of other structural abnormalities[19,21].

The accuracy of diagnosing the presence or absence of CP when CL is detected is important for counselling parents. The existence of CP would imply additional surgical procedures to repair the CP in addition to the CL[21,22], as well as a higher rate requiring further surgery, and audiology and orthodontic services well into the teenage years[22]. Therefore, various 3D USG techniques have been advocated for the evaluation of facial clefts. In this study, when CL was diagnosed, our team commonly used a 2D transverse view starting at the level just below the nasal septum[23] to directly visualise the integrity of the alveolar ridge and the maxilla. This was commonly supplemented by the use of 3D volumes, which employ the flipped face[8] or angulated views[9] approach to visualise the alveolar ridge and hard palate (Figure). However, there was no preset protocol and the sonographer was free to

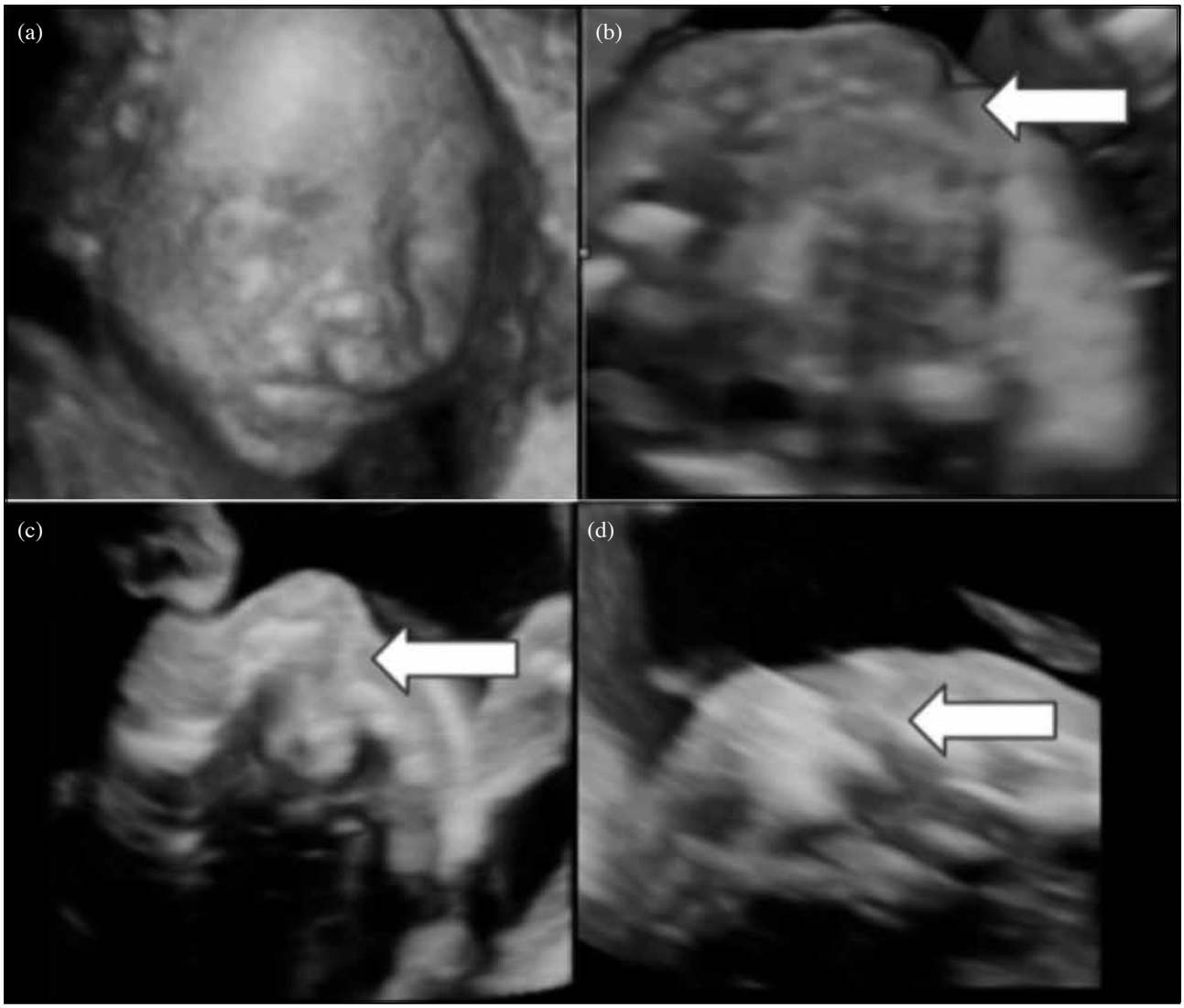

Figure. Cleft lip, alveolar cleft, and cleft palate as visualised by 3-dimensional (3D) ultrasound (USG) surface-rendered images: (a) facial cleft as seen by 3D USG; (b) cleft lip with intact alveolar ridge (arrow); (c) associated alveolar cleft as visualised by rotational 3D views (arrow); and (d) associated cleft palate as visualised by rotational 3D views (arrow)

choose the technique of preference, or a combination of techniques[10-12,16], depending on the sonographer's training and experience, fetal position, precise gestation, presence or absence of associated abnormalities, until the sonographer was satisfied as to the probable extent of the cleft. In this series, as diagnoses were only made after the completion of both 2D and 3D imaging, we were unable to compare the performance of 2D USG alone versus 2D / 3D USG assessment.

One major reason why our team would not want to restrict our protocol to one standard or routine 3D USG technique for the assessment of facial clefts is the lack of evidence on the actual precision, sensitivity or specificity of these various methods. Most of the studies describing new 3D USG techniques were primarily concerned with the practical methodology and sonographic approach for providing images of palatal structures in largely normal fetuses, and the number of pathologies described in these studies was surprisingly small[24]. For instance, the technique described by Faure et al[11] and Wong et al[25] included no abnormal cases, and even the well-known papers by Platt et al[8] and Pilu and Segata[9] described only one abnormal case as an example. Other studies, including Campbell et al[7], Martínez Tens et al,[10] and Wang et al[26] described small case series of eight, 10, and 22 abnormal cases, respectively. Thus, no precise sensitivity or specificity figures can be reliably calculated from these studies. Nevertheless, whatever the technique employed, the diagnostic accuracy is anticipated to be high in skilled hands. In a series of 79 cases of facial clefts, it was reported that 77 (97%) of the associated CPs were diagnosed accurately and the sensitivity of detection of CP was 100% and specificity was 90% in this high-risk population[13]. In a meta-analysis, it was estimated that when CL is detected, careful 2D USG, supplemented with various 3D USG techniques, should detect a cleft of the hard palate in around 86% to 90% of cases[23]. Our reported accuracy in this cohort of around 95% is in line with this reported performance.

There are also limited data in the literature comparing the accuracy of different 3D USG techniques in delineating associated CP. In one of the only such studies that included 50 normal and 10 abnormal fetuses (gestation of 23-33 weeks), it was found that the upper lip and alveolar ridge were well visualised by either the reverse face, flipped face, or oblique face methods. Involvement of the hard palate was accurately diagnosed in 71% of cases with the reverse face view, in 86% with the flipped face view, and in 100% with the oblique face view[10]. Involvement of the soft palate was diagnosed correctly in only one in seven of the fetuses with secondary palate defects in the flipped face and oblique face views[10]. The authors favoured using these latter two views, which could allow visualisation of the soft palate in selected cases[10]. In our experience, actual visualisation of the soft palate requires fluid between the tongue and soft palate, and a curving plane to follow the structure of the palate, which is not possible practically with the reverse face view. We thus also prefer the flipped face or oblique face view because of the higher chance of satisfactory visualisation. Another possible source of error in the visualisation of CLA or CP could be motion artefacts that frequently occur in the rendered images obtained from rotational views. The use of multi-slice views was suggested to reduce such artefacts. In a series of 22 CLs, oblique views detected only eight of the nine associated CPs while multi-slice views detected all of them[26]. The value of using multi-slice views, together with rotational views, should be further explored.

Our results showed that the diagnostic precision was greater when there was CP. All of the true CPs were detected in this cohort. However, overdiagnosis was common when there were clefts in the alveolar ridge and some were misdiagnosed as CP. This could be expected when visualisation by manoeuvring of the 3D volume was suboptimal, and artefacts would easily be taken as palatal clefts. This was particularly true in high-risk cases, for example those with bilateral clefts, when the sonographer was more likely to overdiagnose due to expecting to see more serious pathology, often quoted as 'context bias'. In addition, this was a retrospective case series, and the results were compiled based on the diagnosis reported by the sonographer at the time of assessment, rather than by reviewing the stored images or volumes. Therefore, we have not excluded possible inter-observer discrepancies in the diagnosis if the actual images were reviewed by the investigators.

We conclude that with our current practice of a combination of 2D and 3D USG techniques, our prediction of the presence or absence of CP in those diagnosed with CL was good and the results were on a par with those reported in the literature. However, overdiagnosis and underdiagnosis did occur in some cases, particularly when associated with assessment of alveolar ridge clefts. The limitations of such USG predictions should be explained to parents at the time of counselling.

References

1. Cash C, Set P, Coleman N. The accuracy of antenatal ultrasound in the detection of facial clefts in a low-risk screening population. *Ultrasound Obstet Gynecol* 2001; 18:423-6.
2. Tonni G, Centini G, Rosignoli L. Prenatal screening for fetal face and clefting in a prospective study on low-risk population: can 3- and 4-dimensional ultrasound enhance visualization and detection rate? *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; 100:420-6.
3. Tolarová MM, Cervenka J. Classification and birth prevalence of orofacial clefts. *Am J Med Genet* 1998; 75:126-37.
4. Walker SJ, Ball RH, Babcook CJ, Feldkamp MM. Prevalence of aneuploidy and additional anatomic abnormalities in fetuses and neonates with cleft lip with or without cleft palate: a population-based study in Utah. *J Ultrasound Med* 2001; 20:1175-80.
5. Royal College of Obstetricians and Gynaecologists (RCOG). Routine ultrasound screening in pregnancy — protocol, standards and training. A Working Party report by the RCOG. *London: RCOG Press*, 2000.
6. ISUOG Clinical Standards Committee; Salomon LJ, Alfirevic Z, Berghella V, et al. Practice guidelines for performance of the routine mid-trimester fetal ultrasound scan *Ultrasound Obstet Gynecol* 2011; 37:116-26.
7. Campbell S, Lees C, Moscoso G, Hall P. Ultrasound antenatal diagnosis of cleft palate by a new technique: the 3D "reverse face" view. *Ultrasound Obstet Gynecol* 2005; 25:12-8.
8. Platt LD, Devore GR, Pretorius DH. Improving cleft palate/cleft lip antenatal diagnosis by 3-dimensional sonography: the "flipped face" view. *J Ultrasound Med* 2006; 25:1423-30.
9. Pilu G, Segata M. A novel technique for visualization of the normal and cleft fetal secondary palate: angled insonation and three-dimensional ultrasound. *Ultrasound Obstet Gynecol* 2007; 29:166-9.
10. Martínez Ten P, Pérez Pedregosa J, Santacruz B, Adiego B, Barrón E, Sepúlveda W. Three-dimensional ultrasound diagnosis of cleft palate: 'reverse face', 'flipped face' or 'oblique face' — which method is best? *Ultrasound Obstet Gynecol* 2009; 33:399-406.
11. Faure JM, Captier G, Bäumler M, Boulot P. Sonographic assessment of normal fetal palate using three-dimensional imaging: a new technique. *Ultrasound Obstet Gynecol* 2007; 29:159-65.
12. Rotten D, Levaillant JM. Two- and three-dimensional sonographic assessment of the fetal face. 2. Analysis of cleft lip, alveolus and palate. *Ultrasound Obstet Gynecol* 2004; 24:402-11.
13. Offerdal K, Jebens N, Syvertsen T, Blaas HG, Johansen OJ, Eik-Nes SH. Prenatal ultrasound detection of facial clefts: a prospective study of 49,314 deliveries in a non-selected population in Norway. *Ultrasound Obstet Gynecol* 2008; 31:639-46.
14. Gillham JC, Anand S, Bullen PJ. Antenatal detection of cleft lip with or without cleft palate: incidence of associated chromosomal and structural anomalies. *Ultrasound Obstet Gynecol* 2009; 34:410-5.
15. Demircioglu M, Kangesu L, Ismail A, et al. Increasing accuracy of antenatal ultrasound diagnosis of cleft lip with or without cleft palate, in cases referred to the North Thames London Region. *Ultrasound Obstet Gynecol* 2008; 31:647-51.
16. Sommerlad M, Patel N, Vijayalakshmi B, et al. Detection of lip, alveolar ridge and hard palate abnormalities using two-dimensional ultrasound enhanced with the three-dimensional reverse-face view. *Ultrasound Obstet Gynecol* 2010; 36:596-600.
17. Bäumler M, Faure JM, Bigorre M, et al. Accuracy of prenatal three-dimensional ultrasound in the diagnosis of cleft hard palate when lip cleft is present. *Ultrasound Obstet Gynecol* 2011; 38:440-4.
18. Paterson P, Sher H, Wylie F, et al. Cleft lip/palate: incidence of prenatal diagnosis in Glasgow, Scotland, and comparison to other centers in the United Kingdom. *Cleft Palate Craniofac J* 2011; 48:608-13.
19. Maarse W, Pistorius LR, Van Eeten WK, et al. Prenatal ultrasound screening for orofacial clefts. *Ultrasound Obstet Gynecol* 2011; 38:434-9.
20. Maarse W, Bergé SJ, Pistorius L, et al. Diagnostic accuracy of transabdominal ultrasound in detecting prenatal cleft lip and palate: a systematic review. *Ultrasound Obstet Gynecol* 2010; 35:495-502.
21. King NM, Samman N, So LL, Cheung LK, Whitehill TL, Tideman H. The management of children born with cleft lip and palate. *Hong Kong Med J* 1996; 2:153-9.
22. Schnitt DE, Agir H, David DJ. From birth to maturity: a group of patients who have completed their protocol management. Part I. Unilateral cleft lip and palate. *Plast Reconstr Surg* 2004; 113:805-17.
23. Hassan WA, Lees CC. Facial cleft detected: is the palate normal? *Best Pract Res Clin Obstet Gynaecol* 2014; 28:379-89.
24. To WW. Prenatal diagnosis and assessment of facial clefts: where are we now? *Hong Kong Med J* 2012; 18:146-52.
25. Wong HS, Tait J, Pringle KC. Examination of the secondary palate on stored 3D ultrasound volumes of the fetal face. *Ultrasound Obstet Gynecol* 2009; 33:407-11.
26. Wang LM, Leung KY, Tang M. Prenatal evaluation of facial clefts by three-dimensional extended imaging. *Prenat Diagn* 2007; 27:722-9.