MEDICAL PRACTICE

Prenatal diagnosis and assessment of facial clefts: where are we now?

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Orofacial clefts are one of the most common non-syndromic congenital structural abnormalities. Prenatal diagnosis of such defects has traditionally been made by ultrasound examination. With the advent of routine second-trimester ultrasound screening for morphological abnormalities in the recent two decades, the prenatal detection rate of such abnormalities has progressively increased. While conventionally, two-dimensional scanning has been used for screening of lip clefts, the development of three-dimensional ultrasound scanning technology has allowed more easy visualisation of the defects, as well as more accurate evaluation of palatal clefts. Various three-dimensional scanning techniques to assess such defects have been advocated in the recent 5 to 6 years, but as yet there is no consensus as to the most effective and practical methods. As fetal magnetic resonance imaging gradually becomes an accessible modality of imaging in modern obstetrics, it is likely to become an additional tool to assess these defects.

Introduction

Facial clefts are among the most common congenital anomalies, with a point prevalence of approximately 1:500 to 1:1000 live births.[1,2] Prenatal detection and diagnosis has been recognised as useful to facilitate prenatal counselling, to evaluate genetic risks, and to prepare the parents psychologically to accept and plan for neonatal surgery after birth. To improve the evaluation of these defects—particularly those of the palate—three- and four-dimensional ultrasound (3D/4D US) has been widely introduced as an additional tool to complement conventional two-dimensional ultrasound (2D US).

Clinically, it is important to differentiate between the different types of orofacial clefts due to their implications on fetal prognosis. The genetic risks are believed to be increased when the alveolus or the palate or both are involved in the facial cleft.[3] There appear to be more associated malformations and more karyotype abnormalities associated with these more complex defects, as many syndromes have clefting as part of their phenotype.[4] While isolated clefts have low perinatal mortality and morbidity, and primarily pose functional and aesthetic problems after birth, complicated clefts are associated with a much poorer prognosis. In addition, children with cleft lip plus cleft palate need to undergo more surgical correction procedures than those with cleft lip alone, and their follow-up more frequently involves additional orthodontic and orthophonic treatment.[5,6] Thus, when cleft lip is found on screening using 2D US, precise information about the anatomy of the palate is important to deliver adequate counselling to the parents on genetic, surgical, and functional prognostic aspects. A variety of new 3D techniques have been described in recent years with a view to visualisation of the hard and soft palate, and the use of magnetic resonance imaging (MRI) has also been advocated. At present, however, there is no consensus as to the best means to visualise the palate prenatally. This review aims at outlining these newly developed techniques and discusses their practical utility and applications.

Key words
Cleft lip; Cleft palate; Karyotyping; Pregnancy; Ultrasonography, prenatal

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Prenatal detection rates for the different types of clefts

The likelihood of encountering alveolar clefts and palatal clefts with cleft lip varies in different studies, and probably depends on the population being studied. There are also wide variations in the reported incidence of associated structural abnormalities. They depend on whether the figures are largely based on an obstetric cohort evaluated prenatally, or whether the statistics were collected from a cleft centre receiving referrals to treat babies with significant clefts.

In one classical study, cleft lip was associated with cleft alveolus in around 6% of patients, cleft alveolus plus palate in up to 75%, and cleft palate alone in 1%,[7] in which

case cleft lip not associated with any palatal clefts occurred in only around 20% of cases. In a survey of the detection rates from 1999 to 2008 in patients referred to a specialist cleft centre in Glasgow, the overall detection rate was only 15%, but there was a progressive increase in detection rate from 11% in 1999 to 50% in 2008. Routine US for anomaly screening was shown to significantly improve the detection rates compared to scanning high-risk pregnancies only.[8]

In a prospective screening in Norway from 1987 to 2004, a total of 101 fetuses or newborns with facial clefts were found in a population of 49 314 deliveries. The distribution of clefts was: 25% cleft lip, 51% cleft lip plus cleft palate, and 24% cleft palate. No cleft palate was detected antenatally. Cleft lip with or without cleft palate was detected prenatally in 45% of the cases, with a significant increase in the detection rate from 34% in 1987-1995 to 58% from 1996 to 2004; 69% of all the cases were first detected at routine second-trimester ultrasound examinations; 43% of the cases of cleft lip plus cleft palate and 58% of those with cleft palate only had associated anomalies. Overall, 12% of these patients had associated chromosomal aberrations, and in 18% the clefts were part of a syndrome or sequence.[9]

In a recent large prospective US screening of 35 000 low-risk and 2800 high-risk pregnant women in the Netherlands, orofacial clefts were detected in 62 fetuses, giving a point prevalence of 1:613. The distribution of abnormalities was: 29% cleft lip alone, 40% cleft lip plus cleft palate, and 27% cleft palate only; there was also one rare median cleft and one atypical cleft. Regarding these anomalies, 61% were unilateral, 37% were bilateral, and 39% had associated abnormalities (chromosomal defects in the cleft lip with cleft palate group and cleft palate only patients). The sensitivity of detecting cleft lip with or without cleft palate prenatally was 88%. Cleft palate only was not detected prenatally in any conceptus. There were three false-positive cases, two of whom had other multiple abnormalities. It was concluded that in a low-risk population, US screening to detect cleft lip with or without a palatal cleft had high sensitivity.[10]

In a series of 570 children referred to a facial cleft centre in the United Kingdom, it was found that the frequency of associated structural abnormalities varied with the anatomical type of the cleft, being 9.8% for unilateral cleft lip plus palate, 25% for bilateral cleft lip plus palate, and 100% in those with a midline cleft lip and palate. Of the 252 cases with isolated cleft palate, 5.6% had either karyotypes or associated structural abnormalities and 21% had a genetic syndrome as an underlying diagnosis. However, none of the palatal clefts without facial clefts were identified antenatally.[11]

產前診斷及評估胎兒唇裂的現況

口面裂是其中一種最普遍的無症狀先天性結構異常，傳統上都會利用超聲作產前常規檢查。過去二十年實施的中期妊娠診斷胎兒異常例行超聲篩查，大大提高了胎兒唇裂的產前檢出率。目前除了二維超聲檢查外，三維超聲掃描術對病變能進行更細緻的觀察，並更加準確地評估腭裂的情況。近五至六年間出現多種三維超聲掃描技術，但對於哪種才是最有效及最可行的掃描術則未有共識。胎兒磁共振成像漸漸成為現代產科的一種可行方法，很可能成為產前診斷胎兒唇裂的另一種工具。

Accuracy of prenatal diagnosis of the different types of clefts

The accuracy of antenatal ultrasound diagnosis of cleft lip and palate was studied in a series of 96 cases, with a mean gestational age at examination of 28 (standard deviation, 4) weeks; the sonographic appearance of cleft lip, cleft lip with cleft alveolus, and cleft lip plus cleft palate was subsequently confirmed in 88% of the cases. Overestimation of the degree of cleft occurred in eight cases, and under-estimation occurred in three. Thus, the authors believed that inclusion of 3D and 4D US imaging allows easier and more precise evaluation of the different cleft constituents.[12]

In another retrospective review of surviving cases between 2002 and 2003 at a cleft surgical referral centre in London, of 149 with a cleft lip with or without cleft palate, 59% were diagnosed based on antenatal ultrasound examination, though 25% of the latter entailed minor reporting errors. The latter included: errors in describing the side and type of the lip cleft (12%), predicting the possibility of cleft palate (12%), and recognising the anomaly (1%). There were 102 cases of isolated cleft palate, of which none were detected antenatally. It was concluded that inaccuracies in antenatal ultrasound reports occur frequently when attempting to determine the type of cleft lip and when assessing whether there was a cleft palate.[13]

To verify the accuracy of prenatal axial 3D US in predicting the absence or presence of cleft palate, in the presence of a cleft lip, 79 patients with a prenatal 2D US screening diagnosis of unilateral or bilateral cleft lip at 22 to 25 weeks were subjected to axial 3D US of the fetal palate. The findings were compared to those noted at births. It was found that 77 out of 79 prenatal predictions were correct, yielding a sensitivity and specificity to detect cleft lip and palate (in this high-risk population) of 100% and 90%, respectively. Thus, the study confirmed that 3D US of the hard palate showed high accuracy in identifying prenatal cleft palate when cleft lip is identified at mid-trimester screening scan.[14]

In 124 cases of suspected orofacial clefting diagnosed by routine 2D US, there were 110 who had isolated facial clefts, and 100 having successful reverse face views were analysed. The sensitivity of the 2D enhanced with 3D reverse view technique for the diagnosis of cleft lip was 95% (false positive rate, 8%), for alveolar ridge 85% (7%) and for hard palate 90% (16%). It was concluded that the reverse face view was possible in 90% of fetuses in whom 90% have a correct classification of clefts of the lip, alveolar ridge and palate.[15]

A recent systematic review reveals the diagnostic accuracy of second-trimester transabdominal ultrasound in detecting orofacial clefts in low- and high-risk populations and to compare 2D US and 3D US techniques.[4] This review included 27 studies, of which 21 involved unselected low-risk populations and six entailed high-risk populations. There was a diversity in the gestational age at which the ultrasound examinations were performed, ranging from 15 to 36 weeks. There were also considerable variations in the diagnostic accuracy of 2D US in low-risk women; prenatal detection rates ranged from 9 to 100% for cleft lip with or without cleft palate, 0 to 22% for cleft palate only, and 0 to 73% for all types of clefts. Notably, 3D US in high-risk women resulted in a detection rate of 100% for cleft lip, 86 to 90% for cleft lip with cleft palate, and 0 to 89% for cleft palate only. The inclusion of older studies with less advanced ultrasound machines and the varying levels of training and expertise in individual studies all contributed to the very wide range of detection rates quoted in this review. However, such variations could be a true reflection of the very heterogeneous performance in the detection of orofacial clefts in practice. Thus, 2D US screening for cleft lip and palate in a low-risk population has a relatively low detection rate, approaching 0% for isolated cleft palate, but is associated with few false positives. Three-dimensional ultrasound can achieve a reliable diagnosis, but not for isolated cleft palate.[4]

Conventional two- versus three-dimensional ultrasound

Conventional 2D examination of the face requires the mid-sagittal plane and that a series of images in the anterior coronal plane be obtained by probe manipulation by moving out from the nose and oral cavity to the edge of the lips so as to obtain the nose-mouth view. Examination of the palate is more difficult with conventional 2D US. The most common method is to obtain serial axial/transverse images from the nose down through the oral cavity to the lower edge of the mandible. By this means, the alveolar ridge, palate, tongue, and mandible can be visualised consecutively. Sagittal views are useful for visualising the facial profile; particularly in bilateral cleft lips a protrusion of the detached pre-maxillary mass may be visualised.[16] Other 2D US approaches that might increase detection rates include the use of transvaginal ultrasound early in the second trimester,[17] or the addition of colour flow Doppler,[18] though both of these techniques seem to have become obsolete with the advent of 3D US.

Standard 3D US assessment of the facial profile included the orthogonal display mode and surface rendering (Fig 1). The orthogonal display mode allows the simultaneous analysis of the three reference planes: sagittal, transverse, and coronal.

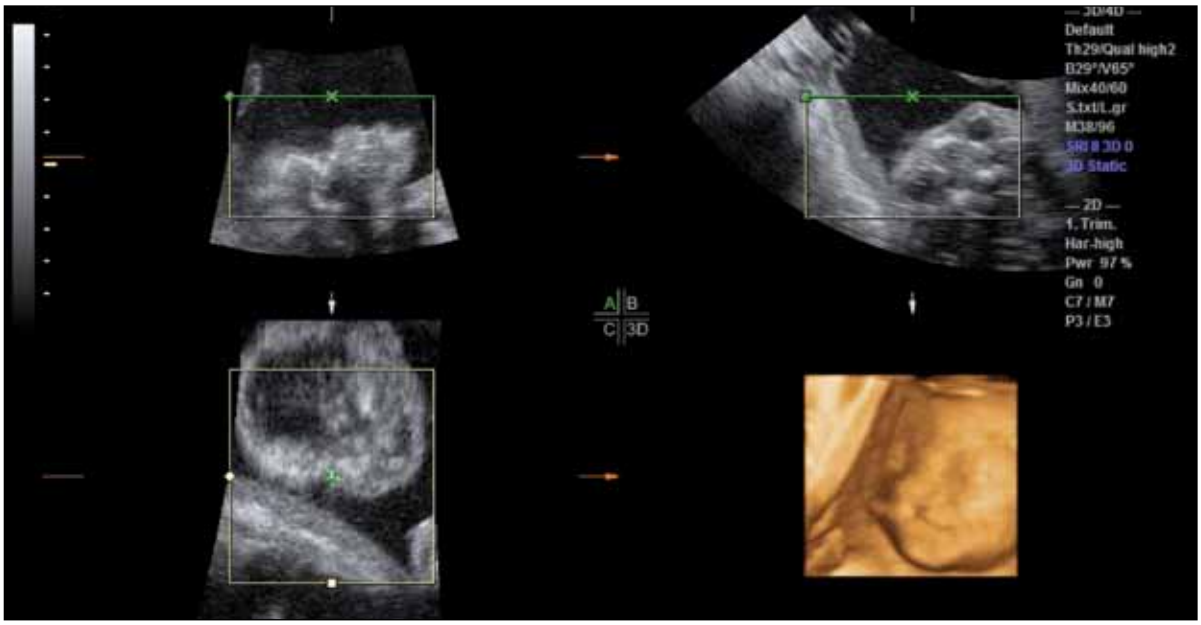

FIG 1. Three-dimensional examination with three orthogonal plans and surface rendering

Thus, once the presence of a facial cleft is suspected, the three reference planes are imaged to characterise the anatomical defect. The alveolus and palate can usually be identified in the transverse plane by visualising the front tooth buds and alveolar ridge and then by rotating the volume slightly to examine the symmetry of the palate. The surface rendering allows imaging of the soft tissue of the face and its relationship to underlying bony structures.

Currently, standard 2D US is used for routine mid-trimester morphology scans, screening for cleft lip being an essential part of the protocol for most centres. When a cleft lip is diagnosed, efforts are then made to evaluate the extent of the lesion and the presence or absence of associated alveolar and palatal clefts. Rendered 3D images may also provide more-easy-to-understand landmarks for the planar views, and at the same time facilitate counselling of the family and a consultation with a surgeon to explain the abnormality.[19] Thus, at present, 3D/4D imaging is most commonly employed for such secondary evaluation and joint counselling. Recourse to 3D/4D scanning as a primary tool for screening of facial clefts could be time-consuming and has not been shown to be cost-effective. The use of rendered images alone has been reported to introduce false positives due to the appearance of pseudo-clefts that are usually due to rendering artefacts or acoustic shadows, which lead to a loss of specificity for the ultrasound diagnosis.[20,21]

Notwithstanding the emphasis on 3D US techniques, a novel marker for the diagnosis of isolated fetal cleft palate using 2D US has been recently described and is termed the "equals sign".[22] This uses a transverse plane to visualise the uvula and epiglottis as well as a mid-sagittal pane to visualise the soft palate and the uvula. In this German series of 667 consecutive women examined between 20 and 25 weeks, a normal uvula could be visualised with the typical echo pattern (equals sign) in 90.7% of cases and the soft palate could be completely visualised in the median sagittal section in 85.3%. However, the number of actual abnormalities included in this series was small, and only one case of isolated cleft palate and one case of cleft lip and palate were correctly diagnosed.[22] Further clinical experience with this technique for routine use is required to evaluate its sensitivity and specificity for the detection of isolated palatal clefts.

New techniques with three-dimensional ultrasound

A new 3D US technique called the 3D reverse view was first described by Campbell et al in 2005.[23] The case series described eight consecutive cases of suspected orofacial clefting that were examined by 3D surface rendering. The fetal lips and alveolar ridge were examined in the frontal plane and the face was then rotated through 180 degrees on the vertical axis to examine the secondary palate by 3D reverse face view. The investigators concluded that the 3D reverse face technique allowed relatively straightforward assessment of the fetal palate with a high degree of accuracy.

Platt et al[24] then described the flipped face view in 2006. The fetal face was initially examined with the fetus in the supine position, and using 3D US, a static volume was acquired. The acquired volume was then rotated 90 degrees so that the cut plane was directed in a plane from the chin to the nose. The volume cut plane was then scrolled from the chin to the nose to examine the lower lip, mandible, alveolar ridge, tongue, upper lip, maxilla and alveolar ridge, and hard and soft palates, in sequential order. The authors promoted the practicality of this approach to identify the full length and width of the structures of the mouth and palate, which allowed the examiner to identify normal anatomy as well as the clefts of hard and soft palates.

The oblique face view was described by Pilu and Segata[25] in 2007 to visualise the secondary palate. To avoid acoustic shadowing from the alveolar ridge, the secondary palate was insonated at a 45-degree angle in the sagittal plane and 3D US was used to reconstruct axial and coronal planes. In this small series, the secondary palate was successfully visualised in 10 of 15 fetuses, both in the axial and coronal planes. In the only fetus in this series with cleft lip, the palatal lesion was clearly demonstrated in the coronal plane.[25]

In a study to compare the performance of the reverse face, flipped face, and oblique face methods for visualisation of the hard and soft palate, a total of 60 fetuses (10 of which had facial clefts) with a gestation of 23 to 33 weeks were examined, with the result that the upper lip and alveolar ridge were well visualised in all cases with the three methods. Involvement of the hard palate was diagnosed accurately in 71% with the reverse face view, in 86% with the flipped face view, and in 100% with the oblique face view. The hard palate was correctly found to be normal in 78%, 84% and 86% of the 50 normal fetuses, respectively. Involvement of the soft palate was diagnosed correctly in only one of seven fetuses with secondary palate defects in the flipped face and oblique face views, and was correctly considered to be intact in only 16% and 26% of normal fetuses using these two views, respectively. It was concluded that the oblique or flipped face views make it possible to visualise the soft palate in selected cases.[26] Actual visualisation of the soft palate requires an excellent initially acquired volume, fluid between the tongue and the palate, and a curving plane to follow the structure of the palate; evidently this was not possible with the reverse face view (Fig 2).

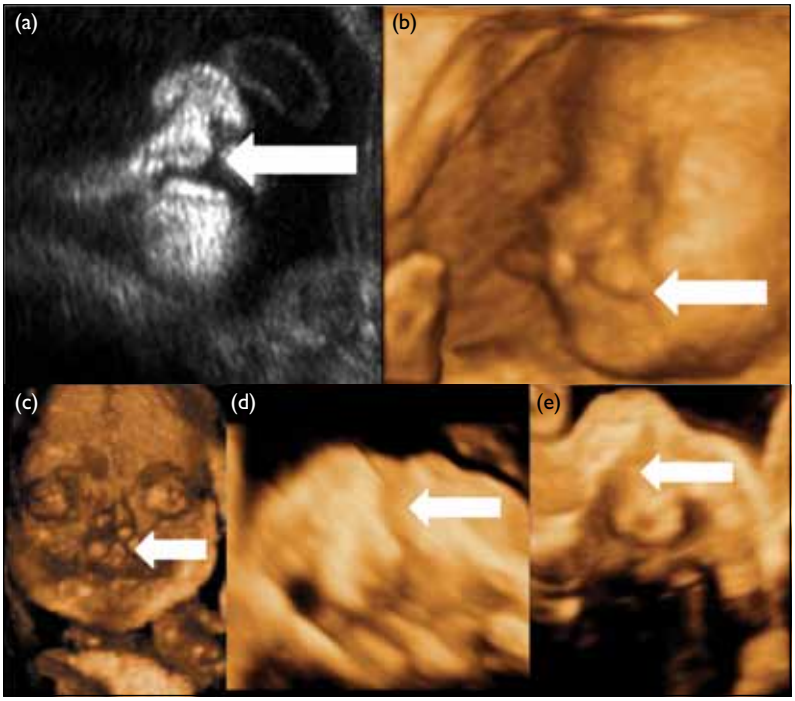

FIG 2. Facial cleft as visualised by two-dimensional (2D) ultrasound (US) and 3D rendering

(a) Cleft lip as visualised by 2D US; (b) cleft lip as visualised by 3D US; (c) cleft palate seen in coronal plane reverse face view; (d) cleft alveolar and palate in axial plane visualised by flipped face view; and (e) cleft alveolar and palate in axial plane as visualised by oblique face view

Other three-dimensional ultrasound techniques

In a series of 100 fetuses at advancing gestations from 17 weeks to 32 weeks, US scans were performed using the strict anterior axial plane of the reconstruction volume and the underside 3D view of the fetal palate. This 3D view of the fetal palate was then compared with the normal anatomical view of the fetal palate obtained by surgical fetopathological examination of the palate for fetuses of corresponding gestation. Three-dimensional imaging of the fetal maxilla and secondary palate was possible and the overall reliability of visualisation across the gestational ages was medium to very high (0.73 to 0.96). It was concluded that this technique of anterior axial 3D view reconstruction of the fetal palate seen by an underside view can provide useful information of the integrity of the secondary palate.[27]

Using acquired routine 3D volume, a technique to obtain a sweeping view of the fetal soft and hard palates has been reported. The secondary palate was viewed in three oblique planes targeted at the uvula: the oblique axial, the oblique sagittal, and the reverse face view in 31 normal fetuses between 15 and 35 weeks. It was found that the various surfaces of the secondary palate could be viewed in all fetuses in the oblique axial and the reverse face views, and in all except two fetuses of less than 19 weeks in the oblique sagittal view. Thus, rotating or tilting of these orthogonal planar images of the fetal head allowed the visualisation of the various aspects of the palate in most fetuses, with the uvular as a useful landmark. However, due to the relatively small size of the uvula, its demarcation at an early gestation before 20 weeks is not easy.[28]

Three-dimensional extended imaging (3DTI; Accuvix, Medison Co Ltd, Seoul, Korea) has been described since 2005 as a new modality to examine various fetal structures. In a pilot study, Leung et al[29] reported the results in examining six cases of facial clefts. The method was found to be advantageous over 2D US in at least one of the cases by allowing simultaneous display of bilateral cleft lip and palate which were located in two different axial plans.[29] However, the diagnostic accuracy for facial cleft between 2D US and 3D US was not directly compared.

In a subsequent study by the same group,[30] fetuses suspected of having a facial cleft by previous ultrasound examination or family history were examined with 2D and then 3D US. A total of 30 cases were analysed to compare the performance of 2D US and 3DTI, of which 22 had cleft lip and nine also had cleft palate at birth. The use of 2D US with or without 3D US correctly identified all cases of cleft lips prenatally. However, the use of 2D US in conjunction with 3D US correctly identified more palatal clefts than 2D US alone (89% vs 22%, P<0.01). Primary palatal cleft was well-demonstrated in both multi-slice view (MSV; Accuvix, Medison Co Ltd, Seoul, Korea) and orthogonal display modes. There were no false positives as all unaffected fetuses were reported as having no cleft palate with the use of the MSV mode. The combined approach using 2D US and 3D US with the 3DTI techniques offering both orthogonal display and MSV modes significantly improved the prenatal detection rate for cleft palate compared to 2D US alone, without any decrease in specificity.

It has to be noted, however, that the studies quoted in these two sections were primarily concerned with the methodology and the sonographic approach used to provide images of the palatal structures in largely normal fetuses, whilst the number of pathologies described was relatively small. Faure et al[27] and Wong et al[28] included no abnormal cases at all, Platt et al[24] and Pilu and Segata[25] showed one abnormal case as an example, Campbell et al[23] and Ten et al[26] described eight and 10 cases, respectively and Wang et al[30] described 22 cases. In addition, while 3D US techniques appeared to improve the diagnosis of palatal cleft with associated cleft lip, as with studies on 2D US, none of the 3D studies described the detection of an isolated cleft palate. Further large prospective trials to compare

the efficacy and accuracy of these techniques are obviously needed.

Fetal magnetic resonance imaging

To investigate the role of fetal MRI as a complement to US in the evaluation of cleft lip and cleft palate, whether isolated or in association with syndromic conditions, 27 fetuses with US-diagnosed cleft lip or cleft lip/palate were recruited to undergo fetal MRI examination. Their facial skeleton, central nervous system, and fetal body was studied at a mean gestational age of 24 weeks. The diagnosis of cleft lip/palate was confirmed in 16 of 25 fetuses, and additional information about the extent of the cleft and the degree of involvement of the anterior and posterior palate was obtained in eight of these fetuses. The MRI ruled out the diagnosis in one of the 25 fetuses. It was concluded that MRI was able to define the degree of involvement of the posterior palate and the lateral extent of the cleft with higher diagnostic accuracy than US. Furthermore, MRI provides a complete study of the fetal head and biometric development of the facial bones, thus enabling early detection of potential syndromic conditions.[31]

To assess whether the use of fetal MRI could provide a definitive prenatal diagnosis of cleft palate, 49 pregnant women with fetuses with diagnosed facial clefts from routine 20-week morphology scans were subjected to fetal MRI at between 24 and 37 weeks. The positive predictive value of fetal MRI for involvement of the palate was 96%, and the negative predictive value was 80%, even when the radiologist was blinded to the US findings. The accuracy of the radiologist in predicting palatal clefting from different MRI signs improved significantly over a short learning curve. Thus, fetal MRI enabled more accurate prediction of the extent of a cleft palate after ultrasound diagnosis of a cleft lip.[32]

In a series of 34 Austrian women with a mean gestation of 26 weeks (range, 19-34 weeks), in-utero MRI performed after ultrasound examination had identified either a facial cleft and/or other structural abnormalities. In all, 32% of the cases had primary palatal clefts alone, 59% had clefts of the secondary palate, and three had isolated clefts of the secondary palate. In all cases, the primary and secondary palate were visualised successfully with MRI. Compared to ultrasound that detect 15% of the facial clefts and misclassified 44% of them, the MRI classification correlated well with the postnatal or postmortem diagnosis. It was concluded that MRI allowed detailed prenatal evaluation of the primary and secondary palate, and that by demonstrating palatal involvement, it provided a better detection rate and classification of facial clefts than ultrasound alone.[33]

It must be noted, however, that most of these data on MRI studies of orofacial clefts were performed at 24 to 37 weeks of gestation, and the utility of earlier MRIs (around 20 weeks of gestation) when ultrasound diagnoses were usually made remained untested. Further studies are needed to compare the performance of ultrasound and MRI at equivalent gestation ages. The use of MRI findings for clinical counselling remains limited at present.

Prenatal diagnosis leading to prenatal surgery?

Recent developments in video-endoscopic technology have boosted the development of operative techniques for feto-endoscopic surgery, which has been demonstrated to be less invasive than the open approach. Experimental intrauterine correction of cleft lip and palate has been recently performed using such an approach. The main advantages of prenatal surgery for this non–life-threatening condition included scarless fetal wound healing and bone healing, enabling better or normal maxillary bone growth and better cosmesis[34] by correcting the primary deformity. Scarless fetal lip and palate repairs may prevent the ripple effect of postnatal scarring with its resultant secondary dentoalveolar and midface growth deformities, and might dramatically reduce the number of postnatal reconstructive procedures that these children might need to undergo.[35] Nevertheless, such advantages of prenatal surgery remain theoretical, and clinical data on its effects are still not yet available in the literature.

Conclusion

While there were wide variations in the reported prenatal detection rates of facial clefts, it is evident that the performance of 2D US screening has progressively improved in recent years. While 3D US screening alone should not be used due to the higher false-positive rates, the development of 3D US techniques has improved the detection of palatal clefts associated with cleft lip, by allowing direct visualisation of at least part of the secondary palate. On the other hand, the performance, precision and clinical practicality of these new techniques at different gestational ages have not been thoroughly compared or evaluated. More experience in learning and applying these techniques needs to be accumulated. Isolated palatal clefts remain problematic, and detection rates remain low even with the addition of 3D US. The use of MRI to facilitate prenatal assessment of facial clefts should be further developed, with the increasing availability of fetal MRI in many centres. Prenatal surgery for congenital facial clefts remains a goal for the future.

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