

Three-dimensional Ultrasound and Genetic Syndromes

¹M Lanna, ¹MA Rustico, ¹A Pintucci, ¹L Spaccini, ²F Lalatta, ¹U Nicolini

¹UO Ostetricia e Ginecologia-Ospedale V. Buzzi, Milano, ²Genetica Medica, IRCCS Policlinico, Milano

Correspondence: M Lanna, M Rustico U.O. di Ostetricia e Ginecologia, Ospedale Buzzi, Via Castelvetro 24 20154 Milano, Italy. e-mail cast@interware.it

INTRODUCTION

The term *syndrome* refers to the association of signs, symptoms, features, or characteristics which occur together in the same individual (from the ancient Greek = *run together*).

Clinical dysmorphology is the study of abnormal human development with particular emphasis on rare syndromes causing malformations or alterations in body form. Many syndromes are associated with mental retardation indicating that genes affecting physical development are also likely to be important in the development of the central nervous system.

The pioneers of dysmorphology concentrated on the delineation of syndromes by clinical description. Where specific malformations were present, a syndrome would be defined by a particular combination—so called major criteria, essential to the diagnosis—together with minor findings, that might be absent. In cases without malformations, syndromes were defined by a specific facial appearance. It takes a particular skill to be able to delineate a syndrome in this way. This attitude has been called “pattern recognition” or “gestalt”. The etiology of each syndromic condition is not always easily identifiable, despite the ability to recognize those features that could recall a known syndrome, and search for other signs that could help in the formulation of the exact diagnosis. On the other hand the diagnosis is important especially in the delineation of the best care for the patient, to identify the correct recurrence risk and the best approach to monitor future pregnancies.

A great number of syndromes have been described but new entities are still coming to the attention of clinical geneticists, as genetic basis of these new conditions are discovered.

According to their etiology, syndromes can be grouped into chromosomal and non-chromosomal condition.

Prenatal diagnosis for chromosomal syndromes can be achieved with conventional karyotype of different tissues such as chorionic villi, amniocytes or lymphocytes. In the remaining cases, unless the phenotype can be disclosed by fetal imaging and the responsible gene can be tested, they can only be suspected during pregnancy by obstetric ultrasound.

Every syndrome is associated with the prevalent involvement of a system or of an organ, so the search for

characteristic features of the suspected syndrome is essential in the affected child as well as the affected fetus.

As already stated, genetic syndromes in children are often diagnosed on the basis of craniofacial dysmorphism,¹ so the aim of researchers has been the definition of similar dysmorphic features in the fetus with the help of clinical geneticists and pediatricians.

Three-dimensional ultrasound has improved the detection rate of facial anomalies,²⁻⁵ and helped the definition of syndromic entities.

Three-dimensional Ultrasound: Technical Aspects and Clinical Applications

Three-dimensional (3D) ultrasound is a powerful new addition to the tool-box of medical sonographers. With 3D ultrasound it is possible to obtain a volume scan starting from the classic two-dimensional (2D) image. In fact, the system acquires pixels from each of the three orthogonal planes of the space, and elaborates a volume box. Obtaining volumes rather than a single tomographic slice, makes it possible to display information on any plane and from any angle. When the planes are reformatted, surface rendering shows a 3D image, and it is these post-processing capabilities which make 3D ultrasound such a useful instrument for the visualization of normal and abnormal fetal anatomy. Clearly, being able to visualize structure in any plane in real time or simultaneously in multiple planes has great potential for medical diagnosis with ultrasound.

There have been extensive research into the clinical applications of 3D ultrasound in obstetrics, and many papers have shown the usefulness of this new technology, and in particular, when and where it compares favorably to conventional 2D ultrasound. One of the strongest areas is the visualization of fetal anatomy, where the realistic images it provides are far more readily comprehended by both clinicians and patients. In particular, 3D imaging of the fetal face, either with multiplanar reconstruction (Fig. 1), or with surface rendering (Fig. 2), has led to a better understanding of facial anomalies and may well assist in a better definition of syndromes.

Systematic analysis of the fetal face using 3D ultrasound was described by Rotten and colleagues in 2004.⁶

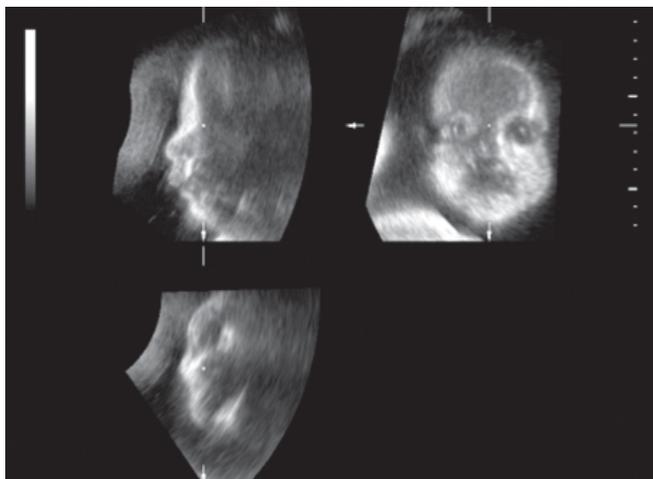


Fig. 1: Multiplanar display of the fetal face



Fig. 2: Surface rendering of the fetal face

The midsagittal plane is the best section for obtaining information on the fetal profile and measuring nasal bone length, as well for evaluating the appearance of the forehead, lips and chin, and for calculating facial angles, both superior and inferior.

The parasagittal section plane allows for analysis of the size, shape and position of the ears. The axial plane allows measurement of outer and inner interorbital diameters and the size of the mandible. The rendered image gives subjective information on the fetal face.

The criteria for diagnosing fetal dysmorphism are based on the same parameters used in the postnatal evaluation:

- the shape of head, with identification of flat or prominent occipital bones;
- closure of sutures;

- variation in interorbital diameters resulting in hyper- or hypotelorism;
- reduction in mandible width or reposition of the mandible, resulting in micro- or retrognathia;
- low-set or abnormal conformation of the ears and presence of preauricular tags;
- asymmetry of the face;
- variation of the facial angles: the superior (between nasal bone and forehead), and the inferior (between nasal root and chin);
- malformations such as cleft lip or palate, microphthalmia, etc.

One of the most important is the Jaw-Index, defined by the ratio between anteroposterior diameter of the mandible and biparietal diameter. This makes definition of micrognathia possible in presence of a ratio less than 0.23.⁷

Recently, a craniofacial variability index has been described to be used to evaluate fetal facial anatomy, and distinguish between normal and abnormal craniofacial development. Its modifications have been correlated with syndromic features, especially in fetuses with cleft lip/palate.^{8,9}

The role of 3D ultrasound is also unique in achieving a subjective evaluation of the fetal face:¹⁰ it should be born in mind that fetal phenotype should always be compared with parental phenotype.

The syndromes associated with craniofacial anomalies can be grouped as follows: craniosynostoses, orofacial clefting, abnormal development of the branchial arches (Goldenhar, Treacher Collins) and simply unusual face.

Syndromic craniosynostoses (Apert, Crouzon, and Pfeiffer), are autosomal dominant condition whose differential diagnosis is based on associated anomalies and molecular analysis of fetal DNA.

Fetal craniosynostoses can be suspected by the observation of the deformation of the skull and of the premature closure of the cranial bone sutures:^{11,12} synostosis of the coronal sagittal and lambdoid sutures and subsequent acrocephaly is present in Crouzon syndrome; brachycephaly is a feature of Pfeiffer and Apert syndrome, due to synostosis of coronal and sagittal sutures.

The associated anomalies have been reported in several cases of prenatal diagnosis.

The visualization of fetal cranial sutures with the help of 3D ultrasound has been the aim of many studies:¹³⁻²² surface rendering combined with the transparent maximum mode enables visualization of the progressive ossification of skull bones and the onset of fusion of frontal bones (Figs 3 and 4).

It has been demonstrated that in fetuses with Apert syndrome there is a premature closing of the coronal suture between the frontal and parietal bones, associated with a wide gap between frontal bones.¹⁷ A view of fetal profile can show frontal bossing and the depressed nasal bridge, but only a three-dimensional scan can reveal typical midfacial hypoplasia.

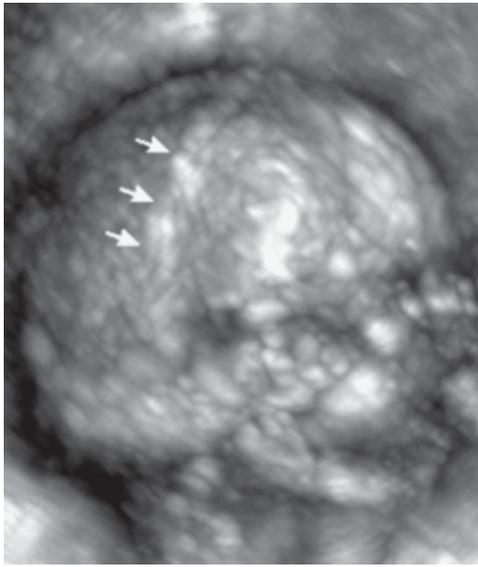


Fig. 3: Craniosynostosis: rendering of the skull



Fig. 4: Craniosynostosis: surface rendering of the fetal face

Abnormal development of first and second branchial arches can result in orofacial clefting or in mandible and ears anomalies. Cleft lip/palate is one of the most frequent fetal anomaly. It can be isolated or part of a syndrome.

Prenatal diagnosis of this malformation can be easily achieved with classic 2D ultrasound, but many studies have stressed how 3D can improve its detection rate beyond the second trimester,²³⁻²⁶ especially in cases of isolated cleft lip: using the modification of threshold, the surface-rendered image

can be manipulated to ensure that the defect observed is not due to artifacts and to evaluate the level of the defect (isolated cleft lip or associated cleft lip and palate). The area of the defect can be observed on the three planes of the volume and its exact location can be identified.

The mixture of surface and light rendering mode has been demonstrated to be the most appropriate for viewing facial clefts (Figs 5 and 6).

Another technique described for a correct diagnosis of this anomaly is the 3D “reverse face” view:²⁷ It consists in rotating the frontal facial image through 180° along the vertical axis,



Fig. 5: Labioschisis. Surface rendering of the fetal face



Fig. 6: Palatoschisis. Rendering of the fetal palate

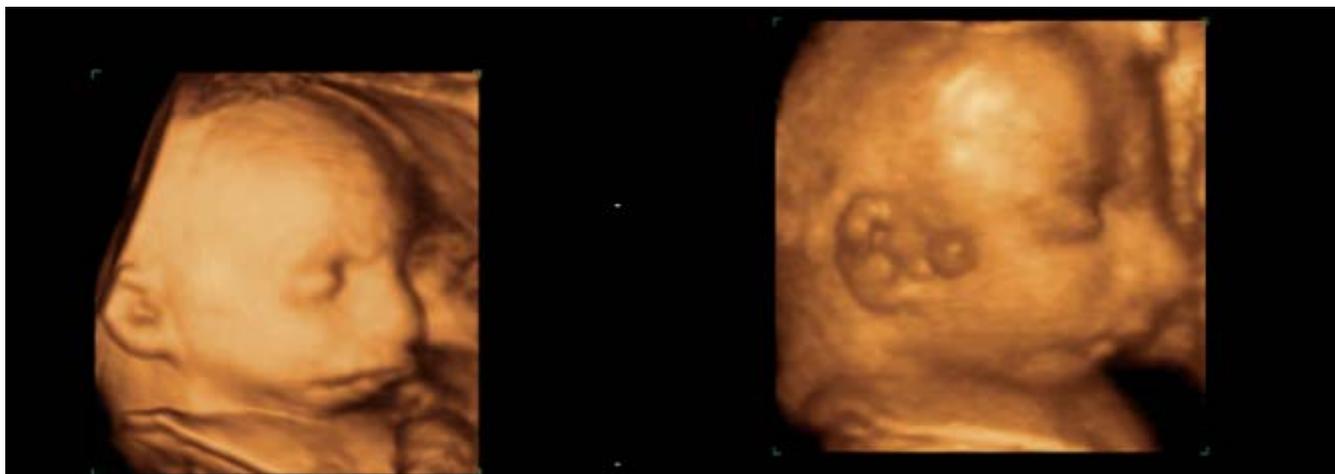


Fig. 7: Micrognathia. Surface rendering of the fetal profile (Note the preauricular tags in Figure)

thereby obtaining the reverse side of facial bones. It is worth pointing out that isolated cleft palate is less common than cleft lip/palate, but more undiagnosed.

A new challenge for 3D is the identification of isolated secondary palate cleft. The secondary palate consists of both hard and soft palates: a cleft of the hard palate always affect the soft palate but not *vice versa*.

There have been recent reports of identification of a cleft in the soft palate using new 3D techniques,²⁸⁻³⁰ which would mean that MRI might no longer be necessary.

Prenatal diagnosis has been greatly facilitated by 3D ultrasound especially in presence of syndromes characterized by an abnormal development of mandible and ears.

Mandible anomalies are usually defined only subjectively, while it is important to distinguish between retrognathia, a position anomaly, from micrognathia, an anomaly of size (Figs 6 and 7).

The study by Rotten and colleagues³¹ introduced a new measure of great help in differential diagnosis. One of these is the inferior facial angle (IFA) commonly used by orthodontics, which in the fetus has a mean value of 65.5°.

Other authors have analyzed the role of measures such as fetal mandible length³¹⁻³⁴ or anteroposterior and transverse diameters, but the one which has proved the highest sensitivity is the Jaw-Index⁷. In this case, 3D ultrasound is extremely useful in keeping the length of the examination to a minimum, since once the images of the area concerned have been captured and stored, they can be manipulated at leisure until the required section planes are obtained.

Given their common embryological origin in the branchial arches, the finding of a mandible anomaly should be followed up with an examination of fetal ear, which can be studied thoroughly only by means of 3D ultrasound, since it gives information on the size, position and shape of the ears.³³

Mandible and ear anomalies are common feature of many conditions, such as Goldenhar's and Treacher Collins' syndrome.

In Goldenhar's syndrome there is usually a unilateral hypoplasia of the mandible (Fig. 8) and condyle which is related to the asymmetric hypoplasia of the face, whereas in Treacher Collins syndrome, the hypoplasia is always bilateral so there is micrognathia (Fig. 9). In both syndromes, microtia along with preauricular tags between the tragus and the mouth has been described.³⁵ Cleft lip/palate and various organ malformations can be associated, typically unilateral in Goldenhar and bilateral in Treacher Collins. Successful prenatal diagnosis of these



Fig. 8: Surface rendering of Goldenhar's syndrome, with asymmetry of the face



Fig. 9: Surface rendering of Treacher Collins 'syndrome, with hypoplasia of the mandible at 14 weeks gestational age

syndromes using 3D ultrasound has been described.³⁶ However, the need to detect or exclude structural malformations of the inner ear and evaluate any cortical development anomaly can make MRI necessary.

The differential diagnosis is with Pierre-Robin and Nager syndromes, so a systematic examination of the limbs, hands and feet, and skeleton is required. The detection of skeletal anomalies is best done with transparent maximum mode.

CONCLUSIONS

The main pitfall in prenatal diagnosis of malformation syndromes is related to clinical variability and genetic heterogeneity of several conditions. Since most of them are an unexpected discovery during an uncomplicated pregnancy, usually with a negative family history, a great caution must be used before counselling the parents about the fetal diagnosis and prognosis.

During the last ten years there has been an increase in the number of reports that have described the prenatal diagnosis of specific syndromes with 3D ultrasound. In most cases a definite diagnosis has been reached only postnatally on the newborn or on the aborted fetus. In these cases the pathological examination was considered a precious tool to correlate the phenotypic manifestation during fetal development with neonatal phenotype.

It is possible to foresee that the development of new techniques and the more and more frequent use of 3D ultrasound, will improve the diagnostic accuracy: however a lot must be done to acquire more knowledge about the early manifestations of genetic syndromes. A multidisciplinary

approach seems to be the best prerequisite to speed up this process and to reach the point when a better communication to the prospective parents will be granted.³⁷

Before that, the clinicians must be conscious that the field of fetal dysmorphology is one the hardest in prenatal diagnosis of congenital defects.

REFERENCES

1. Lacombe D. Development genes and dysmorphology. *Rev Prat* 1997;47:169-73.
2. Donnerfeld AE. Fetal dysmorphology. *Ultrasound Obstet Gynecol* 1997;9:73-5.
3. Merz E, Bahlmann F, Weber G. Volume scanning in the evaluation of fetal malformations: a new dimension in prenatal diagnosis. *Ultrasound Obstet Gynecol* 1995;5:222-7.
4. Merz E, Weber G, Bahlmann F, et al. Application of transvaginal and abdominal three-dimensional ultrasound for the detection or exclusion of malformation of the fetal face. *Ultrasound Obstet Gynecol* 1997; 9: 237-43.
5. Pretorius DH, House M, Nelson TR, et al. Evaluation of normal and abnormal lips in fetuses: comparison between three- and two-dimensional sonography. *Am J Roentgenol* 1995; 165: 1233-7.
6. Rotten D, Levallant JM. Two- and three-dimensional sonographic assessment of the fetal face. I. A systematic analysis of the normal face. *Ultrasound Obstet Gynecol* 2004; 23: 224-31.
7. Paladini D, Morra T, Teodoro A, et al. Objective diagnosis of micrognathia in the fetus: the Jaw Index. *Obstet Gynecol* 1999; 93: 382-6.
8. Roelfsema NM, Hop WCJ, van Adrichen LNA, et al. Craniofacial variability index *in utero*: a three-dimensional ultrasound study. *Ultrasound Obstet Gynecol* 2007; 29: 258-64.
9. Roelfsema NM, Hop WCJ, van Adrichen LNA, et al. Craniofacial variability index determined by three-dimensional ultrasound in isolated vs. syndromal fetal cleft lip/palate. *Ultrasound Obstet Gynecol* 2007; 29: 265-70.
10. Mangione R, Lacombe D, Carles D, et al. Craniofacial dysmorphology and three-dimensional ultrasound: a prospective study on practicability for prenatal diagnosis. *Prenat Diagn* 2003; 23: 810-18.
11. Hsu TY, Hsu JJ, Chang SY, et al. Prenatal three-dimensional sonographic images associated with Treacher Collins syndrome. *Ultrasound Obstet Gynecol* 2002;19:413-4.
12. Delahaye S, Bernard JP, Renier D, et al. Prenatal ultrasound diagnosis of fetal craniosynostosis. *Ultrasound Obstet Gynecol* 2003; 21: 347-53.
13. Narayan H, Scott IV. Prenatal ultrasound diagnosis of Apert's syndrome. *Prenat Diagn* 1991; 10: 187-92.
14. Filkins K, Russo JF, Boehmer S, et al. Prenatal ultrasonographic and molecular diagnosis of Apert syndrome. *Prenat Diagn* 1997; 17:1081-4.
15. Bernstein PS, Gross SJ, Cohen DJ, et al. Prenatal diagnosis of type 2 Pfeiffer syndrome. *Ultrasound Obstet Gynecol* 1996;8: 425-8.

16. Pooh RK, Nakagawa Y, Pooh KH, et al. Fetal craniofacial structure and intracranial morphology in a case of Apert syndrome. *Ultrasound Obstet Gynecol* 1999;13:274-80.
17. Lyu KJ, Ko TM. Prenatal diagnosis of Apert syndrome with widely separated cranial sutures. *Prenat Diagn* 2000;20:254-6.
18. Skidmore DL, Pai AP, Toi A, et al. Prenatal diagnosis of Apert syndrome: report of two cases. *Prenat Diagn* 2003;23:1009-13.
19. Pretorius DH, Nelson TR. Prenatal visualization of cranial sutures and fontanelles with three-dimensional ultrasonography. *J Ultrasound Med* 1994;13: 871-6.
20. Faro C, Benoit B, Wegrzyn P, et al. Three-dimensional sonographic description of the fetal frontal bones and metopic suture. *Ultrasound Obstet Gynecol* 2005;26:618-21.
21. Chaoui R, Levailant JM, Benoit B, et al. Three-dimensional sonographic description of abnormal metopic suture in second and third trimester fetuses. *Ultrasound Obstet Gynecol* 2005;26:761-4.
22. Faro C, Chaoui R, Wegrzyn P, et al. Metopic suture in fetuses with Apert syndrome at 22-27 weeks of gestation. *Ultrasound Obstet Gynecol* 2006;27:28-33.
23. Johnson DD, Pretorius DH, Budorick NE, et al. Fetal lip and primary palate: three-dimensional versus two-dimensional US. *Radiology* 2000;217:236-9.
24. Chmait R, Pretorius D, Jones M, et al. Prenatal evaluation of facial clefts with two-dimensional and adjunctive three-dimensional ultrasonography: a prospective trial. *Am J Obstet Gynecol* 2002;187:946-9.
25. Ulm MR, Kratochwil A, Lum B, et al. Three-dimensional ultrasonographic imaging of fetal tooth buds for characterization of fetal clefts. *Early Hum Dev* 1999;55:67-75.
26. Lee W, Kirk JS, Shaheen KW, et al. Fetal cleft lip and palate detection by three-dimensional ultrasonography. *Ultrasound Obstet Gynecol* 2000;16:314-20.
27. Campbell S, Lees C, Moscoso G, et al. Ultrasound antenatal diagnosis of cleft palate by a new technique: the 3D "reverse face" view. *Ultrasound Obstet Gynecol* 2005;25:12-18.
28. Benacerraf BR, Sadow PM, Barnewolt CE, et al. Cleft of the secondary palate without cleft lip diagnosed with three-dimensional ultrasound and magnetic resonance imaging in a fetus with Frin's syndrome. *Ultrasound Obstet Gynecol* 2006;27: 566-70.
29. Pihu 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.
30. Faure JM, Captier G, Baumler M, et al. Sonographic assessment of normal fetal palate using three-dimension imaging: a new technique. *Ultrasound Obstet Gynecol* 2007; 29:159-65.
31. Rotten D, Levailant JM, Martinez H, et al. The fetal mandible: a 2D and 3D sonographic approach to the diagnosis of retrognathia and micrognathia. *Ultrasound Obstet Gynecol* 2002; 19:122-30.
32. Otto C, Platt LD. The fetal mandible measurement: an objective determination of fetal jaw size. *Ultrasound Obstet Gynecol* 1991; 1:12-7.
33. Shih JC, Shui MK, Lee CN, et al. Antenatal depiction of the fetal ear with three-dimensional ultrasonography. *Obstet Gynecol* 1998; 91:500-5.
34. Chitty LS, Campbell S, Altman DG. Measurement of the fetal mandible- feasibility and construction of a centile chart. *Prenat Diagn* 1993;13:749-56.
35. Watson WJ, Katz VL. Sonographic measurement of the fetal mandible: standards for normal pregnancy. *Am J Perinatol* 1993; 10:226-8.
36. Tanaka Y, Miyazaki T, Kanenishi K, et al. Antenatal three-dimensional sonographic features of Treacher Collins syndrome. *Ultrasound Obstet Gynecol* 2002;19:414-15.
37. Rustico MA, Lalatta F, Righini A, et al. The role of integrated imaging techniques for prenatal prediction of phenotype in two cases of facial anomalies. *Prenat Diagn* 2004;24:508-12.