Accuracy of the second trimester screening in the diagnosis of cleft lip and palate

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SUMMARY: Accuracy of the mid trimester screening in the diagnosis of cleft lip and palate.

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Objectives. To demonstrate the reliability of the screening of the mid trimester in the diagnosis of facial clefts through a sequential approach with 2D and 3D ultrasound.

Materials and methods. We identified 6 cases of facial clefts in the examination of fetal morphological screening of the mid trimester. All cases were investigated both with two-dimensional ultrasound scans and with reconstructions in 3D ultrasound. The scans used for diagnosis were: axial scan, sagittal and coronal scan; while rendering used for diagnosis were: Surface rendering, Multiplanar Reconstruction Mode and Maximum Mode/Transparent Mode.

Results. All 6 cases identified in screening had a postnatal feedback. Of the 6 cases found, 3 were correctly diagnosed with 2D ultrasound, while for the remaining 3 definitive diagnosis was obtained with the aid of 3D ultrasound. The sensitivity of 2D ultrasound was 50%, while the 3D ultrasound was 100%.

Conclusions. The 2D ultrasound can be used today as an investigation of first level, especially in a sample of low-risk women. Combining ultrasound 2D + 3D is the one that guarantees the best results of sensitivity and specificity.
Clefts are classified in unilateral, bilateral and median types depending on the localization of the defect, and the worst prognosis is for the median ones, they are called frontonasal dysplasia. Cleft lip are distinct in complete and uncomplete depending on their extension until omolateral nostril.

Clefts are called isolated if they aren’t associated with other anomalies, conversely they are associated in a syndrome. Isolated clefts are the most frequent kind, about the 76%; 15,9% are associated with anomalies in other districts and only 7,3% are part of a syndromic form (1).

Chromosomal anomalies are common in facial clefts, and their incidence depends on the type of defect, and are more common in the median types and less common for the isolate cleft lip. These anomalies are present in 0% of cleft lip and until 52% for median types (2).

The most frequent chromosomal anomaly associated with CLP is the Trisomy 13. In Trisomy 13 and Trisomy 18 cleft lip and palate are present in 40,7% and 6,8%, respectively (3).

Syndromes associated with cleft lip and palate are more than 100 (Table 1), and most of these can be detected with sonography.

The study of the defect is executed during the screening of the second trimester, between the 19th and the 22nd week of gestation. During the screening of the second trimester, the visualization of the upper lip is recommended (Guidelines of Società Italiana di Ecografia Ostetrica e Ginecologica - SIEOG, 2010).

Despite these recommendations, cleft is not so easy to identify: bigger defects are easier to see, while smaller ones need targeted sonographic evaluations and more specialist.

Diagnosis is also conditioned by fetal position, amount of amniotic fluid and maternal obesity that can make harder the identification of these structures.

The conventional valuation of the fetal face and the fore part of the palate includes axial and coronal planes, with a variable success between 68 and 95% (4, 5).

Fetal lips are detectable with coronal scansion, but the discontinuity of the upper lip can be detectable with a transverse scansion (6).

Sagittal plane is especially used for bilateral clefts because the protrusion of premaxilla is often clear (7, 8), and parasagittal planes are indicated for unilateral types. The identification of isolated cleft palate is harder, and the most efficient plane is the axial one (6).

Today the possibility to identify the cleft is quite higher, but the sensibility of the screening is relatively low, especially for the smallest defects and isolated forms (9).

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### Table 1 - Syndromes that are more frequently associated with facial clefts.

<table>
<thead>
<tr>
<th>Syndromes associated with facial clefts</th>
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<tbody>
<tr>
<td>Amniotic bands sequence</td>
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<tr>
<td>Arthrogryposis</td>
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<tr>
<td>Camptomelic dysplasia</td>
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<tr>
<td>CHARGE association</td>
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<tr>
<td>Crouzon</td>
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<tr>
<td>4p deletion (Wolf-Hirschorn Syndrome)</td>
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<tr>
<td>Ectodactyly, ectodermal dysplasia, cleft</td>
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<tr>
<td>Goldenhar syndrome</td>
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<tr>
<td>Gorlin syndrome</td>
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<tr>
<td>Holoprosencephaly</td>
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<tr>
<td>Klippel-Fleil syndrome</td>
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<tr>
<td>Larsen syndrome</td>
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<tr>
<td>Marfan syndrome</td>
</tr>
<tr>
<td>Meckel-Grubel syndrome</td>
</tr>
<tr>
<td>Frontonasal dysplasia</td>
</tr>
<tr>
<td>Multiple pterygium</td>
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<tr>
<td>MURCS association</td>
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<tr>
<td>Nager syndrome</td>
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<tr>
<td>Mohr syndrome</td>
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<tr>
<td>Cantrell pentalogy (rarely)</td>
</tr>
<tr>
<td>Pierre-Robin syndrome</td>
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<tr>
<td>Roberts syndrome</td>
</tr>
<tr>
<td>Smith-Lemli-Opitz syndrome</td>
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<tr>
<td>Treacher-Collins syndrome</td>
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<tr>
<td>Trisomy 13 (Patau syndrome)</td>
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<tr>
<td>Trisomy 18 (Edwards syndrome)</td>
</tr>
<tr>
<td>Trisomy 22</td>
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<td>Van der Woude syndrome</td>
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</tbody>
</table>
With standard technology, cleft lip is identified by a groove extending from the nostril inside to the lip and sometimes until the alveolar ridge. Coronal and axial scansions are the most used for detecting cleft lip and palate. With standard sonography, facial clefts can be classified by a combination of coronal, sagittal, oblique and axial scansions.

Different studies investigated the sensibility and specificity of 2D ultrasound in the diagnosis of cleft lip and palate, and, although specificity is quite high, sensibility is rather low, about 20% (10), even if in variable between different Centers among 9 and 50%.

The reason of this low sensibility is not completely known, and could depend by different factors.

One of the first reason may be the fact that, in the absence of significant risk factors, no particular attention is paid to scans of the palate, although the increased incidence of cleft is in the absence of known risk factors (11). The number of diagnosis is higher when associated with cleft there are other abnormalities of fetal development, when compared to the isolated cleft (9, 12, 13), probably because the cleft are larger or because there are risk factors that require greater caution. In these cases the sensitivity can increase even to 38% (14).

Also the number of scans has been reported as an important factor for improving the sensibility, and in particular ultrasound evaluations later in the pregnancy can increase the chances of diagnosis because the fetal anatomy is more easily identifiable. However, the maximum sensitivity period is a time window between the 20th and the 22nd week (11).

The examination of the face can be difficult, and false negatives may result from the position of the fetus, umbilical cord, hands, maternal obesity, multiple pregnancy, the presence of oligohydramnios. Also the operator’s experience is an important factor, and for this reason it is required a certain skill.

A further problem derives from isolated cleft palate, which are very difficult to identify with traditional ultrasound techniques for the acoustic shadows that are created by the presence of the massive facial bone. Certain ultrasonographic signs may be suggestive of cleft palate, such as an increase of the excursion of the tongue within the oral cavity (15), or an increase in the transverse diameter of the alveolar ridge (16).

The sensitivity of screening is definitely improved by the introduction of 3D ultrasonography in the study of the structures of the face. The splanchnocranium is one of the districts that most benefits from the survey carried out by three-dimensional technique, both in multiplanar and surface reconstruction (rendering). The use of three-dimensional technique allows to characterize the best possible anomalies of the bony structures and soft tissues of the fetal face. The volume acquisition is usually performed starting from the two-dimensional sagittal scan of the fetal profile. However, when the higher interest region is that of the lip and of the fetal palate, the acquisition can be carried out starting from an axial scan of the fetal face, at the level of the maxilla. Once obtained the volume, the multiplanar display enables accurate assessment of bone structures and facial integuments. In the case of complex defects of the lip and palate, the multiplanar evaluation allows to accurately assess the extent and the defect subtype due to the comparison between the various investigative plans. Once evaluated the anatomy in multiplanar, the rendering mode can be activated. For the study of soft tissue should be used a surface rendering mode (Figure 1), while for the study of bone structures using the “Maximum Mode/Transparent mode”: this filter allows to make transparent acquired volume, showing its underlying bony structures. The recent literature reports of the use of different 3D methodical techniques for the study of facial cleft. Each has its advantages and disadvantages, but the major limitation is that after the acquisition of the palate area both in its bony and soft component, in most cases is obscured by shadows created by the maxillary alveolar ridge. This make the study of the posterior part of the bony palate and, especially, of the sofy palate very hard in most of cases.

The sensitivity of the different three-dimensional techniques is variable depending on the methods used and the type of defect, being able to attest to a value between 90 and 100% for the cleft lip and cleft lip and palate and between 70 and 100% for the clefts that affecting the hard palate (17). The study of the soft palate is still difficult even with the three-dimensional acquisitions, and the sensitivity in this case oscillates between 15% and 25% (17).

Materials and methods

Our working group is conducting a prospective longitudinal study in order to assess the reliability of the screening in the second quarter and correspon-
Figure 1 - Evaluation of the surface structures of the fetal face with Surface rendering technique.

- Median sagittal section of the fetal head. In the median sagittal section we can identify the structures of the upper lip, alveolar ridge and hard palate, while having greater difficulties in identifying the soft palate, located posteriorly.
- Coronal front section of the lips, nose, chin.

At first, the cleft lip and palate diagnosis was confirmed or excluded from 2D ultrasonography. The hard palate, the alveolar arch and the palatine bone, have been shown in the axial plane, after which there is provided an acquisition of 3D surface. Each sonographer interprets its images and the diagnosis is immediately communicated to the parents. In order not to have only diagnostic but also prognostic information, the results are sent to a prenatal counseling team (gynecologist, neonatologist, geneticist, pediatric surgeon, psychologist). Ultrasound diagnosis is better specified as follows: CL (cleft lip without alveolar cleft or cleft palate); CL + A (cleft lip with cleft alveolar); CLP (cleft lip with cleft of alveolar ridge and palatine bone); CL + CP (cleft lip with cleft palate without alveolar cleft).

And more specifically, CL was diagnosed when the cleft lip was not associated with a disruption of the alveolar process of the maxilla or the horizontal palatal bone plate. CL + A was diagnosed when the cleft lip was associated with a visible interruption of the maxillary alveolar process without interruption of palatine bone.

CLP was diagnosed when there was, in addition to CL + A, an interruption of the horizontal plate palatine bone.

CP was diagnosed when there was no interruption of the upper lip and the alveolar ridge, but only the palatine bone.

CL + CP was diagnosed when the cleft lip was not associated with disruption of the alveolar process of the maxilla but was associated with an interruption of the horizontal plate isolated of palatine bone (no case in our clinical study).

In the same way were expressed the clinical diagnostic judgments at birth. The same pediatric plastic surgeons had already discussed with parents in the prenatal period, examined the mouth of infants and assessed the presence of CL, CL + A, CLP, CL + CP, CP.

All data are entered into a database, which is updated during the continuation of pregnancy. For all diagnosed cases has been performed a fetal karyotype and an ultrasound of the second level.

The transabdominal ultrasound is performed with a volumetric multiplanar sensor (Voluson E6). The echographic sections used for the diagnosis are:

- Surface Mode to study the soft tissues of the face.
- Transparency Mode to study the bony structures; this makes rendering transparent surface structu-
Table 2 - Our Cases.

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<thead>
<tr>
<th>Defect</th>
<th>Unilateral</th>
<th>Bilateral</th>
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<tbody>
<tr>
<td>CL</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL+A</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>TOT</td>
<td>5</td>
<td>1</td>
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Results

In this small study, 6 cases of facial clefts were reported. Of the 6 identified fetuses with cleft, 3 had a cleft lip isolated without involvement of the alveolar ridge and palate (CL), 2 had a cleft lip + disruption of the alveolar ridge (CL + A), of which in one case unilateral and bilateral in another, and it has been identified only one case of isolated cleft palate (Table 2).

All 6 cases identified in the morphological examination during the second quarter were investigated both with two-dimensional scans and with three-dimensional reconstructions, and have been certified later in the neonatal physical examination.

Of the three cases of CL, the two-dimensional sagittal scans, axial and coronal allowed to properly define the defect in two fetuses, and among these, the coronal scan was the one that best allowed to identify the defect. The last case of CL was not possible to properly identify the defect with only two-dimensional scans, and thus the diagnosis was completed with a three-dimensional reconstruction of type Surface Rendering.

Of the two cases of CL + A, one has been properly diagnosed with axial, sagittal and coronal scans, and in particular the axial scan allowed the evaluation of the extension of the defect along the alveolar ridge and the hard palate. In the second case, the two-dimensional scans have failed to identify the defect that was diagnosed with three-dimensional reconstructions of Multiplanar Reconstruction, Surface Rendering and Maximum Mode/Transparency Mode. Finally, in our study it was identified only one case of CP which covered the hard palate. This was identified by the combination of two-dimensional scans, where the most significant was the axial, and three-dimensional reconstructions, with particular reference to the Maximum Mode/Transparency Mode and Multiplanar Reconstruction.

The 2D ultrasound has identified correctly 3 out of 6 reported cases, with a sensitivity of around 50%, comparable to the data reported in the literature, and one false negative.

With three-dimensional reconstructions were identified all 6 reported cases, with a sensitivity of 100%. In the course of the study false positives were not found (“pseudo clefts”), which, however, are described in the literature.

Conclusions

From the description above we can deduct that the 2D ultrasound can still be considered as a method of first level investigation, especially if we consider women at low risk (lack of familiarity, negativity in the previous ultrasound examinations, the absence of other malformations). For this sample, the relative low incidence of the defect does not justify a more expensive approach as 3D ultrasound or MNR. Moreover, with advances in technology, the new machines have gained a lot in terms of sensitivity, and although this still remains fairly low, the number of false positives is significantly reduced compared to a three-dimensional approach.

Ultimately, systematic screening 2D ultrasound requires at least two scans (18). The median sagittal section planes. The median sagittal plane can be used to identify the presence of a protrusion of the philtrum at the level of the premaxilla, and posteriorly to the hard palate, which is continuous in a straight line. The parasagittal
scans analyze the nostrils. The examination should be extended to the ears for a possible syndromic association.

- **Plans of coronal section.** The serial scans, from front to back, allow the display of the upper lip. Subsequently, it must be tested for the maxillary alveolar ridge and confirmed the integrity of the hard palate. The difficulty of interpretation of the images increases going in the anteroposterior direction.

- **Axial section planes.** The axial planes allow visualization of the soft tissues of the upper lip that are at the front of the jaw, the jaw (alveolar ridge, alignment of the dental buds) and confirms the integrity of the hard palate.

As with sagittal scans, the difficulty increases in anteroposterior sense.

The 3D ultrasound is a second level method of investigation to confirm the suspect place with the two-dimensional survey; there is indeed a significant increase of diagnostic ultrasound if you add the two-dimensional display of the face in 3D compared to only use of ultrasound standards for facial cleft (20). Using 3D Surface-rendering mode, fetal face can be easily reconstructed and a lack of a protrusion of the upper lip or philtrum is immediately apparent. The multiplanar 3D reconstruction allows a rapid and simultaneous analysis of two fundamental planes for screening, for example the median sagittal and coronal front. Moreover, without further measures, the axial plane can be easily resumed. When you want to assess the extent of the defect to the secondary palate, only the 3D ultrasonography allows to study this structure both on the axial and coronal back plane.

The combination 2D + 3D ultrasound is one that allows the best combination of sensitivity and specificity: an approach of this type is shown in Figure 2.

This approach is valid for women at low risk, the majority of subjects in which it is offered the screening. It is appropriate for women called “high-risk” receive an approach to three-dimensional ultrasound, as this approach appears to increase the possibilities for diagnosis after the bidimensional investigation (21, 22).

Finally, a proper diagnosis requires a correct clinical management of pregnancy and newborn, as it allows an accurate definition of the defect, the search for any other anomalies, to complete the study with fetal echocardiography and with the karyotype study. It also allows to reduce the stress of the couple thanks to proper informations of the disease and the therapeutic process, and, if there are fetal abnormalities such as to cause a state of high-risk pregnancy, pregnancy monitoring and delivery programming.

### References


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**Figure 2 - Ultrasound diagnostic iter in the study of lip and palate in fetal morphological screening. A satisfactory examination requires the execution of at least two scans in the three planes; in case of suspicion always proceed in the 2D ultrasound with more scans in the three orthogonal planes, and in the case where this approach has not given satisfactory results we proceed with an examination of the second level as the 3D ultrasound.**
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