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68 Micrognathia and Retrognathia

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Introduction

The fetal mandible is a common site for defects caused by numerous genetic conditions and adverse environmental factors. When an anomaly in the fetal mandible is detected on ultrasound (US), the clinician should look for other anomalies in the fetal anatomy because such associations are frequent.

Disease

DEFINITION

Retrognathia refers to a facial malformation characterized by abnormal development of the mandible with an abnormal position in relation to the maxilla (Fig. 68.1).[1] *Micrognathia* refers to a facial malformation characterized by mandibular hypoplasia causing a small receding chin (Fig. 68.2).[1,2]

PREVALENCE AND EPIDEMIOLOGY

Fetal micrognathia has an incidence of 1:1000 births. It is always accompanied by retrognathia, although fetal retrognathia can be present without micrognathia.

ETIOLOGY AND PATHOPHYSIOLOGY

The etiology of mandibular hypoplasia is unclear.[3] It may be the result of a positional malformation, intrinsic growth abnormalities, or a connective tissue disorder. Attempts have been made to explain why fetal micrognathia is associated with different syndromes.[3] The harmonious development of different anatomic structures in the mandible and the overall growth of the mandible are regulated by several factors, such as the prenatal activity of the masticatory muscles, the growth of the tongue, the inferior alveolar nerve and its branches, and the development and migration of the teeth. Because normal development of the fetal mandible is a multifactorial process, the maldevelopment of the masticatory muscles or nerves may lead to a hypoplastic mandible. Also, the failure of mandibular formation displaces the tongue upward, which prevents the lateral palatine shelves from medial migration and midline fusion, and explains the high association of micrognathia with cleft palate.[3]

The normal development of the mandible can be disrupted by genetic or environmental factors (chromosomal and non-chromosomal syndromes) or environmental ones (Table 68.1). Some neuromuscular conditions in which a fixed contracture of the temporomandibular joint prevents the opening of the mouth are associated with micrognathia secondary to impaired development of the mandible.[1]

Also, micrognathia has been associated to exposure to different teratogens, such as in fetal alcohol syndrome and the use of tamoxifen and isotretinoin during pregnancy.[3] The spectrum of anomalies related to retinoic acid embryopathy includes facial

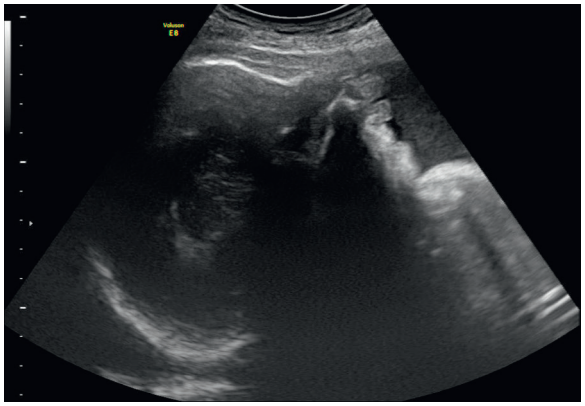

Fig. 68.1 Two-dimensional image of a fetal profile in a case of retrognathia in the third trimester. There is a receding chin with a normal size.

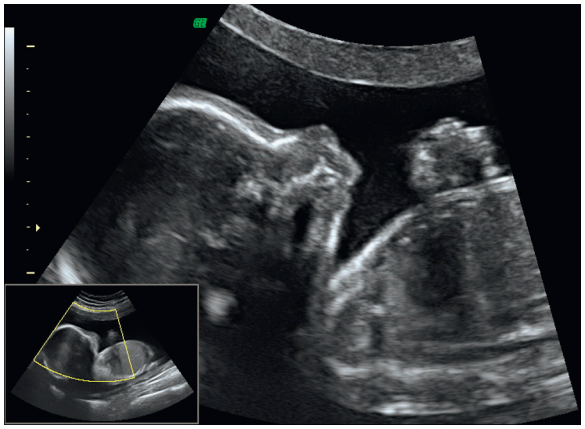

Fig. 68.2 Two-dimensional image of a fetal profile in a case of micrognathia. There is marked hypoplasia of the mandible that also displaces it.

TABLE 68.1 ASSOCIATED CLINICAL FINDINGS IN FETAL MICROGNATHIA

Syndrome	Predominant Features	Inheritance	Prenatal Diagnosis
Acrofacial dysostosis	Preaxial limb deficiencies, CHD, CNS anomalies	AD	Yes
Treacher-Collins	Hypoplasia of facial bones, ear anomalies, cleft palate	AD	Yes
Rodriguez type	Preaxial limb deficiencies, CHD	AR	Yes
Nager type	Microcephaly, preauricular tags, CHD, preaxial limb defects	Sporadic	Yes
Miller (Genee-Widemann) type or POADS (postaxial)	Syndactyly, thumb hypoplasia, absence of fifth digit	AR	—
Branchiooculofacial syndrome	Microcephaly, ear anomalies, hypertelorism, microphthalmia, renal anomalies, polydactyly, vermian agenesis	AD	Yes
Cerebrocostomandibular syndrome	Microthorax, CHD, small thorax, abnormal ribs, renal ectopia, polyhydramnios	AD-AR	Yes
Mandibuloacral dysplasia	Joint contractures, wide cranial sutures	AD	—
Oral-facial-digital I syndrome	Facial asymmetry, bifid tongue, polycystic kidney, syndactyly, CNS anomalies	X-linked dominant	Yes
Oral-facial-digital II syndrome or Mohr syndrome	Hypertelorism, polydactyly, porencephaly	AR	Yes
Oral-mandibular-limb hypogenesis spectrum	Acral hypoplasia, syndactyly	Sporadic	—
Otopalatodigital syndrome type II	Hypertelorism, omphalocele	X-linked dominant	—
Robin sequence	Glossoptosis, cleft palate		Yes
SKELETAL AND NEUROMUSCULAR DISEASES FREQUENTLY ASSOCIATED WITH MICROGNATHIA			
Achondrogenesis types IA and IB	Severe micromelia, short ribs	AR	Yes
Amyoplasia congenita disruptive sequence	Diffuse joint contractures, gastroschisis, polyhydramnios	Sporadic	Yes
Atelosteogenesis type I	Frontal bossing, midface hypoplasia, small thorax, 11 ribs, rhizomelia, talipes, encephalocele, polyhydramnios	Sporadic	Yes
Camptomelic dysplasia	Large anterior fontanelle, hypertelorism, CHD, small thorax, sex reversal in males, hydronephrosis, bowing of tibiae and less so of femora	AD	Yes
Cerebrooculofacioskeletal syndrome	Microcephaly, microphthalmia, CHD anomalies, contractures	AR	Yes
Chondrodysplasia punctata, X-linked dominant type	Microcephaly, rhizomelia	X-linked dominant	Yes
Diastrophic dysplasia	Hitchhiker thumbs, scoliosis, short limbs	AR	Yes
Langer mesomelic dysplasia	Mesomelia	AR	Yes
Multiple pterygium syndrome	Pterygia of neck, axillae, antecubital region, popliteal region	AR	Yes
Neu-Laxova syndrome	Microcephaly, exophthalmos, CNS anomalies, joint contractures, syndactyly, subcutaneous edema	AR	Yes
Pena-Shokeir phenotype (fetal akinesia deformation sequence)	Diffuse joint contractures, cystic hygroma, microstomia	AR	Yes
CHROMOSOMAL SYNDROMES FREQUENTLY ASSOCIATED WITH MICROGNATHIA			
Cat-eye syndrome	Preauricular tags, TAPVR, renal agenesis	AD inv dup (22)q11	Yes
Deletion 3p syndrome	Microcephaly, malformed ears, polydactyly in hands	Del 3p	—
Deletion 4p syndrome (Wolf-Hirschhorn)	Hypertelorism, preauricular tags, CHD, polydactyly, talipes, CNS anomalies	Isolated 4p16.3	Yes
Deletion 5p syndrome (cri du chat)	Microcephaly, hypertelorism, CHD	5p15.2	Yes
Deletion 9p syndrome	Trigonocephaly, abnormal ears, hypertelorism, CHD	AD, isolated	—
Deletion 11q syndrome	Trigonocephaly, microcephaly, joint contractures		—
Deletion 13q syndrome	Microcephaly, CHD, small or absent thumbs	Isolated	—
Deletion 22q 11.2 syndrome	Conotruncal CHD, thymus aplasia	AD	Yes
Monosomy X (Turner) syndrome	Left-sided CHD, cystic hygroma	Sporadic	Yes
Pallister-Killian syndrome	Thin upper lip, CDH, CHD, CNS anomalies, rhizomelia	Sporadic	Yes
Triploidy syndrome	IUGR, hypotonia, hypertelorism, syndactyly, CHD, CNS anomalies	Sporadic, 69,XYY	Yes
Trisomy 8 mosaic syndrome	Hypertelorism, joint contractures	Sporadic	Yes
Trisomy 9 mosaic syndrome	Joint contractures, CHD	Sporadic	Yes
Trisomy 13 syndrome	IUGR, microcephaly, microphthalmia, cleft palate, CNS anomalies, CHD, renal anomalies, polydactyly	Sporadic	Yes
Trisomy 18 syndrome	Clenched hands, CHD, omphalocele, renal anomalies, CHD anomalies	Sporadic	Yes

AD, Autosomal dominant; *AR,* autosomal recessive; *CDH,* congenital diaphragmatic hernia; *CHD,* congenital heart disease; *CNS,* central nervous system; *IUGR,* intrauterine growth restriction; *TAPVR,* total anomalous pulmonary venous return.
From: Palladini D. Fetal micrognathia: almost always an ominous finding. *Ultrasound Obstet Gynecol.* 2010;35:377-384.

asymmetry, microtia, micrognathia, and clefts of the secondary palate. Similar malformations have been observed in some infants exposed to tamoxifen. It is possible that these two agents could produce comparable embryotoxic effects if they function in a similar way during embryogenesis.

MANIFESTATIONS OF DISEASE

Clinical Presentation

The importance of differentiating retrognathia from micrognathia has been highlighted[1,4] because of the different prognoses and associated anomalies of each one. Fetal retrognathia is usually an isolated finding with a favorable prognosis. Although micrognathia could be a solitary finding, most affected infants have additional abnormalities, and it has been considered an ominous finding.[1,3] Vettraino et al.[5] reported a retrospective study of 54 fetuses with subjectively diagnosed micrognathia, which appeared to be isolated in 26% of cases prenatally, although almost all cases thought to be isolated before birth were found postnatally to have additional abnormalities, most frequently cleft palate. Half of the neonates in this study needed respiratory support, and one-third had feeding difficulties. More than one-third of the cases also had developmental delay.[5]

Mandibular anomalies are frequently associated with different syndromes (see Table 68.1). In these cases, the prognosis is usually dictated by the associated anomalies, as follows[3]:

1. Some syndromes and disorders typically affect the development of the fetal mandible, such as the Pierre Robin sequence, various forms of acrofacial dysostosis (Treacher-Collins or Franceschetti, Rodriguez, Nager, Miller, or Genee-Wiedemann), and oral-facial-digital syndromes. Pierre Robin sequence should be diagnosed if micrognathia is associated with glossoptosis and cleft palate.[6] It is associated with a normal life expectancy and good quality of life. Some of the other syndromes manifest with severe micrognathia that is more commonly associated with multiple anomalies, such as otocephaly or dysgnathia complex.
2. Some skeletal dysplasias and neuromuscular disorders may affect and compromise the development of the fetal mandible (see Table 68.1).
3. Some chromosomal aberrations are characteristically associated with fetal micrognathia. In some series, 66% of fetuses with micrognathia had chromosomal abnormalities.[7] Micrognathia is especially prevalent in trisomy 18 and triploidies, in which up to 80% of cases manifest with micrognathia; trisomy 13; and translocations or gene deletions.[7,8]
4. Exposure to teratogens such as alcohol, tamoxifen, retinoic acid, and mycophenolate mofetil has been associated with maldevelopment of the fetal mandible leading to micrognathia.[9]

Facial anomalies sometimes may be the most identifiable abnormality in a fetus with aneuploidy or a congenital syndrome.[3] Because of the high association of micrognathia with other anomalies and malformations in the fetus, a dedicated US evaluation should be performed to define the pathogenesis of the mandibular hypoplasia based on the associated findings, and to determine if it is part of a nonchromosomal syndrome. For this purpose, we perform the following examinations:

- Echocardiogram is performed because of the high association with congenital heart defects.
- Fetal long bones are measured for skeletal dysplasia evaluation.
- A fetal karyotype study should be offered in all cases of micrognathia because of the high association with chromosomal and genetic aberrations.
- Amniotic fluid is measured to evaluate for the presence of polyhydramnios.
- Maternal use of drugs and family history should be evaluated.
- Parental facial physiognomy should be taken into consideration because a receding chin can be a family trait.

Fetuses with mandibular anomalies are at risk of neonatal airway compromise,[4] which can lead to hypoxic-ischemic encephalopathy.[2] It was reported that 54% of newborns with micrognathia required an immediate intervention for this reason.[2] The most severe forms of micrognathia, such as isolated severe micrognathia, dysgnathia complex, isolated dysgnathia, and agnathia (Video 68.1), although rare, may have more difficult airways at birth and are often lethal secondary to airway obstruction.[2] In these cases, the tongue may obstruct the upper airway, leading to suffocation of the neonate. Prenatal recognition of these conditions allows potential treatment to be planned during the perinatal period or attendance of a neonatologist at the moment of delivery and thereafter.[4] In some cases, *ex utero* intrapartum treatment (EXIT) may be helpful, with intubation before cutting the umbilical cord.

Imaging Technique and Findings

Ultrasound. To detect both retrognathia and micrognathia prenatally, the fetal profile should be studied in the anatomic US scan. These anomalies can go undetected with the two-dimensional (2D) mentonasal coronal view that is used to assess the integrity of the lips (Fig. 68.3). The fetal mandible can be studied in a sagittal view from the 10th week of gestation virtually until term if the position of the head is favorable (Fig. 68.4).

Initially, a subjective diagnosis can be made by assessing the geometric relationship between the mandible and the rest of the profile in a midsagittal view (Fig. 68.5). When an alteration of the fetal mandible is suspected, the axial planes of the mandible and maxilla should be assessed to evaluate the mandibular bone, the alveolar ridge, the rami, and the maxilla, and the integrity of the palate.[1]

After micrognathia or retrognathia has been detected by a subjective examination, an objective diagnosis should be made. For this purpose, different indices, ratios, or facial angles have

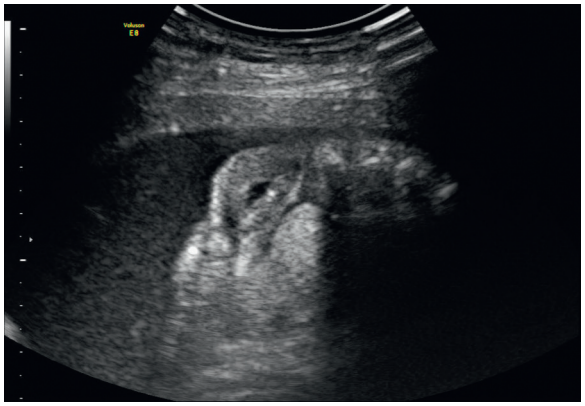

Fig. 68.3 Two-dimensional coronal view of the nose and lips. This case of micrognathia would have gone undetected in an anatomic US scan if a sagittal view had not been obtained.

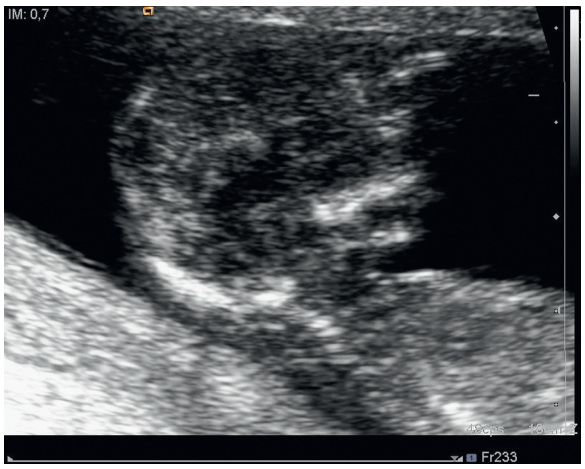

Fig. 68.4 Two-dimensional US in an early pregnancy. In this sagittal view, a retrognathic profile can be detected despite the early gestational age. Diagnosis can be made from the 10th week of pregnancy.

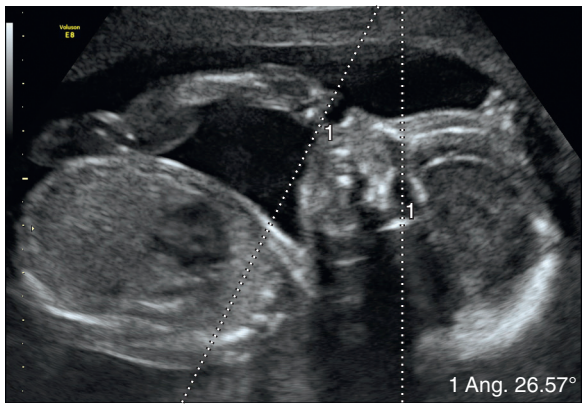

Fig. 68.6 Measurement of the IFA of the fetal profile. The upper line is orthogonal to the vertical process of the frontal bone, and the second line is traced considering the tip of the mentum and outer limit of the fetal lip. The angle that is delimited is 25 degrees, which is considered retrognathism.

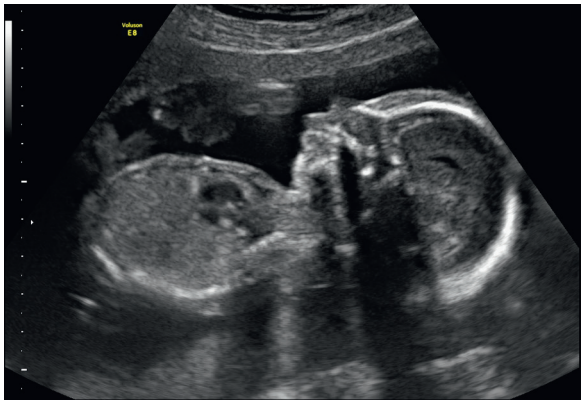

Fig. 68.5 Two-dimensional US of the fetal profile. A subjective diagnosis can be made based on the position of the mandible with respect to the maxilla.

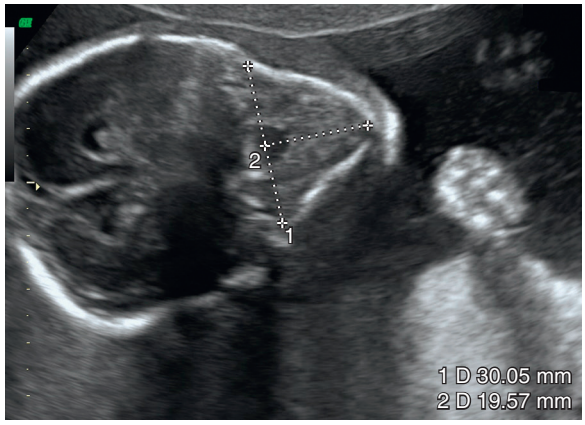

Fig. 68.7 Two-dimensional axial view of the fetal mandible. Mandibular width *(1)*; anteroposterior diameter (APD) *(2)*.

been described in the literature,[3,10–15] although not all of them are used in routine clinical practice. It is especially relevant to use measurements that are easy to obtain and ideally that are independent of gestational age. Also, because of the different prognosis of micrognathia and retrognathia, a combination of measurements should be used to discriminate both conditions and establish the severity of micrognathia. The inferior facial angle (IFA), the jaw index, the mandibular width/maxillary width ratio (MD/MX ratio), and the mandibular ratio (MR) are especially useful.

The IFA is measured in a sagittal view of the fetal face at the crossing of one line orthogonal to the vertical part of the forehead drawn at the level of the synostosis of the nasal bones and a second line traced joining the tip of the mentum and the anterior border of the more protrusive lip (Fig. 68.6).[4] Nomograms have been published of the IFA,[4] and it does not change over different gestational ages. Rotten et al.[4] reported that the average value of IFA was 65 degrees in their series from 18 to 28 weeks of gestational age. An IFA less than 49.2 degrees defined retrognathia (see Fig. 68.6). Fetuses diagnosed with a syndrome that affects primarily the development of the fetal mandible, such as Pierre Robin sequence, Treacher-Collins syndrome, or postaxial acrofacial dysostosis, had an IFA two standard deviations (2 SD) below normal values.[4]

The jaw index is measured on an axial view of the fetal mandible (Fig. 68.7). A line is drawn connecting the bases of the two rami, and the anterior-posterior diameter (APD) is measured drawing a second line from the symphysis mentis to the middle of the lateral-lateral diameter. This value is normalized to the biparietal diameter (BPD) to derive a ratio (the jaw index) and is calculated as APD/BPD × 100, which is independent of the gestational age.[13] The jaw index has been developed to predict objectively the severity of micrognathia. Using a cutoff value of less than 23 that corresponds to 2 SD below normal to define fetal micrognathia has improved the detection rate (100% sensitivity and 98% specificity) compared with subjective evaluation of the facial profile (72% sensitivity and 99% specificity).[13]

The MD and the MX are measured on an axial plane caudal to the base of the cranium, at the level of the dental arch in the maxilla (MX) and on the mandible (MD) (Fig. 68.8; see Fig. 68.7).[4] A line orthogonal to the sagittal axis is drawn 10 mm posteriorly to the anterior osseous border. Measurements are obtained from one external bone table to the other.[4] The MD/MX ratio is derived from these two measurements and is constant

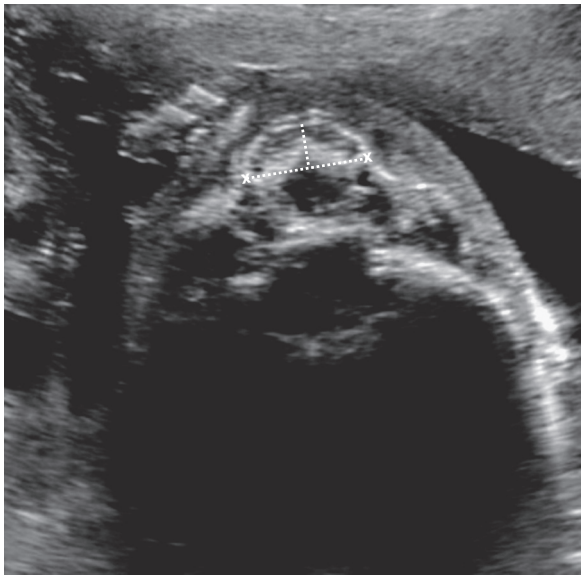

Fig. 68.8 Axial view of the fetal maxilla. On this slice, the maxillary width (MX) is traced to obtain the MD/MX ratio.

among different gestational ages. The mean value of MD/MX is 1.017 in fetuses of 18 to 28 weeks' gestation. A value less than 0.785 defines micrognathia. Cases of Treacher-Collins syndrome and postaxial acrofacial dysostosis showed MD/MX ratio values below 2 SD from the normal values. Cases with Pierre Robin sequence had moderately smaller mandibles than normal fetuses.[4]

To measure the MR, using the same view as for the jaw index, the transverse diameter and the APD are measured from inner point to inner point. The ratio between the APD and transverse diameter is the MR (see Fig. 68.7).[3] It shows a very small and nonsignificant decrease during pregnancy. Zalel et al.[3] established a constant of 1.5 for the MR for the whole period of pregnancy. To calculate the value of 2 SD to establish a diagnosis of micrognathia, the following equation is used: $MR = 1.7759 - 0.01047 \times w$, where w is the number of gestational weeks.

Each measurement has a different purpose; the IFA is to determine if there is a receding chin or retrognathia based on the angle determined by different facial structures. An advantage of the IFA is that it can be measured retrospectively with an image of the fetal profile, which is usually stored as part of anatomic US scan imaging. Alternatively, the jaw index and MD/MX ratio analyze the development of the fetal mandible independently of the gestational age and are able to determine if it is hypoplastic or not. These measurements cannot be retrospectively analyzed from a normal US examination because axial views of the mandible and maxilla are not conventional views in an anatomic scan. However, when an anomaly of the mandible is suspected, axial views may be easier to obtain. US is useful to evaluate signs of aerodigestive tract obstruction secondary to a malformed mandible, such as polyhydramnios or the absence of a stomach bubble, or to diagnose a decrease in fetal swallowing with use of color Doppler.[2]

Magnetic Resonance Imaging. Prenatal magnetic resonance imaging (MRI) has been proposed to obtain a precise study of the airway in cases in which severe micrognathia is present and the need of perinatal intubation is suspected.[2,16] The use of fetal MRI provides a more comprehensive field of view with an excellent contrast resolution from T2-weighted sequences, and multiplanar images provide more detail of the pharynx and hypopharynx, which may facilitate the diagnosis of glossoptosis.[2]

Other Applicable Modality

Three-Dimensional Ultrasound. Although views are normally obtained with 2D US, three-dimensional (3D) scanning can be more advantageous to assess mandibular anomalies for the following reasons:

1. Retrieving the right views to study suspected micrognathia and retrognathia from a stored volume is generally not time-consuming.[4] The success rate reported by some authors in obtaining acceptable measurements using 3D scanning was greater than 90%.[17]
2. It is easy to obtain perfectly symmetric views because they are computer-generated, allowing a more accurate determination of the biometry of the facial structure of interest (Fig. 68.9).[4,17]
3. A surface rendering of the face can be obtained from the stored volume, which can be useful to detect some other dysmorphic features in the fetal face that may be associated with the mandibular abnormalities (Figs. 68.10 and 68.11; Videos 68.2 and 68.3).

However, with advancing gestation, the acquisition of a good-quality 3D image may become a more difficult task because the fetus is more often in cephalic presentation with the chin on the chest, with less amniotic fluid, and the limbs and umbilical cord are more often situated in front of the chin, which may complicate the visualization of the lower face.[17]

Differential Diagnosis From Imaging Findings

In some normal fetuses, the lower lip may lie posterior to the upper lip causing a false impression of retrognathia.[7] In cases of cleft lip/palate, this protruding lip is more prevalent, leading to a false subjective impression of an associated retrognathia. However, when images of such a protruding lip were objectively analyzed using the IFA, results were normal in all cases with clefts.[4]

Synopsis of Treatment Options

PRENATAL

In severe cases of micrognathia when there is significant polyhydramnios, an amnioreduction should be considered to reduce intrauterine pressure and prolong pregnancy.

POSTNATAL

Treatment in cases of severe micrognathia should be carefully planned. To prevent an airway obstruction and a difficult intubation of the neonate at the time of delivery, EXIT should be considered before birth.[2] EXIT is designed to maintain the uteroplacental circulation and stabilize the infant while the airway is being secured.[2]

There are no standardized criteria to select cases of micrognathia that may be sufficiently severe to warrant the potential maternal and fetal risks of EXIT. Morris et al.[2] recommended using as selection criteria micrognathias with a jaw index below the fifth centile and with signs of aerodigestive tract obstruction.

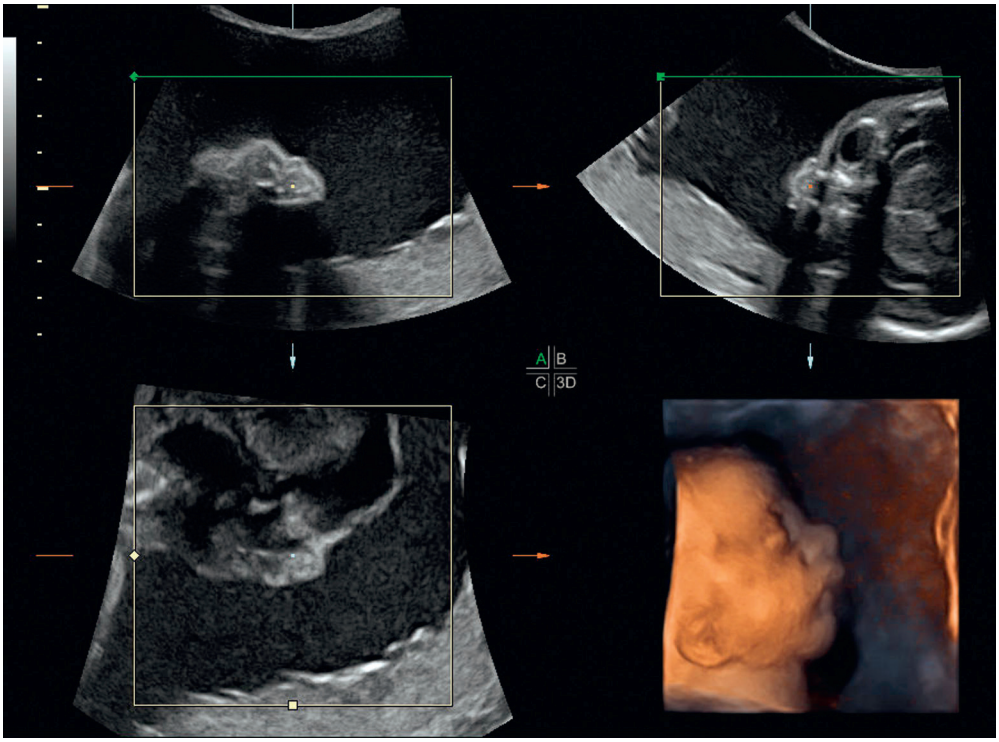

Fig. 68.9 Three-dimensional reconstruction of a micrognathia. The planes to perform measurements can be analyzed from a stored volume.

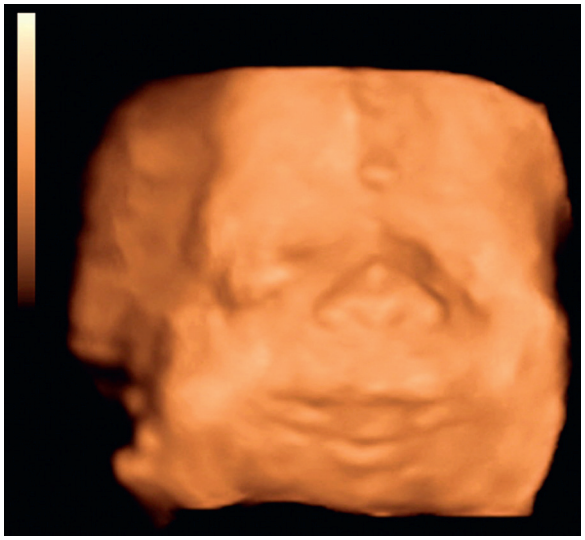

Fig. 68.10 Surface rendering of a micrognathia.

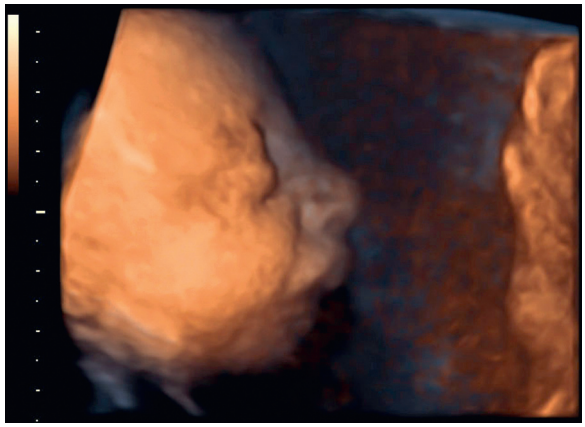

Fig. 68.11 Surface rendering of a micrognathia.

In severe cases, some authors favor proceeding directly to tracheostomy while on uteroplacental support, to ensure a safe transition from maternal oxygenation to postnatal gas exchange.

Neonates with severely hypoplastic mandibles may have severe airway obstruction, which is traditionally managed with tracheostomy. Distraction osteogenesis (DO) is considered an alternative treatment. This technique is used to induce new bone formation between bony surfaces under tension across a surgically created osteotomy. The distraction usually progresses at a rate of 0.5–1.2 mm/d. At the same time, the airway must be secured by some other means (endotracheal tube or, less frequently, tracheotomy) and intensively monitored throughout the distraction.[6] Most preliminary reports show favorable mandibular growth after DO for children with Pierre Robin sequence. DO allows the child to be successfully extubated or decannulated and typically allows the child to begin a regular oral diet.[6] This therapy option as an alternative to tracheotomy is especially important because the mortality rate from tracheotomy alone independent of the underlying diagnosis is 5%. DO avoids a tracheotomy in 90% to 95% in patients with Pierre Robin sequence.[6]

Before performing a DO, the surgeon must consider if the patient has an adequate mandibular bone stock and the level of

anoxia. If the proper criteria are not met, tracheotomy should be strongly considered.[6]

In isolated retrognathias, mandibular displacement very rarely becomes a threat for the neonatal upper airway integrity, so perinatal treatment or treatment during early childhood generally is unnecessary. Treatment of retrognathia is based on the resulting malocclusion and esthetic considerations. For this purpose, mandibular distraction is becoming a prevalent surgical treatment.[18] Many reports have shown that this technique provides great clinical benefits for mandibular deficiency and other craniofacial deformities,[18] and it can reliably remodel this craniofacial deformity.

WHAT THE REFERRING PHYSICIAN NEEDS TO KNOW

- An adequate view of the fetal profile during the anatomic US scan is very important because it is the only way to detect alterations such as retrognathia or micrognathia.
- Both anomalies in the development of the fetal jaw are different. Retrognathia implies a receding chin with a good prognosis if isolated. Micrognathia is a hypoplastic mandible, generally associated with retrognathia and mostly associated with other malformations, chromosomal abnormalities, and syndromes.
- When maldevelopment of the fetal mandible is suspected, objective measures such as IFA to determine retrognathia and the jaw index or MD/MX ratio or MR can help determine if the mandible is hypoplastic.
- When micrognathia is detected, a karyotype study should be offered to the patient, and a detailed US scan and echocardiography should be performed.
- Severe micrognathia can lead to polyhydramnios owing to a lack of swallowing. Some cases require an amnioreduction. Based on the same mechanism, severe micrognathia may cause a potentially lethal upper airway obstruction.
- Prenatal identification of severe micrognathia may improve perinatal outcome planning if EXIT and other orthopedic strategies such as DO become necessary.

KEY POINTS

- Retrognathia and micrognathia are different conditions with a different prognosis that can readily be assessed separately *in utero* using US.
- Micrognathia is frequently seen in syndromes such as Pierre Robin sequence and hemifacial microstomia and is associated with various chromosomal anomalies, such as trisomies 18 and 13, triploidy, and anomalies involving gene deletions or translocations.
- A good diagnostic strategy is to use both IFA and jaw index or MD/MX ratio to assess a fetal mandible anomaly. IFA assesses mandible position in a sagittal view. The MD/MX ratio and jaw index assess the mandible size in an axial view.
- Prenatal identification of severe forms of micrognathia implies a scheduled management of the upper airway obstruction.

SUGGESTED READING

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Ramos GA, Ylagan MV, Romine LE, et al. Diagnostic evaluation of the fetal face using 3-dimensional ultrasound. *Ultrasound Q.* 2008;24:215-223.

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