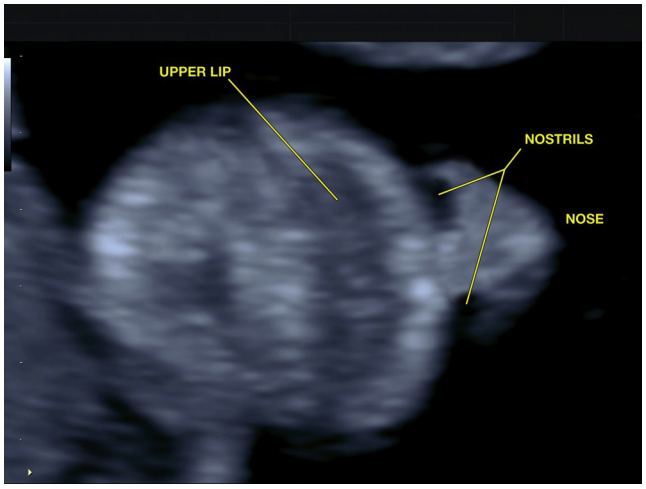
SMFM Fetal Anomalies Consult Series #1: Facial Anomalies

Society for Maternal-Fetal Medicine (SMFM); Beryl R. Benacerraf, MD; Bryann Bromley, MD; Angie C. Jelin, MD

Introduction: Facial Anomalies

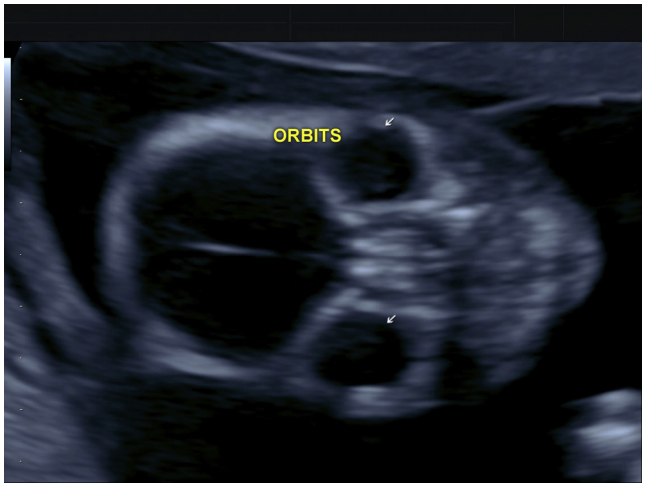
Anomalies of the fetal face can be isolated or a component of a complex syndrome. The syndromic involvement of multiple other organ systems can result in adverse outcomes. Evaluation of the fetal face is a basic part of the sonographic fetal survey, and detection of fetal facial anomalies is a key component of prenatal diagnosis. A

FIGURE 1
Coronal view of nostrils, lips, and nose



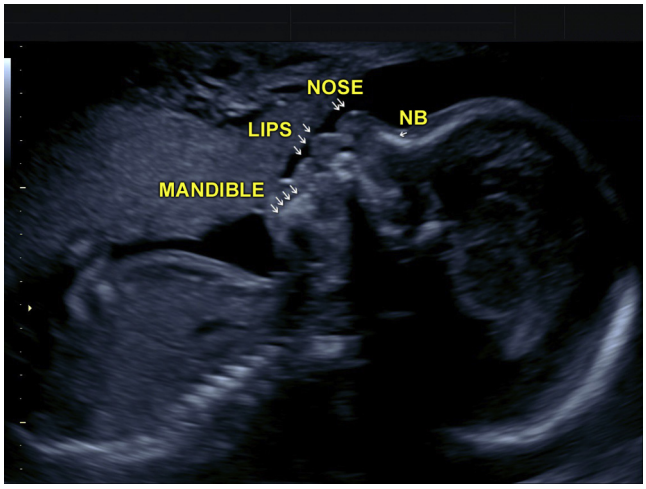
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FIGURE 2
Coronal view of orbits and mandible



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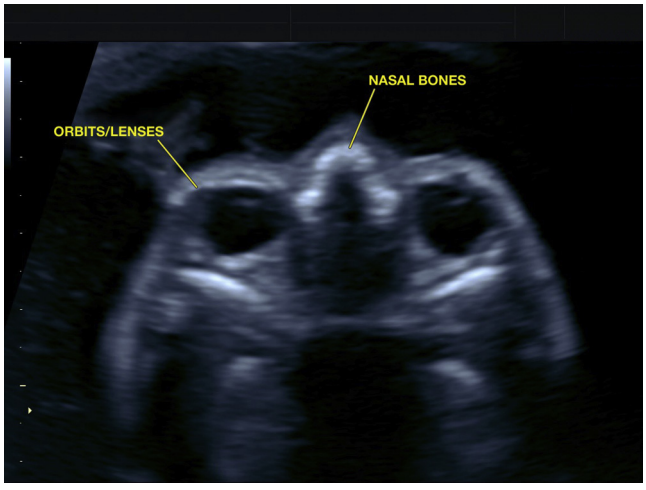
FIGURE 3
Midsagittal view of fetal profile



NB, nasal bone.

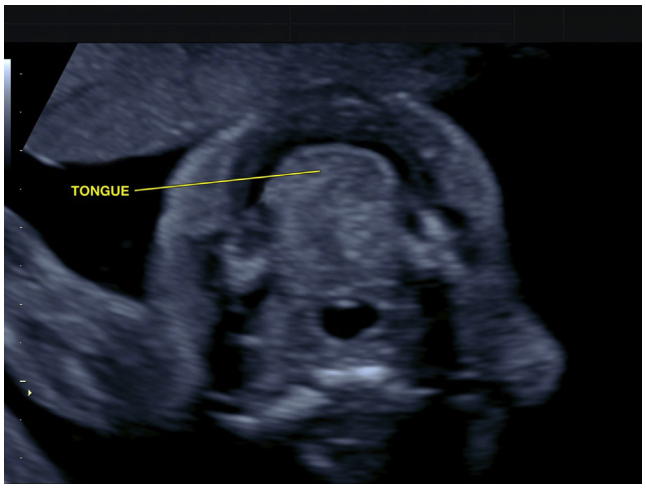
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FIGURE 4
Transverse plane and axial view of lenses, orbits, and nasal bones



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FIGURE 5
Transverse plane and axial view of tongue



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FIGURE 6
Transverse plane and axial view of alveolar ridge



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standard obstetric ultrasound examination requires only evaluation of the upper lip and is suboptimal for the identification of a range of fetal facial anomalies.[1,2] A detailed obstetric ultrasound examination is more comprehensive and is required if a facial cleft or other facial dysmorphologic condition is suspected on the standard obstetric anatomic scan or if the patient is at risk based on medical or family history. A detailed obstetric ultrasound examination of the face includes the profile, nose, lips, orbits and lenses, palate, maxilla, mandible, and tongue as well as the size and position of the fetal ears, depending on clinical suspicion.[3]

The fetal face should be evaluated in a systematic method with the use of 3 orthogonal planes. This cross-sectional approach to imaging will maximize the detection of facial abnormalities. The coronal view is used to evaluate the integrity of the soft tissue of the fetal lips and appearance of the nostrils (Figure 1). It also allows for evaluation of the fetal lenses and mandible (Figure 2). The midsagittal plane is used to demonstrate the fetal profile, which highlights the appearance of the forehead, presence of the nasal bone, contour of the nose and lips, and position and appearance of the fetal chin (Figure 3). In this plane, one can also evaluate the bones of the maxilla and mandible. The transverse (axial) view can be used to evaluate the fetal orbits and lenses, paired nasal bones (Figure 4), the tongue (Figure 5), and the alveolar ridge that comprises the primary palate (Figure 6). Surface rendering with three-dimensional imaging may be helpful in the demonstration of soft tissue defects. Nomograms are available for various biometric measurements.

The practice of medicine continues to evolve, and individual circumstances will vary. This opinion reflects information available at the time of its submission for publication and is neither designed nor intended to establish an exclusive standard of perinatal care. This presentation is not expected to reflect the opinions of all members of the Society for Maternal-Fetal Medicine.

Reprints will not be available.

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If a facial anomaly has been detected and a search for other abnormalities has been completed, the patient must be counseled properly about the ramifications of the findings, further genetic counseling with options for detailed diagnostic testing, prognosis, and further pregnancy management. A multidisciplinary team should be convened to discuss postnatal surgery, genetic evaluation, and alimentary support, if necessary.

This series reviews the sonographic diagnosis, genetic evaluation, and potential treatment and outcome of the following facial abnormalities:

- Absent nasal bone
- Paramedian orofacial cleft
- Micrognathia
- Hypotelorism
- Hypertelorism
- Anophthalmia and microphthalmia
- Median facial cleft

Coding

When coding for fetal facial anomalies (such as fetal cleft lip, fetal cleft palate, micrognathia, microopthalamia, hypotelorism, hypertelorism, or absent nasal bone), the SMFM Coding Committee recommends utilizing the ICD-10 code series O35.8xx0 - O35.8xx9.

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Absent nasal bone

Society for Maternal-Fetal Medicine; Beryl R. Benacerraf, MD; Bryann Bromley, MD; Angie C. Jelin, MD

Introduction

In euploid fetuses, nasal bone length increases with advancing gestational age.[1-4] Absent nasal bone in any trimester is a marker for fetal aneuploidy, most notably trisomy 21, although this has also been described in fetuses with trisomies 18 and 13, sex chromosome abnormalities, and other rarer aneuploidies.[1,2,5-8] Reported rates of absent nasal bone among fetuses with trisomy 21 vary widely; however, approximately 36% of fetuses with trisomy 21 will have an absent nasal bone, compared with 0.5% of euploid fetuses.[9] The influence of ethnicity on nasal bone appearance in the second trimester is controversial but may influence screening test performance. Nasal bone length has been reported for many different ethic groups and appears to be notably shorter in some groups, especially fetuses of Afro-Caribbean ancestry.[2,10,11]

Definition

The nasal bone is considered absent when it is not visualized on a midsagittal view of the profile; nasal bone hypoplasia occurs when the nasal bone appears short or hypoechoic. Criteria for defining nasal bone hypoplasia have not been uniform, and the significance of this finding is controversial.[1,2,12,13]

Ultrasound Findings

In the second trimester, a true midsagittal view of the fetal profile is obtained and magnified to fill the majority of the image space. The nasal bone appears as an echogenic linear structure below the skin edge. The optimal angle of insonation is 45 degrees to the longitudinal axis of the fetal nasal bone. If the angle of insonation is 0 or 180 degrees, the nasal bone may appear artificially absent. The presence or absence of the nasal bone may be determined at the time of the 11- to 14-week ultrasound examination and used as part of the risk assessment for aneuploidy (Figure).[14,15]

Associated Abnormalities

The identification of an absent nasal bone during the second-trimester anatomy scan should prompt a detailed anatomic assessment of the fetus to look for other structural anomalies and markers of aneuploidy. An absent nasal bone may occur as an isolated finding in fetuses who are euploid or aneuploid. This finding may be associated with other described markers for trisomy 21, such as a thickened nuchal fold and hyperechoic bowel, as well as with structural abnormalities that are associated with aneuploidy, including congenital heart defects.[1,16] The nasal bone may be absent in various craniofacial anomalies, such as frontonasal dysplasia, midface hypoplasia, or arrhinia. An absent nasal bone is also associated with several genetic and chromosomal syndromes.

FIGURE
Midsagittal view of a second-trimester fetus



The midsagittal view shows the correct angle of insonation that is required to determine the presence or absence of the fetal nasal bone. This second-semester fetus has no echogenic line under the nasal bridge and therefore has an absent nasal bone.

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Differential Diagnosis

Differential diagnosis will depend largely on associated markers and structural anomalies. An absent nasal bone is associated with an increased risk of aneuploidy, most notably trisomy 21.[17] The likelihood ratio for aneuploidy will vary depending on the presence of other sonographic markers, structural abnormalities, and ethnicity.[10,16]

The significance of an absent nasal bone can be estimated with the use of Bayes' theorem and likelihood ratios, although ethnicity-specific risks are not well-defined. In a metaanalysis of second-trimester sonographic markers, the pooled estimates of positive and negative likelihood ratios of absent nasal bone for trisomy 21 were 66.75 (95% confidence interval, 40.62–109.69) and 0.71 (95% confidence interval, 0.65–0.78).[16] In another recent metaanalysis, the pooled estimates of positive and negative likelihood ratios for trisomy 21 were 40.08 (95% confidence interval, 18.10–88.76) and 0.71 (95% confidence interval, 0.64–0.79).[9]

Genetic Evaluation

Evaluation of an absent nasal bone is dependent in part on the gestational age at detection. If noted at the time of first-trimester screening with an otherwise normal ultrasound image, this finding should be incorporated into the

first-trimester screening, and the patient should be counseled based on those results. An absent nasal bone at the time of a second-trimester anatomy screen is primarily important as a risk factor for Down syndrome, and counseling should incorporate results of any testing for aneuploidy that has been performed. Given the high likelihood ratio and specificity of this finding for Down syndrome, diagnostic testing with amniocentesis or screening with cell-free DNA should be offered. In the setting of low-risk cell-free DNA or normal fetal diagnostic testing results (karyotype or chromosomal microarray analysis [CMA]), an isolated absent nasal bone most commonly represents a normal variant. Chromosomal microarray analysis should be offered in the presence of additional anomalies that are not consistent with aneuploidy or if the prenatal karyotype is normal. If there are additional anomalies, consanguinity, or a family history of a specific condition, gene panel testing or exome sequencing is sometimes useful because CMA does not detect single-gene (Mendelian) disorders. If exome sequencing is pursued, appropriate pretest and posttest genetic counseling by a provider who is experienced in the complexities of genomic sequencing is recommended.[18]

Pregnancy and Delivery Management

A detailed ultrasound examination is recommended. A fetal echocardiogram should be performed in the setting of associated findings. Referrals to additional specialists should be based on additional sonographic findings and genetic testing results. Pregnancy termination is an option that should be discussed with all patients in whom a fetal anomaly is detected, although an isolated absent nasal bone in the second trimester is most often associated with a normal outcome. Antenatal monitoring is dependent on the presence of associated anomalies and the underlying diagnosis. Mode of delivery should be based on the usual obstetric indications, and site of delivery should be based primarily on other abnormalities or syndromic diagnosis.

Prognosis

Prognosis is dependent on the presence of associated anomalies and underlying cause. Support groups for parents of patients with trisomy 21 are available, and patients can be referred if a diagnosis is suspected or confirmed. As an isolated finding in euploid fetuses, a normal outcome is anticipated.[5]

Summary

An absent fetal nasal bone is associated primarily with an increased risk of aneuploidy. A detailed ultrasound examination should be performed to exclude other structural anomalies or markers of aneuploidy. Genetic counseling is recommended. As an isolated finding in a euploid fetus, a favorable outcome is anticipated. In the setting of other anomalies, the outcome will depend on the underlying cause.

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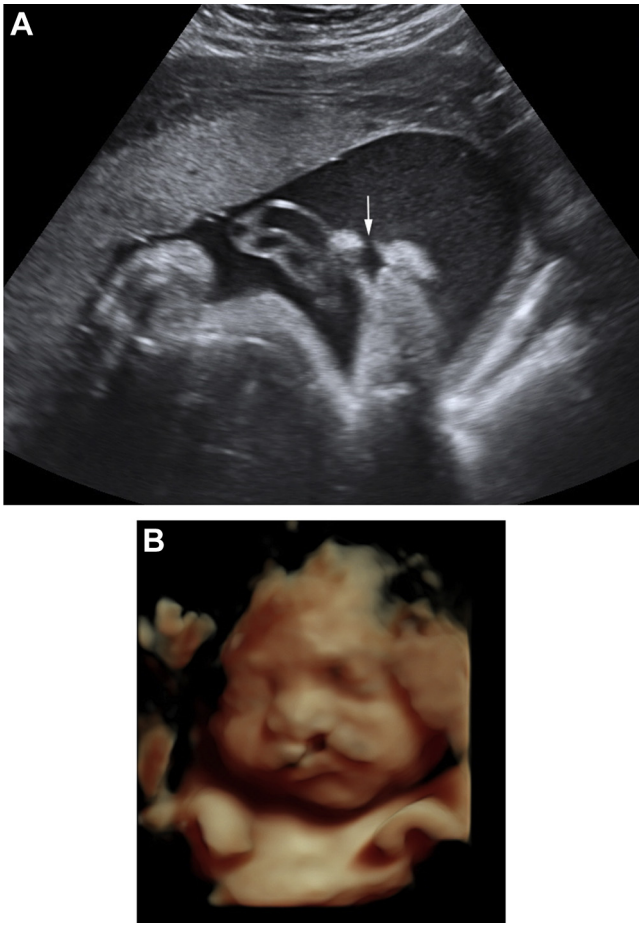
Paramedian Orofacial Cleft

Society for Maternal-Fetal Medicine; Beryl R. Benacerraf, MD; Bryann Bromley, MD; Angie C. Jelin, MD

Introduction

Orofacial clefts occur globally with a prevalence of 1:700 births. They are more common in individuals of Asian ancestry and less common in African American individuals.[1] The anatomic components that can be involved in lower facial clefts include the lip and nose, alveolus/premaxilla, and the secondary palate. Cleft lip with cleft palate (CL+CP), which is the most common type of lower facial clefting, occurs in 50% of cases. Isolated CL or CP each comprise 25% of cases.[2] Most clefts are paramedian: 64% are unilateral, and 34% are bilateral.[2] Median (midline) clefts are rare and are described separately because of their different associations.[3]

FIGURE 1
Unilateral complete cleft lip



A, Two-dimensional coronal view of the fetal face at 32 weeks of gestation shows a unilateral complete cleft lip (*arrow*). **B,** Three-dimensional coronal surface rendering of the same fetus shows a wide unilateral complete cleft lip and flaring of the affected nostril. The fetus also has a cleft palate (not shown).

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Definition

A unilateral CL is identified when there is a separation or notching of the lip on one side of the face with the contralateral side being normal. Bilateral paramedian cleft occurs when there is a separation of the lip on each side of the face, although the degree of discontinuity may differ between the sides. A complete cleft extends through the vermillion to the nostril and may cause widening and flaring of the nostril. Clefts may be incomplete when the gap does not extend to the nostril and may be so subtle as to involve only a notch in the vermillion border. Both complete and incomplete clefts may be associated with a CP. Clefts of the palate may include the primary palate (alveolar ridge and premaxilla) or the secondary palate (hard and soft) dorsal to the alveolar ridge. Isolated CP occurs with an intact lip and alveolar ridge and often evades prenatal diagnosis.[3]

FIGURE 2
Unilateral complete cleft lip



Three-dimensional coronal surface rendering of a third-trimester fetus shows a unilateral complete cleft lip. Note that the gap in the lip is narrow compared with the fetus in Figure 1, B.

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FIGURE 3
Unilateral incomplete cleft lip



Three-dimensional coronal surface rendering of a third-trimester fetus with a unilateral incomplete cleft lip. Note that the gap in the lip does not extend to the nostril.

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FIGURE 4
Bilateral facial cleft



Three-dimensional surface rendering of a fetus with a bilateral facial cleft at 16 weeks of gestation.

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Ultrasound Findings

The fetal face should be evaluated in a systematic method using 3 orthogonal planes.[4] The coronal view allows for the evaluation of the integrity of the soft tissue of the fetal lips and appearance of the nostrils. The sagittal plane allows for the assessment of the fetal profile by highlighting the appearance of the forehead, presence of the nasal bone, and contour of the nose, lip, and chin. The transverse (axial) view can be used to evaluate the alveolar ridge, which comprises the primary palate and the orbits and eyes, which are integral to the diagnosis of facial anomalies. Surface rendering with three-dimensional sonography may be helpful in the identification of soft tissue defects and for a discussion of the sonographic findings with parents and the multidisciplinary team that is involved in the care of the fetus and newborn infant (Figures 1–5).

The coronal view shows the extent of any separation of the lip along with flaring or widening of the nostrils. In the sagittal plane, a premaxillary protuberance may be seen that corresponds to displaced tissue of the intermaxillary segment (Figure 6). The axial scan may identify a disrupted alveolar ridge.[5] Evaluation of the palate is challenging; several studies have reported poor sensitivity for the detection of isolated CP.[2,3] Imaging of the fetal palate can be enhanced with specialized techniques such as a reverse-face or flipped-face technique.[6-8]

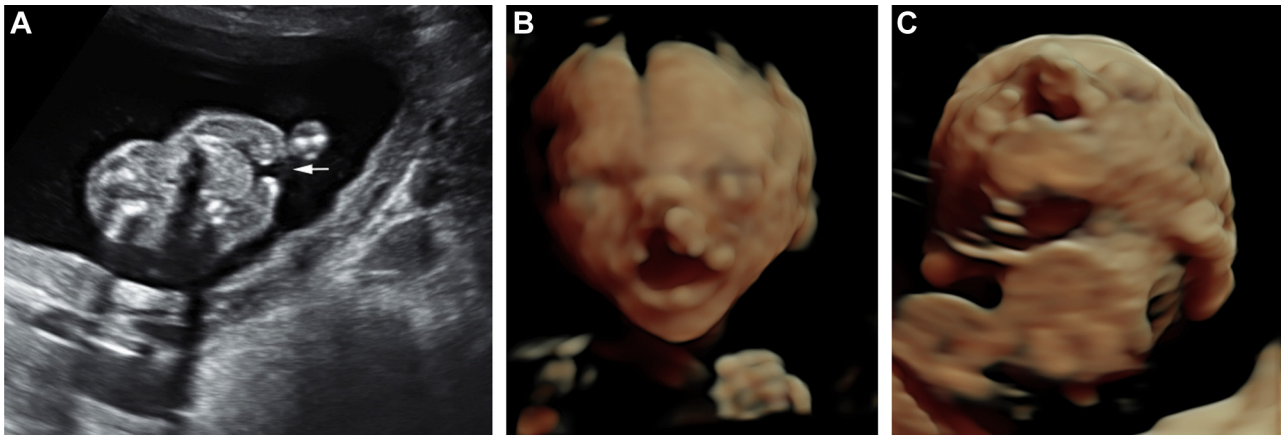
Use of uniform terminology to describe the sonographic findings is encouraged. The location of the cleft should be identified (unilateral, bilateral, or median) and the extent of soft tissue involvement (complete or incomplete) should be reported. The appearance of the nares and involvement of the palate and other facial structures also should be reported.

The diagnosis of a facial cleft is possible in the first trimester and may be suspected on the standard midsagittal view that is used to measure the nuchal translucency. A premaxillary protrusion can be seen on the midsagittal profile. Examination of the palate for a maxillary gap can help in identification of a facial cleft because the presence of a maxillary gap of $>$1.5 mm is considered abnormal (Figure 7).[9] The retronasal angle view, which is obtained on the coronal plane of the fetal face, shows the two frontal processes of the maxilla and the palate; if disrupted, it can be a marker of an oral cleft.[10-13]

Associated Abnormalities

If an orofacial cleft is identified, a detailed examination of the fetus is required to identify other anomalies. The prevalence of associated anomalies varies with the degree of clefting. Approximately 13% of fetuses with CL will have associated anomalies.[14] Structural anomalies are seen in

FIGURE 5
Unilateral clefts



A, Two-dimensional modified coronal view of a fetus with a large unilateral cleft (*arrow*) at 18 weeks of gestation. **B,** Three-dimensional rendered coronal image of the same fetus shows a wide unilateral cleft lip that extends into and distorts the fetal nose. **C,** Three-dimensional rendering of the fetal palate shows an extensive defect of the palate.

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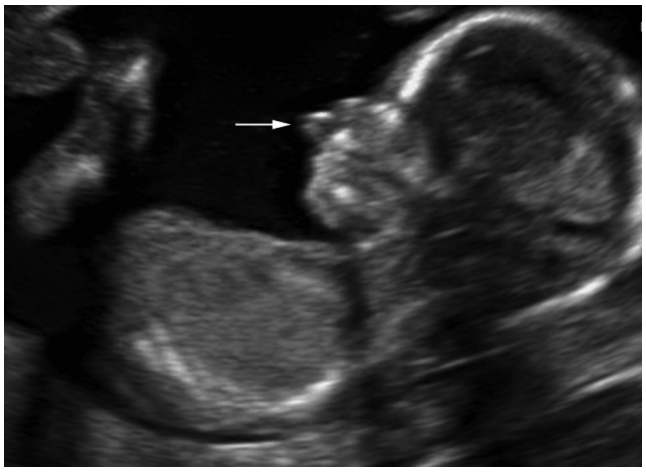
approximately 10% of fetuses with unilateral CL±CP compared with 25% of those with bilateral CL±CP.[3] Special attention should be paid to other craniofacial features such as the orbits, lenses, palate, position of the tongue, and appearance of the chin. Evaluation of the fetal ears may suggest more severe craniofacial anomalies.

Differential Diagnosis

It is critical to differentiate an isolated orofacial cleft from one with other associated anomalies, which increases suspicion for a chromosomal abnormality or genetic condition or syndrome. The spectrum and distribution of anomalies will narrow the differential diagnosis. Bilateral facial cleft with asymmetry in defect size may be mistaken for a unilateral cleft. Viewing the fetal lips from several angles and over time is important so as not to mistake overlying extremities or the umbilical cord for a facial cleft. Identification of isolated CP is challenging and may not be recognized with prenatal imaging.

Isolated orofacial clefting is multifactorial, with a 40–60% concordance in monozygotic twins.[15] It is associated with environmental exposures, which include organic solvents,

FIGURE 6
Large maxillary protuberance



Midsagittal view of a second-trimester fetus shows a large maxillary protuberance (*arrow*) that is characteristic of a facial cleft.

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FIGURE 7
Maxillary protuberance and gap



Midsagittal view of a fetus at 13 weeks of gestation shows a maxillary protuberance (*arrow*) and maxillary gap (*parallel lines*) that are characteristic of the diagnosis of a facial cleft in the first trimester.

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alcohol, cigarette smoking, retinoids, and antiepileptic agents (phenytoin/hydantoin, oxazolidinones, and valproic acid).[16,17] Deficiencies in folic acid and zinc have also been implicated.

Genetic Evaluation

The majority of orofacial clefts are isolated, although CL±CP can be a manifestation of over 400 different syndromes. Diagnostic testing (amniocentesis or chorionic villus sampling) with chromosomal microarray analysis (CMA) should be offered when an orofacial cleft is detected. Microdeletions and duplications are reported in 10.3% of orofacial clefting cases, which includes DiGeorge (22q11.2 microdeletion) syndrome.[18] If a common aneuploidy is suspected, it is reasonable initially to perform karyotype analysis or fluorescence in situ hybridization, with reflex to CMA if these test results are normal. If there are additional anomalies, consanguinity, or a family history of a specific condition, gene panel testing or exome sequencing is sometimes useful because CMA does not detect single-gene (Mendelian) disorders. Gene panel testing should be tailored to associated sonographic findings, and appropriate panels may include genes that are associated with Stickler, oral-facial-digital, or Van der Woude syndromes. If the cleft is isolated, identification of an underlying genetic cause is less likely. If exome sequencing is pursued, appropriate pretest and posttest genetic counseling by a provider who is experienced in the complexities of genomic sequencing is recommended.[19] After appropriate counseling, cell-free DNA screening is an option for the patient who declines diagnostic testing when a common aneuploidy is suspected.

Pregnancy and Delivery Management

A neurosonogram should be performed to look at the midline structures, such as the corpus callosum and cerebellar vermis.[20] The most commonly associated defect is cardiac; therefore, a detailed evaluation of the fetal cardiac anatomy is essential, and a fetal echocardiogram should be considered. Fetal magnetic resonance imaging can be considered if there is concern for associated cerebral anomalies or if ultrasound imaging is not complete.[20] A consultation with a pediatric plastic surgeon, oral maxillofacial surgeon, or craniofacial clinic for prenatal counseling is recommended. Pregnancy termination is an option that should be discussed with all patients in whom a fetal anomaly is detected; although for isolated paramedian cleft, the prognosis is typically excellent after repair. The patient should be provided information on presurgical nasoalveolar molding and neonatal feeding, and a breast pump should be prescribed if desired. No change in route of delivery is needed, although delivery should occur at a center that can provide teaching and support regarding neonatal feeding.

Prognosis

The overall prognosis is dependent on the extent of facial clefting, the association with other anomalies, and the presence of a genetic syndrome. Although surgical results of orofacial repair are excellent, the long-term prognosis is dependent on postnatal genetic evaluation. Patients may benefit from a consultation with a craniofacial surgeon and the opportunity to review outcomes of CL±CP before and after reconstructive surgery.

Summary

Orofacial clefts may be identified during a prenatal anatomic assessment of the fetus, in some cases as early as the end of the first trimester. A detailed anatomic evaluation is required and should include the evaluation of other craniofacial structures, a neurosonogram, and a comprehensive cardiac evaluation. Genetic consultation with an experienced provider is critical to determine the breadth and depth of prenatal diagnostic testing that should be offered. Counseling by a multidisciplinary team is optimal to discuss the potential postnatal course that includes newborn feeding, surgical repair, and the necessity of postnatal genetic evaluation. Three-dimensional surface rendering of the orofacial cleft may help in these discussions. Vaginal delivery at term is anticipated unless other indications that require preterm or operative delivery become apparent.

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Micrognathia

Society for Maternal-Fetal Medicine; Beryl R. Benacerraf, MD; Bryann Bromley, MD; Angie C. Jelin, MD

Introduction

Micrognathia is a condition in which the mandible is undersized for the fetal face, giving the fetus the appearance of a small jaw and overbite on profile facial views.

Definition

Micrognathia and retrognathia both refer to an abnormal mandible. Micrognathia is an abnormally small mandible; retrognathia is a mandible that is displaced posteriorly (although not necessarily small) with respect to the maxilla. Most fetuses who are diagnosed with micrognathia by prenatal ultrasound imaging have a combination of these two disorders.[1] Agnathia (otocephaly) is complete or almost complete agenesis of the mandible, with the temporal bones rotating medially; this results in the ears being horizontal and adjacent to each other or even fused in the expected location of the mandible. This extreme form of micrognathia is very rare.[1]

Ultrasound Findings

The midsagittal view of the face is necessary to evaluate the size of the mandible; care must be taken to avoid a flexed neck or chin-tuck fetal position that makes it difficult to see the size and position of the mandible. The chin and mandible are normally easily assessed subjectively and should be aligned with the upper lip and nose in the midsagittal view of the fetal face. The fetus with micrognathia or retrognathia will appear to have an overbite caused by the small and/or posteriorly displaced mandible. Measurement tables are available but are often unnecessary when the finding is clear on inspection of the fetal profile view.[2-4] The diagnosis of micrognathia can be suspected in the first trimester (12–14 weeks of gestation) on the midsagittal view of the fetal face. The sagittal profile must be observed carefully to ensure that the plane of section is truly midline. It is easy to create the impression of micrognathia if the view is not truly midline, although a normal profile cannot be visualized when micrognathia is present. The retronasal triangle view is also useful in the first-trimester evaluation of suspected micrognathia. There is normally a gap where the two mandibular rami come together on the coronal plane of the fetal face that is displayed in the retronasal triangle view. The absence of this mandibular gap is a useful early sign of micrognathia in the first and early second trimesters.[5] Overcalling this anomaly may lead to unnecessary testing, and micrognathia should not be diagnosed subjectively unless it is clearly seen (Figures 1 and 2).

Associated Abnormalities

Although mild micrognathia can be familial, it can also be associated with genetic disorders such as skeletal or neuromuscular diseases. Associated abnormalities include cleft palate and central nervous system (CNS), spine, limb, and hand anomalies. Micrognathia may appear to be isolated sonographically when associated with Pierre Robin

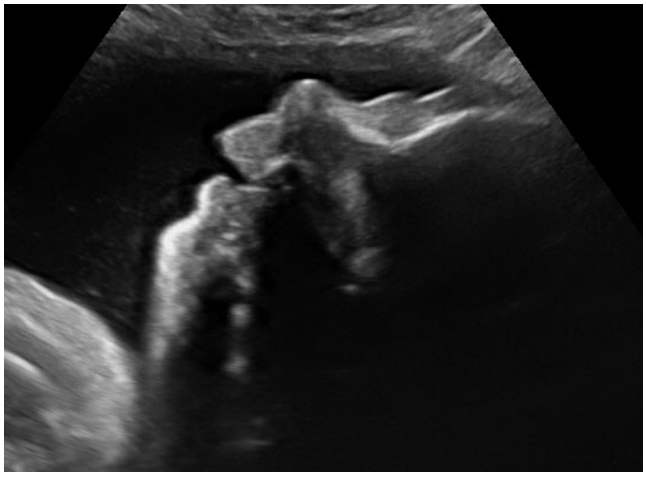
FIGURE 1
A fetus with Pierre Robin syndrome at 18 weeks of gestation



Note the small recessed chin and appearance of an overbite.

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FIGURE 2
A third-trimester fetus with micrognathia



Note the recessed chin caused by the small size of the mandible and the posterior location of the tongue inside the mouth.

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sequence, although there is a cleft palate in most cases. Cleft palate is difficult to detect sonographically in the absence of a cleft lip but can be seen in the third trimester with a three-dimensional and flipped-face view, where the palate is seen en-face looking cephalad from a plane inside the mouth.[6,7] It is also important to search for outer ear anomalies when micrognathia is suspected because this finding suggests Treacher Collins or Goldenhar syndrome. When micrognathia is part of a fetal syndrome, anomalies of additional organ systems (cardiac or lymphatic) can aide in the identification of a recognizable pattern of malformations.

Differential Diagnosis

It is important to distinguish between isolated and syndromic micrognathia. Primary mandibular syndromes include Pierre Robin sequence (micrognathia leading to glossoptosis, which affects palate formation and results in a cleft palate; this is sometimes diagnosable in the third trimester), Nager syndrome (acrofacial dysostosis with associated abnormal radii), Treacher Collins syndrome (ear anomalies), and orofacial digital syndromes (CNS and hand anomalies). Skeletal and neuromuscular diseases that result in micrognathia include multiple skeletal dysplasias (achondrogenesis, campomelic dysplasia, diastrophic dysplasia, and others), craniosynostosis syndromes (Shprintzen-Goldberg syndrome), and Roberts pseudothalidomide syndrome. Micrognathia is a feature of many chromosomal abnormalities, including mosaic trisomies 9, 13, and 18; triploidy, and others. These aneuploidies typically have many associated anomalies, such as cardiac defects, anterior abdominal wall defects, CNS anomalies, and limb malformations; detection of these can lead to the correct diagnosis. DiGeorge (22q11.2 microdeletion) syndrome is also associated with micrognathia. Other syndromes that can include micrognathia are too numerous to list but include Smith-Lemli-Opitz syndrome (genital and limb anomalies), Goldenhar syndrome (hemifacial microsomia with microphthalmia, ear tags, facial cleft, asymmetry, and hemivertebrae), Noonan syndrome (cystic hygroma, hydrops, heart defect), Meckel-Gruber syndrome (cystic kidneys, occipital encephalocele, polydactyly), Fryns syndrome (diaphragmatic hernia, heart defect), Pena-Shokeir syndrome (limb contractures, growth restriction), and Joubert syndrome (Dandy-Walker malformation).[1]

Genetic Evaluation

Diagnostic testing with chromosomal microarray analysis (CMA) should be offered when significant micrognathia is detected, particularly if there are additional features that are suggestive of a syndromic diagnosis. If a common aneuploidy syndrome is suspected, karyotype analysis or fluorescence in situ hybridization, with reflex to CMA, is a reasonable approach. Micrognathia can be inherited; however, a de novo variant is common with severe micrognathia. If there are additional anomalies, consanguinity, or a family history of a specific condition, gene panel testing or exome sequencing is sometimes useful because CMA does not detect single-gene (Mendelian) disorders. If exome sequencing is pursued, appropriate pretest and posttest genetic counseling by a provider who is experienced in the complexities of genomic sequencing is recommended.[8] After appropriate counseling, cell-free DNA screening is a reasonable option for patients who decline diagnostic evaluation if a common aneuploidy syndrome is suspected. If micrognathia is isolated, evaluation of both parents is indicated because mild micrognathia can be a constitutionally inherited variant.

Pregnancy and Delivery Management

In addition to a detailed ultrasound examination, careful evaluation of the fetal cardiac anatomy is important, and a fetal echocardiogram should be considered. Fetal magnetic resonance imaging may be useful if the palate is not clearly visualized or if there is concern for cerebral anomalies. The patient should be referred for pediatric consultation to neonatology, a craniofacial clinic, and other specialty services as appropriate based on sonographic findings. Consultation with an ear, nose, and throat specialist may be helpful if airway obstruction is suspected. The patient should be counseled about potential neonatal difficulties with breathing and feeding. Pregnancy termination is an option that should be discussed with all patients in whom a fetal anomaly is detected, although with isolated, mild micrognathia, the prognosis can be excellent. A third-trimester growth ultrasound examination with reevaluation of the mandible, fetal growth, and amniotic fluid index is recommended. No change in route of delivery is needed, although delivery at a tertiary care center is recommended with pediatrics and potentially ear, nose, and throat specialists present and ready to intubate if needed. A lactation consultation should be requested, and a breast pump should be prescribed if desired.

Prognosis

The prognosis depends on the final syndromic diagnosis. Isolated micrognathia is often associated with Pierre Robin sequence with glossoptosis, and airway obstruction should be anticipated at delivery. In some cases, the growth of the mandible can accelerate and normalize into adulthood. Prognostic counseling should be guided by the suspected diagnosis based on sonographic findings and diagnostic testing.

Summary

Prenatally detected micrognathia is often one finding of an associated syndrome. A detailed ultrasound examination with additional imaging should be performed to characterize the prenatal phenotype appropriately. Diagnostic testing is recommended and should be directed by the composite sonographic findings. Delivery at a tertiary care center with the capability for rapid neonatal intubation is preferable in the majority of cases. ■

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Hypotelorism

Society for Maternal-Fetal Medicine; Beryl R. Benacerraf, MD; Bryann Bromley, MD; Angie C. Jelin, MD

Introduction

Hypotelorism is associated most commonly with the fetal holoprosencephaly spectrum and is rarely an isolated finding. Hypotelorism may also be caused by an abnormal skull shape, such as metopic synostosis or other forms of craniosynostosis.

Definition

Hypotelorism is defined as an interocular distance of <5th percentile for gestational age.[1]

Ultrasound Findings

The coronal view of the fetal face is the best way to evaluate the orbits. The modified coronal view, which shows the upper lip, nose, and lower orbits and is similar to the view used to visualize a facial cleft, is also useful for assessment of the orbits. Charts are available for normative data of the outer-to-outer and inner-to-inner orbital diameters, although most often the hypotelorism is not subtle. Isolated hypotelorism is almost never detected in utero. Other facial, intracranial, or head shape abnormalities are almost always present (Figures 1–3).

Associated Abnormalities

Hypotelorism is most often associated with central facial cleft lip and palate of the type that is seen with holoprosencephaly sequence and midline brain defects, such as septo-optic dysplasia. If the fetus also has heart defects and polydactyly, trisomy 13 is a likely diagnosis.[2,3] Craniosynostosis can also cause abnormal interocular distances; this condition is associated with Crouzon syndrome and other asymmetric forms of craniosynostosis.

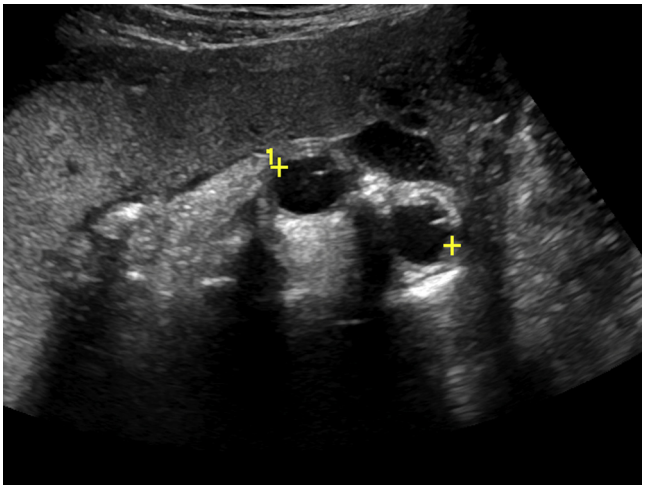
FIGURE 1
Coronal view of a fetus with hypotelorism



Coronal view shows a fetus with hypotelorism at 17 weeks of gestation.

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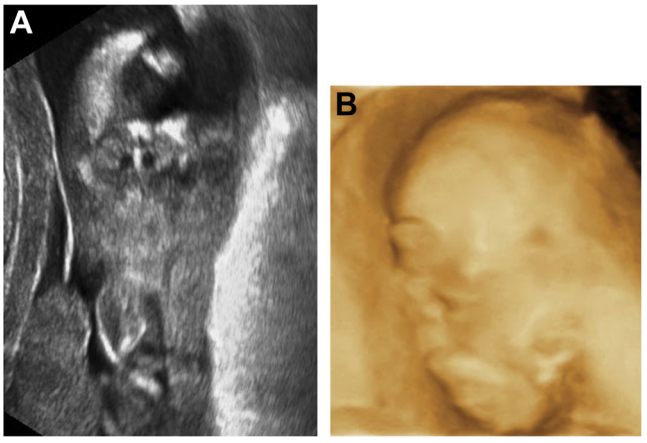
FIGURE 2
Transverse view through the orbits of a fetus with hypotelorism in the third trimester



Note that the orbits are side by side and close together.

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FIGURE 3
Two- and three-dimensional surface rendering



A, Two-dimensional and **B,** three-dimensional surface rendering of the face of a fetus with trisomy 13 and cyclopia with a proboscis above the single orbit.

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Differential Diagnosis

Although the diagnosis of hypotelorism is usually subjective without a true differential diagnosis, the orbits may be distorted or impinged on by masses such as intracranial teratomas (associated with an intracranial component) that can displace an orbit medially. As mentioned earlier, hypotelorism can also result from craniosynostosis and other syndromes. Severe hypotelorism is usually syndromic and rarely is isolated.

Genetic Evaluation

Diagnostic testing (amniocentesis or chorionic villus sampling) with chromosomal microarray analysis (CMA) should be offered when hypotelorism is detected. Given the association with trisomy 13, it is reasonable initially to perform karyotype analysis or fluorescence in situ hybridization with reflex to CMA if these test results are normal, particularly if other suggestive findings (polydactyly or heart defects) are present. If there are additional anomalies, consanguinity, or a family history suggestive of a genetic condition, gene panel testing or exome sequencing is sometimes useful because CMA does not detect single-gene (Mendelian) disorders. Gene panel testing should be tailored to associated sonographic findings, and appropriate panels may include genes that are associated with holoprosencephaly sequence. If exome sequencing is pursued, appropriate pretest and posttest counseling by a provider who is experienced in the complexities of genomic sequencing is recommended.[4] After appropriate counseling, cell-free DNA screening is an option for patients who decline diagnostic evaluation when a common aneuploidy is suspected. In isolated cases, a parental examination occasionally can reveal mild familial hypotelorism.

Pregnancy and Delivery Management

In addition to a detailed ultrasound examination, careful evaluation of the fetal cardiac anatomy is important, and a fetal echocardiogram should be considered. Fetal magnetic resonance imaging can be useful to assess any intracranial findings or for detection of subtle anomalies not detected by ultrasound imaging. Referral to pediatric ophthalmology and craniofacial specialists may be considered. Pregnancy termination is an option that should be discussed with all patients in whom a fetal anomaly is detected, although with truly isolated, mild hypotelorism, the prognosis should be excellent. No change in route of delivery is necessary for isolated hypotelorism, although delivery at a tertiary care center with pediatric genetic, craniofacial, and ophthalmology services should be considered.

Prognosis

Prognosis is dependent on the associated findings and underlying diagnosis. Isolated hypotelorism has a favorable prognosis.

Summary

Hypotelorism is a rare abnormality and is almost always associated with a syndrome, most commonly holoprosencephaly. Associated anomalies are usually present and depend on the underlying syndrome. Detection of such anomalies should help to direct the genetic evaluation.

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Hypertelorism

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Introduction

Hypertelorism is rarely an isolated finding but is associated most commonly with other major abnormalities that are often syndromic. Hypertelorism can also be caused by physical destruction of the facial midline structures, such as by a wide facial cleft, bifid broad nose, or amniotic bands.

Definition

Hypertelorism is defined as an interocular distance of >95th percentile for gestational age.[1]

Ultrasound Findings

The coronal view of the fetal face is the best way to evaluate the orbits. The modified coronal view, which shows the upper lip, nose, and lower orbits and is similar to the view used to visualize a facial cleft, is also useful for assessment of the orbits. Charts are available for normative data of the outer-to-outer and inner-to-inner orbital diameters, although most often hypertelorism is not subtle. Isolated hypertelorism almost never is detected in utero; other facial, intracranial, cranial, or syndromic abnormalities are almost always present (Figure).

Associated Abnormalities

Hypertelorism usually occurs because of physical separation of orbits, as with a wide facial cleft, frontonasal dysplasia (midline facial defects, bifid or broad nose that results in hypertelorism), or an anterior encephalocele or amniotic band sequence. There are hundreds of genetic conditions that have hypertelorism as a feature. Neonatal ophthalmologic abnormalities have also been described.

Syndromes that are associated with hypertelorism include Noonan syndrome (cystic hygroma, hydrops), skeletal dysplasias (camptomelic dysplasia, chondrodysplasia punctata), Larsen syndrome (limb abnormalities including dislocations and hyperextensions at knee joints), multiple pterygium syndrome (multiple contractures and webbing across the joints), Roberts (pseudothalidomide) syndrome, craniosynostosis syndromes (Apert, Crouzon, and Pfeiffer), Pena Shokeir syndrome (multiple joint contractures, facial anomalies), Opitz BBB syndrome (hypertelorism with hypospadias), and CHARGE association (Coloboma, Heart defects, Atresia choanae [choanal atresia], growth Restriction, Genital anomalies, and Ear anomalies).

Chromosomal abnormalities that feature hypertelorism include 4p deletion (Wolf-Hirschhorn syndrome), 9p duplication, tetrasomy 12p (Pallister-Killian syndrome), triploidy, and trisomy 18.[2,3]

FIGURE
Hypertelorism in a fetus with triploidy at 14 weeks of gestation



Note the characteristic large head and small body. The eyes are very wide apart even without measurement of the interocular distance.

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Differential Diagnosis

In addition to the aforementioned genetic causes, the orbits may be distorted or displaced by masses, such as an intracranial teratoma (associated with an intracranial component) or glioma (small mass at the medial aspect of the orbit that displaces the orbit laterally) or by amniotic bands.

Genetic Evaluation

Diagnostic testing (amniocentesis or chorionic villus sampling) with chromosomal microarray analysis (CMA) should be offered when hypertelorism is detected. If ultrasound findings or screening test results are suggestive of a common aneuploidy, it is reasonable initially to perform karyotype analysis or fluorescence in situ hybridization, with reflex to CMA if these test results are normal. If there are additional anomalies, consanguinity, or a family history that is suggestive of a specific genetic disorder, gene panel testing or exome sequencing is often useful because CMA does not detect single-gene (Mendelian) disorders and such genetic disorders are common with hypertelorism. If exome sequencing is pursued, appropriate pretest and posttest counseling by a provider who is experienced in the complexities of genomic sequencing is recommended.[4] After appropriate counseling, cell-free DNA screening is an option for patients who decline diagnostic evaluation.

Pregnancy and Delivery Management

A detailed ultrasound examination should be performed and should include comprehensive imaging of the intracranial structures (eg, a neurosonogram) and the fetal heart with consideration of a fetal echocardiogram, given the frequent association with syndromes that include congenital heart defects and intracranial abnormalities. Referrals to pediatric ophthalmology, craniofacial clinic, plastic surgery, or other subspecialty services should be based on additional sonographic findings. Fetal magnetic resonance imaging and a pediatric neurology consult are indicated if intracranial anomalies are suspected. Pregnancy termination is an option that should be discussed with all patients in whom a fetal anomaly is detected. Shared patient decision-making requires a thorough evaluation and multidisciplinary counseling regarding prognosis. The specific finding of hypertelorism does not generally affect delivery management, although delivery at a tertiary care center with pediatric genetic, craniofacial, and ophthalmology services should be considered, as appropriate for the clinical findings.

Prognosis

Isolated hypertelorism can be physiologic, although hypertelorism that appears to be isolated prenatally may be diagnosed as a syndrome in the neonatal period. Surgical correction may be indicated for cosmetic purposes or in cases of craniosynostosis. The long-term outcome is based on the underlying cause and the complexity of associated findings. Counseling is often driven by associated structural anomalies or a syndromic diagnosis. Cytogenetic and molecular diagnosis can assist with prognostic counseling.

Summary

Hypertelorism refers to increased interorbital distance. It usually is associated with a syndrome but can also be isolated or caused by mass effect. Prenatal evaluation should include an assessment for associated anomalies to guide genetic testing and prognostic counseling. Diagnostic testing with karyotype analysis, CMA, and/or gene panel or exome testing should be considered. No change in route of delivery is needed, although delivery at a tertiary care center with pediatric subspecialty services may be indicated. ■

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Anophthalmia and Microphthalmia

Society for Maternal-Fetal Medicine; Beryl R. Benacerraf, MD; Bryann Bromley, MD; Angie C. Jelin, MD

Introduction

Anophthalmia and microphthalmia are characterized by the complete or almost complete lack of the primary optic vesicle, which results in an absent or very small malformed orbital globe.

Definition

Anophthalmia is the complete absence of the orbital globe. Microphthalmia refers to a small, typically malformed orbital globe. These abnormalities can be unilateral or bilateral. The birth prevalence of these two malformations combined is approximately 1 per 10,000 births.[1]

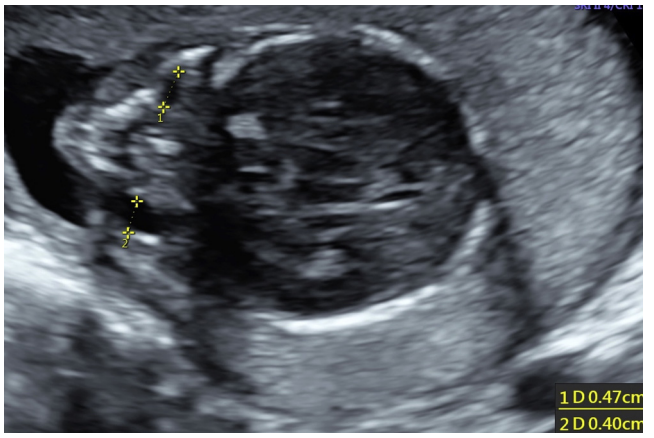
Ultrasound Findings

The fetal orbits typically are detectable by 11–12 weeks of gestation, and the lens is seen as a thin-walled circle within each orbit by 13–14 weeks of gestation.[2] The diagnosis of anophthalmia or microphthalmia is typically a subjective one, although orbital measurements at each gestational age are available.[3] The coronal view of the fetal face is the best way to evaluate the orbits. This view can show the size and shape of the orbits, their positioning on the fetal face, spacing between the two orbits, and associated facial abnormalities. The sagittal view of each orbit is also helpful when the size of the orbit is measured. The lens is seen as a small, thin-walled, circular structure and normally is visible in the anterior aspect of the globe in both the axial and sagittal views. The hyaloid artery is visible traversing the middle of the eye from anterior to posterior usually by 14 weeks of gestation and should disappear by 29 weeks of gestation.[4] Most often, diagnosis of these rare but severe ocular anomalies is made because other fetal anomalies are present and the orbital findings are part of a syndrome. Orbital defects are rarely discovered prenatally as isolated findings (Figure).

Associated Abnormalities

The associated anomalies vary with the fetal syndrome that is involved; therefore, it is crucial to perform a detailed sonographic anatomic evaluation. Triploidy and mosaic trisomies 9 and 13 are among the aneuploidies most likely to feature microphthalmia. Triploidy has early asymmetric fetal growth restriction associated with anomalies of the heart, brain, and face (hypertelorism). Trisomy 13 is associated with midline facial and brain defects, cardiac anomalies, and polydactyly. Trisomy 9 results in early pregnancy loss; survival generally occurs only in mosaic cases. Features of mosaic trisomy 9 include abnormalities of the heart, face, and skull.

FIGURE
Axial view of the fetal head and face



Axial view of the fetal head and face shows the small and asymmetric size of the orbits (*calipers*). This fetus has multiple other anomalies.

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Nonsyndromic conditions that can feature microphthalmia include holoprosencephaly spectrum, congenital viral infections (particularly rubella), and CHARGE association (Coloboma, Heart defects, Atresia choanae [choanal atresia], growth Restriction, Genital anomalies, and Ear anomalies). Other syndromes that are associated with eye anomalies include Aicardi syndrome (female fetus, arachnoid cyst), Fraser syndrome (genitourinary and tracheal anomalies), Fryns syndrome (congenital diaphragmatic hernia), Goldenhar syndrome (ear tags, cleft lip and/or palate, asymmetry of face), Gorlin syndrome (ventriculomegaly), Lenz syndrome (microcephaly), Walker-Warburg syndrome (lissencephaly, ventriculomegaly, cataracts), fetal alcohol syndrome, and others.[5]

Differential Diagnosis

Anomalies of the fetal eye may be bilateral or unilateral and asymmetric. Anophthalmia and microphthalmia refer to the size of the globe and orbit. Congenital cataracts should not be confused with microphthalmia, although both conditions may be present in the same fetus. The orbit may be distorted by masses such as intracranial teratomas (associated with intracranial component), gliomas (usually medial aspect of orbit), or retinoblastomas (rarely seen in utero).

Genetic Evaluation

Diagnostic testing (amniocentesis or chorionic villus sampling) with chromosomal microarray analysis (CMA) should be offered when anophthalmia is detected. If

screening or other ultrasound features are suggestive of a common aneuploidy, it is reasonable initially to perform karyotype analysis or fluorescence in situ hybridization, with reflex to CMA if these test results are normal. Many syndromes are associated with anophthalmia; they can be sporadic, autosomal dominant, autosomal recessive, or X-linked. If there are additional anomalies, consanguinity, or a family history of a specific condition, gene panel testing or exome sequencing may be useful because CMA does not detect single-gene (Mendelian) disorders. If exome sequencing is pursued, appropriate pretest and posttest genetic counseling by a provider who is experienced in the complexities of genomic sequencing is recommended.[6] Maternal infections (rubella), vitamin A deficiency, and teratogenic exposures (thalidomide) have also been associated with anophthalmia; therefore, obtaining a history of maternal exposures and a family history is important. After appropriate counseling, cell-free DNA screening is an option for patients who decline diagnostic evaluation if a common aneuploidy is suspected.

Pregnancy and Delivery Management

A detailed ultrasound examination should be performed and should include comprehensive imaging of the intracranial structures (eg, a neurosonogram) and the fetal heart. A fetal echocardiogram and fetal magnetic resonance imaging to assess for intracranial abnormalities should be considered. Referrals to pediatric ophthalmology, craniofacial clinic, plastic surgery, or other subspecialty services should be based on additional sonographic findings. Pregnancy termination is an option that should be discussed with all patients in whom a fetal anomaly is detected. Shared patient decision-making requires a thorough evaluation and multidisciplinary counseling regarding prognosis. The specific finding of anophthalmia or microphthalmia does not generally affect delivery management, although delivery at a tertiary care center with pediatric genetic, craniofacial, and ophthalmology subspeciality services should be considered as appropriate for the clinical findings.

Prognosis

The prognosis is variable and dependent on the severity, associated anomalies, and underlying genetic cause. Unilateral microphthalmia can have a favorable prognosis other than possible blindness in the affected eye. Mild-to-moderate microphthalmia can be managed with conformers, whereas severe cases may require surgical remodeling. Bilateral microphthalmia is often associated with intellectual disability, and vision is dependent on retinal development. Reported cases of anophthalmia typically represent severe microphthalmia; true primary anophthalmia is rarely compatible with life secondary to associated cerebral anomalies.

Summary

Microphthalmia is a rare abnormality of the eye that generally occurs because of a genetic syndrome, maternal infection, teratogenic exposure, or vitamin deficiency. Diagnostic testing is recommended with CMA and/or molecular genetic testing based on associated anomalies. Prognostic counseling is dependent on the severity of microphthalmia, associated findings, and the underlying diagnosis.

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Median Facial Cleft

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Introduction

Median or midline clefts are rare congenital anomalies and account for approximately 0.38–3% of orofacial clefts.[1,2]

Definition

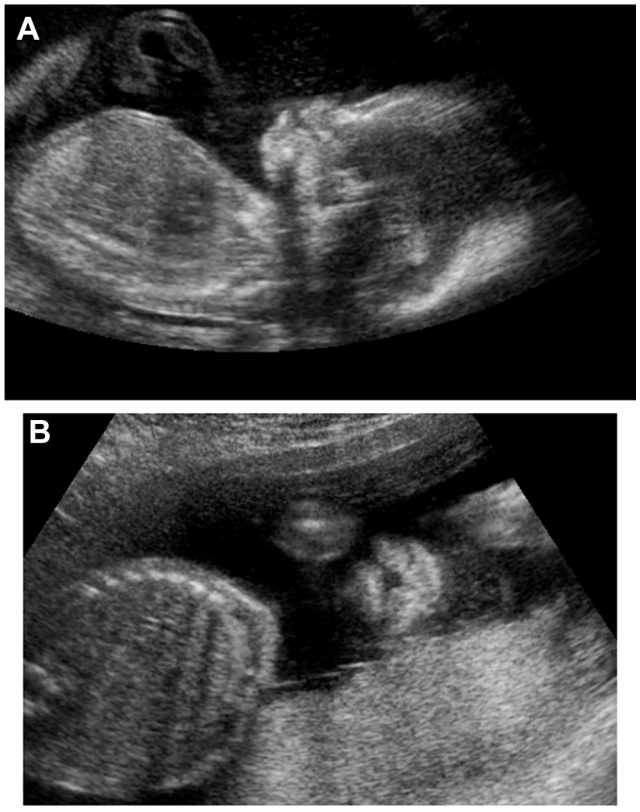
A median cleft occurs when the defect is in the median line of the face. A median cleft may be complete, extending up to and involving the nasal cavity and maxilla, or incomplete, transgressing only a portion of the vermillion.

Ultrasound Findings

The coronal view can demonstrate the extent of separation of the lip in the midline and the appearance of the nares and nasal contour. The sagittal plane is useful in the evaluation of the profile for evidence of midface hypoplasia, the presence of the nasal bone, nasal tissue, the presence of a proboscis, and the appearance of the forehead (Figure 1). The axial scan should be used to assess the size and position of the fetal orbits and to assess for defects of the palate. Imaging the fetal palate can be enhanced with the use of specialized techniques, such as a reverse-face or flipped-face technique.[3-5] In addition, a three-dimensional surface rendering can be helpful to evaluate the size and position of the fetal ears and to evaluate the palate; this can be useful in providing information to inform discussions with a multidisciplinary team (Figure 2).

Uniform terminology to describe the sonographic findings is encouraged. The location of the cleft should be identified (median or midline) and the extent of soft tissue involvement (complete or incomplete) should be reported. The normal or

FIGURE 1
Two-dimensional views



A, Two-dimensional midsagittal view of a second-trimester fetus shows an abnormal contour of the upper lip. **B,** Coronal view of the same fetus shows a median gap in the upper lip (median cleft lip).

SMFM Fetal Anomalies Consult Series #1. Am J Obstet Gynecol 2019.

FIGURE 2
Three-dimensional rendering



Three-dimensional view of a fetus at 14 weeks of gestation shows a large median cleft that involves the lip and nose.

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abnormal appearance of other craniofacial features, such as the palate, nose and nares, and orbits and eyes, should be reported.

The diagnosis of a facial cleft can be made in the first trimester by evaluation of the retronasal angle, the frontonasal space distance, and the continuity of the maxilla.[6-9] Associated abnormalities of the central nervous system, such as holoprosencephaly, should be identifiable between 11 and 13 weeks of gestation.[10]

Associated Abnormalities

A median cleft lip may be small and isolated or may be large and associated with numerous other structural anomalies. A detailed anatomic assessment of the fetal anatomy is required, including a neurosonogram and a detailed evaluation of the fetal heart and distal extremities. Median clefts may be seen with hypertelorism or hypotelorism, which includes cyclopia. There may be arrhinia (absent nose), bifid nose, or a proboscis (a malformed tubular structure usually in a supraocular location). Central nervous system abnormalities, such as holoprosencephaly or agenesis/lipoma of the corpus callosum, may help in the identification of a syndromic cause. Evaluation of the hands (for polydactyly) and the musculoskeletal system is critical.

Differential Diagnosis

The differential diagnosis of a median cleft is largely dependent on the size of the abnormality and the association with other structural anomalies.[2] Primary craniofacial syndromes that are associated with a median facial cleft are typically within the holoprosencephaly spectrum and are often secondary to aneuploidy, particularly trisomy 13. Frontonasal dysplasia or median cleft face syndrome are considerations when a median cleft (either complete or incomplete) is associated with hypertelorism. A median cleft with nasal polyp and lipoma of the corpus callosum should raise the suspicion of Pai syndrome, which is a developmental disorder that can include nasal polyps and other anomalies. Other syndromes that are associated with a median cleft include short rib-polydactyly syndrome type 2 (Majewski syndrome) and orofacial digital syndrome. Numerous chromosomal and genetic syndromes have been associated with median cleft lip.

Genetic Evaluation

Diagnostic testing (amniocentesis or chorionic villus sampling) with chromosomal microarray analysis (CMA) should be offered when a midline cleft is detected. Given the association with holoprosencephaly and trisomy 13, it is reasonable initially to perform karyotype analysis or fluorescence in situ hybridization, with reflex to CMA if these test results are normal. After appropriate counseling, cell-free DNA screening is an option for patients who decline diagnostic evaluation because it will detect most cases of trisomy 13 and other common aneuploidies. If there are additional anomalies, consanguinity, or a family history of a specific condition, gene panel testing or exome sequencing is sometimes useful because CMA does not detect single-gene (Mendelian) disorders. If exome sequencing is pursued, appropriate pretest and posttest genetic counseling by a provider who is experienced in the complexities of genomic sequencing is recommended.[11]

Pregnancy and Delivery Management

A detailed sonographic evaluation should include an assessment of the other structures within the fetal face, including evaluation of the orbits and distal extremities for evidence of finger anomalies, detailed neurosonography, and consideration of a fetal echocardiogram. Fetal magnetic resonance imaging should also be considered if intracerebral findings are suspected. Referrals to a craniofacial clinic or pediatric plastic surgery should be considered, along with additional referrals as indicated. Pregnancy termination is an option for all patients in whom a fetal anomaly is detected and should be discussed with patients with a fetal midline cleft, particularly if other anomalies are present. The finding of a fetal midline cleft does not generally alter the mode of delivery, although delivery should occur at a center that can provide teaching and support regarding neonatal feeding.

Prognosis

Prognosis is variable and favorable if isolated; however, a midline cleft is often associated with intracerebral anomalies or syndromes. More severe clefts, as characterized by facial and eye findings, are more likely to be associated with developmental delay. Prognostic counseling is greatly dependent on these variables and can be aided by appropriate diagnostic testing.

Summary

The finding of a median cleft should prompt a detailed sonographic evaluation of the fetus to look for associated anomalies. Prognosis is dependent on the underlying cause and associated anomalies. Diagnostic genetic testing is recommended. A multidisciplinary team should be convened for consultation concerning postdelivery surgical management, feeding considerations, and genetic counseling. ■

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