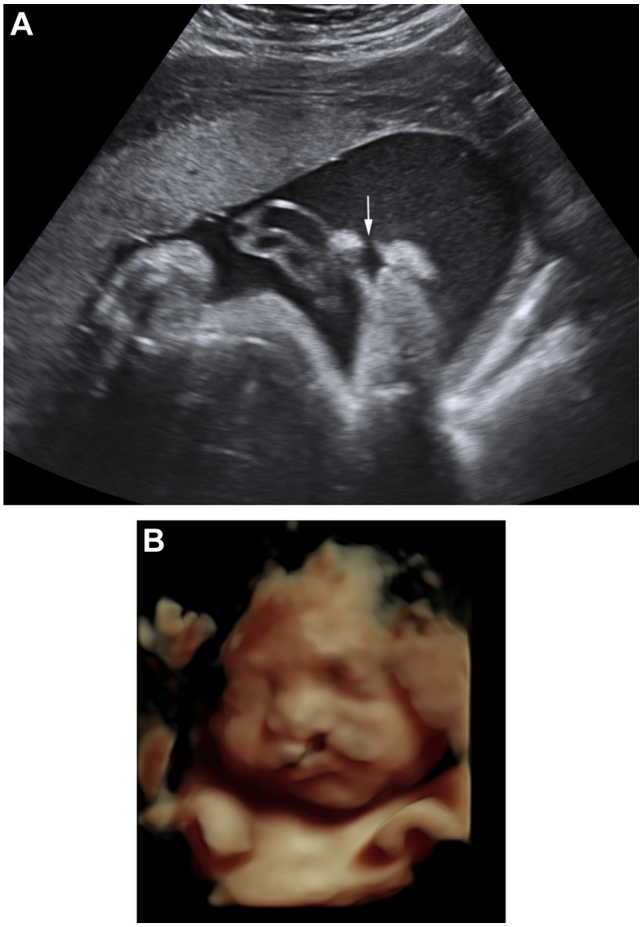
Paramedian Orofacial Cleft

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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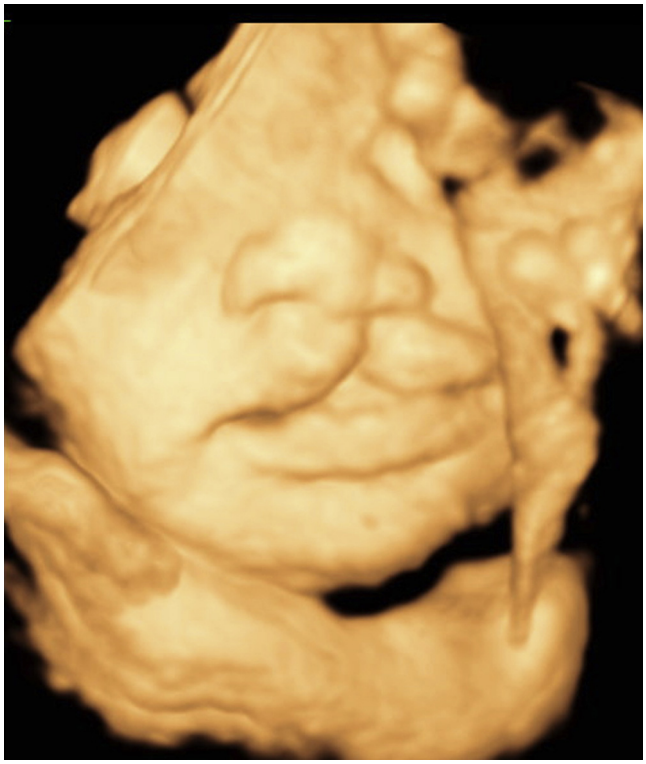
Definition

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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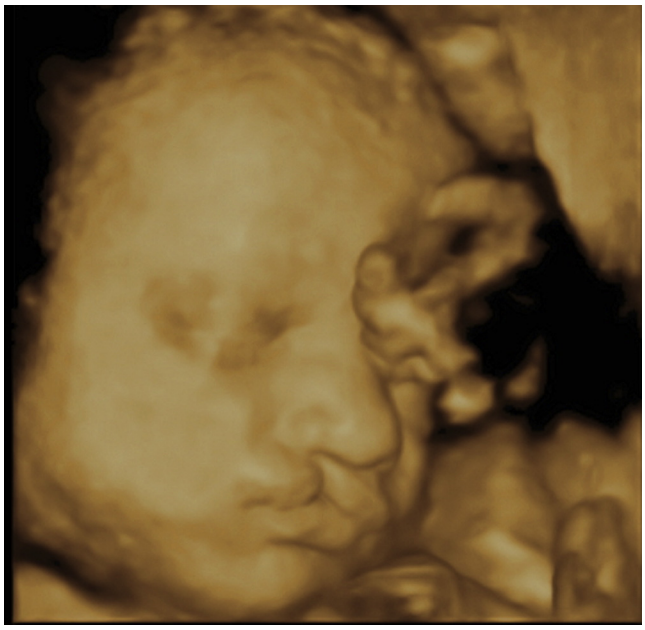
FIGURE 3
Unilateral incomplete cleft lip



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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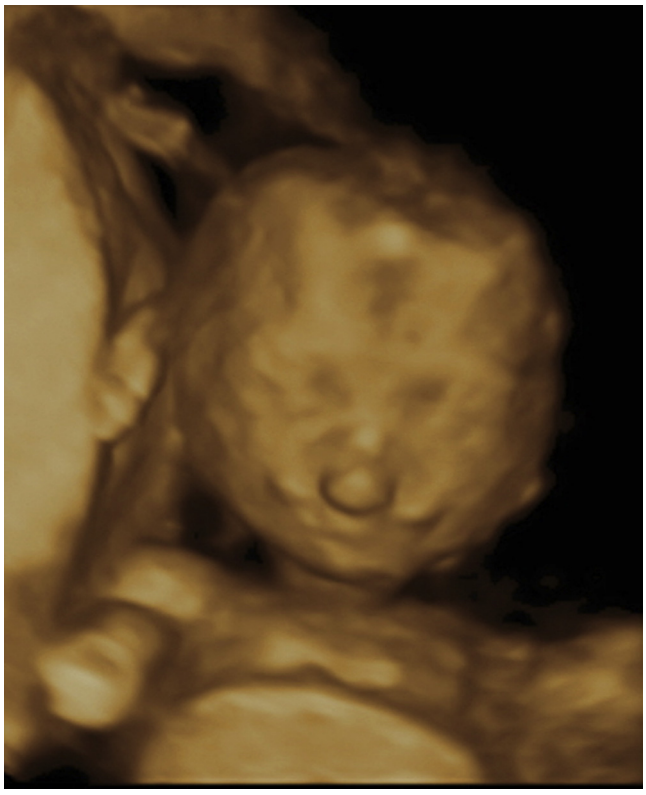
FIGURE 4
Bilateral facial cleft



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]

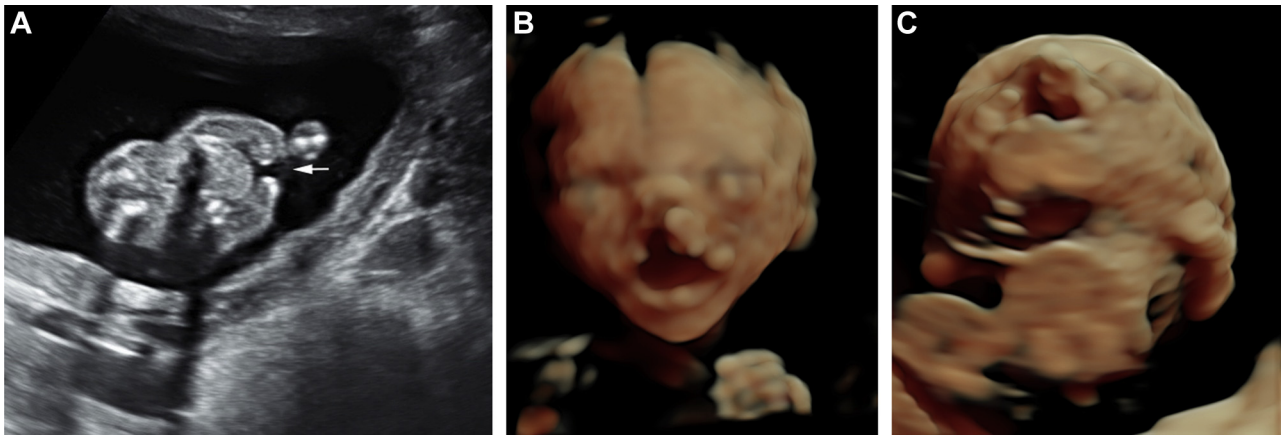
Use of uniform terminology to describe the sonographic findings is encouraged. The location of the cleft should be identified (unilateral, bilateral, or median) and the extent of soft tissue involvement (complete or incomplete) should be reported. The appearance of the nares and involvement of the palate 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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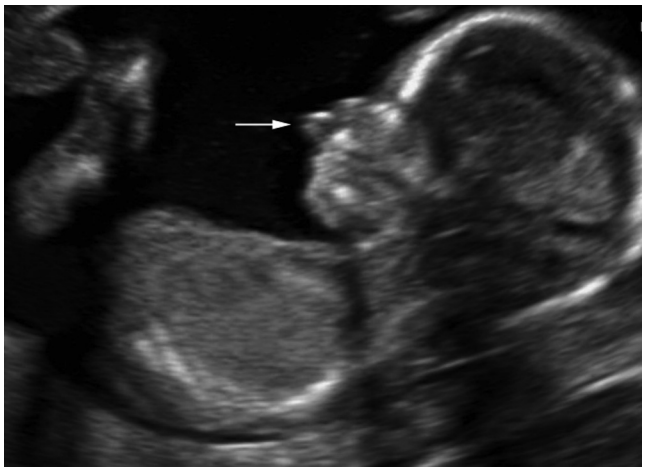
approximately 10% of fetuses with unilateral CL±CP compared with 25% of those with bilateral CL±CP.[3] Special attention should be paid to other craniofacial features such as the orbits, lenses, palate, position of the tongue, and appearance of the chin. Evaluation of the fetal ears may suggest more 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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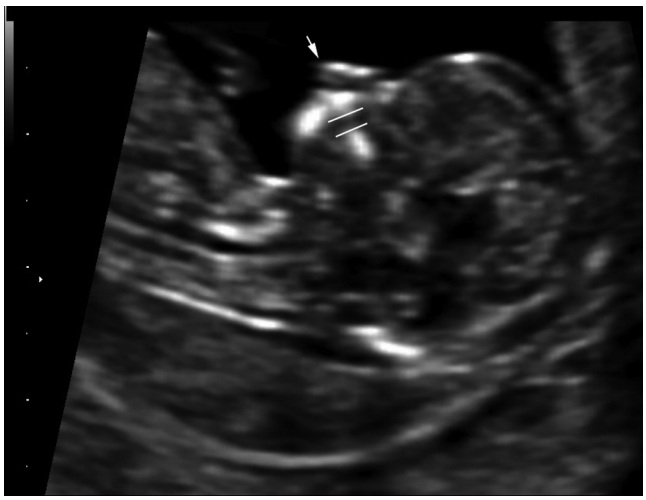
FIGURE 7
Maxillary protuberance and gap



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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