Narrative Review

Fetal Cleft Lip and Palate

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Fetal cleft lip and cleft palate are among the most common craniofacial anomalies, affecting approximately 1 in 1,000 live births worldwide. Cleft lip/cleft palate is caused by a combination of genetic and environmental factors and requires prompt diagnosis and lifelong multidisciplinary care for adequate treatment of anatomic and psychosocial challenges that extend well beyond surgical procedures in infancy. Cleft lip/cleft palate is a complex anomaly present from the first trimester onward that has prenatal and postnatal considerations. Diagnosis of cleft lip/cleft palate is most common in the second trimester through ultrasound visualization of the anatomic defect. However, characterization of the defect may be further performed in the third trimester, possibly with the adjunct of magnetic resonance imaging. Prenatal management depends on the cause, genetic association, or additional anatomic abnormalities that may dictate specific timing and location of delivery. Multidisciplinary management involves perinatology, genetic counseling, orofacial surgery, and lactation specialists and speech and language therapists among experts from other specialties for comprehensive treatment. In this narrative review of cleft lip/cleft palate, the anatomic characteristics, imaging findings, causes, genetic associations, and management are discussed.

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Orofacial clefts are among the most common craniofacial anomalies and are defined by the failure of normal fusion of the lip or palate between the 4th and 7th weeks of gestation. This disruption in embryologic fusion results in a visible discontinuity of the fetal lip or a gap in the palate. The embryologic development of the lip and palate is highly complex, involving tightly regulated processes of cell migration, differentiation, and apoptosis.[1] The anatomy of a cleft lip involves the philtral columns, alveolus, and orbicularis oris muscle fibers failing to fuse normally.[2] A cleft palate can involve the hard, soft, or both palates, which then can disrupt the nasal and oral cavities.

The prevalence of cleft lip with or without cleft palate is approximately 1 in 1,000 live births worldwide; isolated cleft palate occurs in about 6 per 10,000 births.[3] Cleft lip/cleft palate is more frequent among individuals of Asian and Native American descent (2.62/1,000 live births) and less common among those of African descent (fewer than 1 in 1,000 live births).[4] Orofacial clefts are more prevalent in male than female individuals, with 60% of clefts (cleft lip alone, cleft lip/cleft palate, or cleft palate alone) occurring in male individuals.[5] Most cleft lip/cleft palate cases occur in isolation without additional anomalies; however, approximately 30% are related to a genetic syndrome.[6]

Because an intact lip and palate separate the oral and nasal cavities, defects in these structures can adversely affect breathing, swallowing, feeding and eating, and speech. In this review of cleft lip and cleft palate, we highlight the common imaging findings, associated anomalies, genetic predisposition, pregnancy management, and neonatal prognosis.

IMAGING FINDINGS

Ultrasonography is the primary diagnostic modality for identifying cleft lip/cleft palate, with initial findings detectable as early as 13–14 weeks of gestation; however, diagnostic sensitivity improves with advancing gestational age, with diagnosis typically occurring at approximately 20 weeks of gestation.[7] The presence of additional structural malformations may further increase the likelihood of prenatal detection. Despite its utility, the accuracy of ultrasonography is influenced by gestational age, maternal body habitus, fetal positioning, and operator experience.

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The ultrasonographic features of cleft lip/cleft palate vary depending on the type of anomaly present. Figure 1 demonstrates a fetus with a normal cleft lip/cleft palate. In the setting of cleft lip, an anterior lip defect will be visualized with a vertical hypoechoic region either unilaterally or bilaterally (Fig. 2). If cleft palate is present, this hypoechoic region will extend into the palate; however, it is less reliably diagnosed than cleft lip (Fig. 3). Three-dimensional ultrasonography may also improve visualization of the fetal palate or disruption of the alveolar ridge.[8]

Magnetic resonance imaging (MRI) has been shown to be a useful adjunct to ultrasonography in identifying the degree of involvement.[9] Specifically, MRI allows direct visualization of the soft palate in the axial plane, improving identification of the separation in the hard or soft palate that is often associated with defects in the levator palatini muscle.[10] Other features indicative of cleft lip/cleft palate include protrusion of the premaxillary segment and missing tooth buds corresponding to lateral incisors. Magnetic resonance imaging is less dependent on amniotic fluid volume, fetal position, maternal habitus, and the absence of bone shadowing than ultrasonography; however, ultrasonography remains an adequate screening modality with the adjunct of MRI in some cases to provide improved accuracy of diagnosis and extent of involvement.[9]

ASSOCIATED FINDINGS

If cleft lip or cleft palate is identified on ultrasonography, a detailed fetal anatomic second-trimester examination should be performed to assess the profile, nasal bone, orbit, nose and lips, palate, maxilla, mandible, tongue, and ear.[11] The risk of other anomalies is associated with the severity of the cleft(s). Additional anomalies are detected in 9.8% of fetuses with a unilateral cleft lip/cleft palate; this prevalence increases to 25% in fetuses with bilateral cleft lip/cleft palate.[12] Among those with a true midline cleft, 100% have additional midline facial anomalies such as hypertelorism or hypotelorism, cyclopia, and nasal malformations (arrhinia, proboscis).[13] Midline clefts are often associated with central nervous system abnormalities such as holoprosencephaly often attributable to aneuploidy or other genetic conditions.[12,13] Because of a high chance of additional anomalies associated with a diagnosis of cleft lip/cleft palate, fetal echocardiography and neurosonography should be performed on each affected fetus.[14]

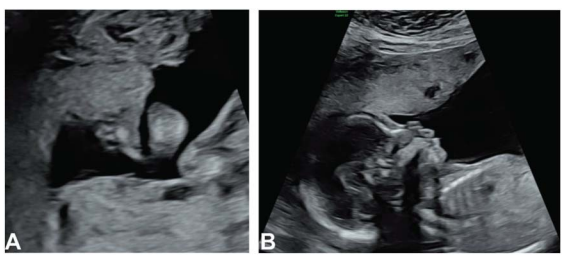

Fig. 1. Normal lip and palate. **A.** Second-trimester coronal ultrasonogram with a normal nose and lips. Palate not visualized. **B.** Second-trimester sagittal ultrasonogram with normal nose, lips, and palate.

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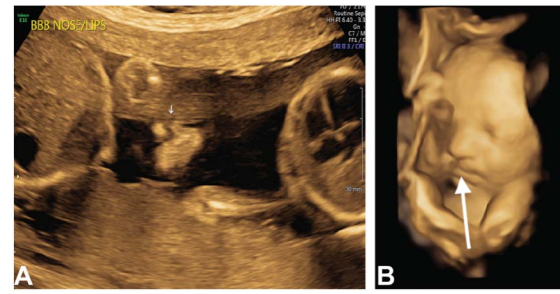

Fig. 2. Right cleft lip. **A.** Second-trimester coronal ultrasonogram with right cleft lip. Palate not visualized. **B.** Second-trimester three-dimensional ultrasonogram with right cleft lip. Palate not visualized. *Arrow* indicates cleft lip.

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CAUSE

Seventy percent of isolated cleft lip/cleft palate cases are nonsyndromic, meaning they occur without other congenital anomalies or recognized syndromes, with

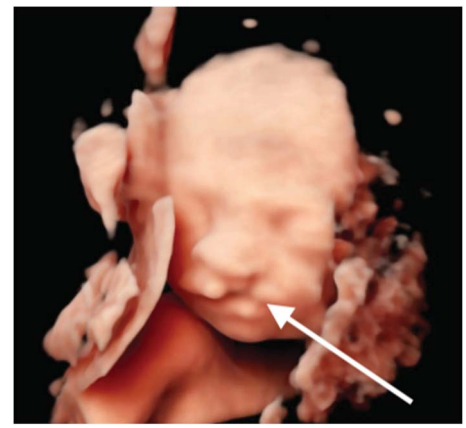

Fig. 3. Left cleft lip and palate. Second-trimester three-dimensional ultrasonogram with left cleft lip and palate. *Arrow* indicates cleft lip with or without cleft palate.

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20% of nonsyndromic cases representing familial cleft lip/cleft palate and the remaining 80% thought to be multifactorial and therefore caused by both genetic and environmental factors.[15] Both chromosomal and monogenic conditions have been associated with cleft lip/cleft palate, with the highest likelihood for a genetic cause when cleft lip/cleft palate is nonisolated.[16,17] Most common chromosomal causes include trisomy 13 and 18, especially when cleft lip/cleft palate is midline or bilateral. The most common chromosome copy number variant associated with cleft lip/cleft palate is 22q11.2 deletion syndrome (DiGeorge syndrome or velocardiofacial syndrome).[12,18] The prevalence of cleft lip/cleft palate in a fetus diagnosed with trisomy 13, 18, and 22q11.2 is approximately 45%, 10%, and 8%, respectively.[19–21]

More than 500 monogenic conditions are associated with cleft lip/cleft palate, including autosomal dominant, autosomal recessive, and X-linked inheritance.[22] Table 1 summarizes some of the key clinical features of the more commonly recognized syndromes associated with cleft lip/cleft palate based on prevalence, additional anomalies, postnatal clinical presentation, family history, and available genetic testing.[22,23]

Although midline clefts and cases of cleft lip/cleft palate with additional anomalies are often genetic in origin, isolated orofacial clefts are generally multifactorial. Environmental risk factors associated with cleft lip/cleft palate include maternal smoking, pregestational diabetes, obesity, alcohol use, malnutrition, uncontrolled phenylketonuria, and certain viral infections.

The evaluation of potential teratogenic medications is complex because of such factors as concurrent drug use, risks from underlying disease, variability in timing of exposure during critical developmental periods, and differences in study design. Despite these challenges, several studies have identified associations between specific medications and increased risk of orofacial clefts when taken in early gestation because the lip and palate fuse from weeks 4 to 7 of gestation.[2] In a previous drug safety communication from the U.S. Food and Drug Administration, topiramate monotherapy was noted to be associated with an increased risk of cleft lip/cleft palate (adjusted odds ratio 6.8 [95% CI, 1.4–20.0]).[24] Evidence shows a dose-dependent response with increased risk of cleft lip/cleft palate with doses greater than 100 mg compared with lower doses.[25] Other medications associated with increased risk of cleft lip/cleft palate include phenytoin, carbamazepine, and valproic acid; however, these medications are not recommended for use in pregnancy given the additional associated congenital malformations and adverse effects on fetal neurodevelopment (valproic acid).[26]

Other medications that have been linked to cleft lip/cleft palate include ondansetron and nitrofurantoin. Ondansetron is commonly used during the first trimester for nausea and vomiting. Multiple studies from the National Birth Defects Prevention study did not identify an association between ondansetron use and cleft lip/cleft palate; however, the same studies showed isolated cleft palate was slightly increased (0.2 vs 0.11) with an adjusted odds ratio of 2.37 (95% CI, 1.18–4.76).[27] A report of more than 600,000 pregnant patients using a comprehensive national database in Denmark found no cases of cleft lip/cleft palate and no association between ondansetron use and cleft lip/cleft palate or isolated cleft palate among 1,233 infants exposed to ondansetron in the first trimester. However, this study was not powered to assess risk of individual defects.[28] The use of nitrofurantoin has conflicting evidence. One study reported increased risks of cleft lip/cleft palate with an odds ratio of 2.1 (95% CI, 1.2–3.9),[29] whereas a different study with more than 40,000 fetuses exposed to nitrofurantoin found no increased association with a weighted risk ratio of 1.15 (95% CI, 0.97–1.37).[30] These two studies differ in size; the former study that showed an increased risk had a total of 28 cases, whereas the latter that showed no increased association contained 52 cases of cleft lip/cleft palate in a much larger cohort of fetuses exposed. Overall data from large cohorts on the use of these medications when indicated are reassuring with low or no attributable risk. Known developmental embryology indicates that there would certainly be no increased risk of cleft lip/cleft palate with exposures outside of the range of 4–7 weeks of gestation.

GENETICS

When oral clefts are identified on prenatal ultrasonography, genetic counseling and prenatal diagnostic testing through CVS or amniocentesis should be offered. A detailed three-generation family history should be elicited, with particular attention to symptoms of conditions with variable expressivity associated with oral clefts such as 22q11.2 deletion or Van der Woude or Stickler syndrome. Testing strategies should be guided by the findings of additional anomalies on ultrasonography, abnormal genetic screening results, and family history. Chromosome microarray analysis is recommended as a first-tier test given that chromosome copy number variants (microdeletions or microduplications) have been identified in approximately 9% of cases of isolated cleft lip/cleft palate and

Table 1. Summary of More Commonly Recognized Syndromes Associated With Cleft Lip and Cleft Palate

Condition	Genetic Cause	Inheritance	Features
22q11.2 deletion syndrome (DiGeorge syndrome, velocardiofacial syndrome)	Microdeletion of 22q11.2 region	Autosomal dominant 90% de novo 10% inherited	Palate abnormalities Congenital heart defects Immunodeficiency Developmental delay, learning difficulties Seizures Autism Psychiatric conditions Hypocalcemia
IRF6-related disorders, including Van der Woude syndrome*	*IRF6*	Autosomal dominant Most inherited	CL/CP Lower-lip pits Pterygium Pyramidal skin on the hallux Genital abnormalities
Stickler syndrome	*COL2A1* *COL11A1* *COL11A* *COL9A1* *COL9A* *COL9A3*	Autosomal dominant Autosomal recessive	CL/CP Lower-lip pits Pterygium Pyramidal skin on the hallux Genital abnormalities
CHD7-related disorders, including CHARGE syndrome	*CHD7*	Autosomal dominant Most de novo	CL/CP Coloboma Heart defect Choanal atresia Growth restriction Developmental delay, intellectual disability Genital hypoplasia Hypogonadotropic hypogonadism Ear anomalies (including hearing loss)
Smith-Lemli-Optiz syndrome	*DHCR7*	Autosomal recessive	Cleft palate Heart defects 2–3 toe syndactyly Prenatal and postnatal growth restriction Microcephaly Genital abnormalities in XY individuals Intellectual disability
TP63-related disorders†	*TP63*	Autosomal dominant 70% de novo 30% inherited	CL/CP Ectodermal dysplasia Split hand–foot malformation Lacrimal duct obstruction Hypoplastic breasts, nipples Hypospadias Hypopigmentation

(*continued*)

Table 1. Summary of More Commonly Recognized Syndromes Associated With Cleft Lip and Cleft Palate (*continued*)

Condition	Genetic Cause	Inheritance	Features
OFD1	OFD1	X-linked Male lethality 75% female individuals de novo 25% female individuals inherited	CL/CP Tongue abnormalities (eg, lobulated) Micrognathia Dental anomalies (eg, extra or missing teeth) Digital anomalies Polycystic kidney disease Brain malformations Intellectual disability

CL/CP, cleft lip/cleft palate; CHARGE, coloboma, heart defects, atresia of the choanae, retardation of growth and development, genital and urinary abnormalities, ear abnormalities, and/or hearing loss; OFD1, oral-facial-digital syndrome type I.
* Most common single-gene cause associated with CL/CP accounting for up to 2–3% of all CL/CP.
† Presenting with CL/CP includes ankyloblepharon-ectodermal defects–cleft lip/palate syndrome, ectrodactyly, ectodermal dysplasia, CL/CP syndrome 3, limb–mammary syndrome, isolated CL/CP (orofacial cleft 8).

up to 11% of cases when additional ultrasound abnormalities are visualized.[31] Given that chromosome microarray analysis can detect common aneuploidies such as trisomy 13, 18, and 21, which are observed in 4–5% of cases of isolated cleft lip/cleft palate and 32–51% of nonisolated cases, chromosome analysis limited to karyotype can be reserved for cases with high suspicion for aneuploidy based on prior genetic screening or clinical presentation (eg, high-risk cell-free DNA screen or ultrasound features consistent with trisomy).[16–18,32]

A monogenic cause is identified in 17–37% of suspected syndromic cases and in approximately 10% of isolated cases of cleft lip/cleft palate.[33–37] Therefore, exome and genome sequencing, which can detect monogenic conditions, may be considered after or concurrently with chromosome microarray analysis, particularly when clefts are midline or bilateral or when additional anomalies are noted. Although prenatal diagnostic testing is the standard of care, screening through cell-free DNA for common aneuploidies and 22q11.2 deletion syndrome can be considered for initial genetic screening before invasive testing; however, the utility of cell-free DNA screening has not been specifically validated for use in the setting of fetal cleft lip/cleft palate.[38] There are no data on the utility and yield of single-gene noninvasive prenatal testing screens in the setting of cleft lip/cleft palate on ultrasonography, and the American College of Obstetricians & Gynecologists does not recommend the use of single-gene noninvasive prenatal testing in the general population.[39]

Recurrence risks depend highly on the underlying cause of cleft lip/cleft palate, presence or absence of teratogenic exposures, and family history. The recurrence risk for an isolated, nonsyndromic cleft lip/cleft palate is approximately 3–5%; however, this risk increases when more than one family member is affected.[40] A consultation with a genetic counselor and perinatologist to discuss anticipated recurrence risks of cleft lip/cleft palate and expectations for screening in current or future pregnancies is reasonable.

PRENATAL AND DELIVERY MANAGEMENT

The timing of cleft lip/cleft palate diagnosis is influenced by both the extent of the defect and the presence or absence of associated anomalies. A complete, detailed anatomic survey should be performed because of the risk for other anomalies, and serial ultrasonograms should be considered for associated risk of other abnormalities. Studies and referrals to offer include referral to a maternal–fetal medicine subspecialist, genetic consultation, diagnostic genetic testing, fetal echocardiogram, neonatology consultation, and pediatric craniofacial surgery consultation.[41,42] Abnormal findings on genetic studies or additional anomalies would dictate antenatal testing recommendations and delivery timing; some genetic syndromes are associated with an increased risk of stillbirth. For a fetus with cleft lip/cleft palate, polyhydramnios is a complication thought to be caused by the inability to swallow or difficulty in swallowing, leading to increased amniotic fluid index. Pending the severity, this may lead to preterm premature rupture of membranes or preterm delivery.[43] If polyhydramnios is identified, counseling on the effects of uterine overdistension should be provided, and the pregnancy should be managed accordingly. In the absence of other complications, isolated cleft

lip/cleft palate is not an indication for antenatal surveillance or modifications of delivery timing.

Delivery location of a fetus with cleft lip/cleft palate will depend on the suspected type of defect. If the fetus is presumed to have an isolated cleft lip, delivery can occur at most institutions. However, if a more complex defect is present, the recommendation is to deliver at a facility with pediatric airway expertise because intubating neonates with craniofacial abnormalities can be challenging. Intubation of neonates is more difficult because of macroglossia, a long and narrow epiglottis, and an increased angle formed by the trachea and vocal cords compared with adults, but even more so in the presence of craniofacial abnormalities.[44] Consultation with a neonatologist may be helpful in delineating the most appropriate delivery location based on available local resources.

POSTNATAL MANAGEMENT

The care of a child with a craniofacial abnormality such as cleft lip/cleft palate should begin prenatally, ideally with a perinatologist coordinating a multidisciplinary team to adequately care for the neonate after birth. The American Cleft Palate-Craniofacial Association recommends early evaluation and treatment after birth by a multidisciplinary team that often consists of a pediatrician, craniofacial surgeon, otolaryngologist, nurse, feeding specialist or therapist, and audiologist.[45] On discharge from the initial birth hospitalization, these children should have close follow-up with a craniofacial team.

In the delivery room and in the immediate postnatal period, neonates with cleft lip/cleft palate should undergo prompt evaluation for respiratory or airway compromise and should be treated accordingly should an airway issue be identified. The extent and characteristics of the craniofacial abnormality should be assessed. A comprehensive physical examination should be performed to identify any additional congenital anomalies; if present, a referral for genetic evaluation should be considered, especially if no testing was performed in the prenatal period.[46] The level of neonatal intensive care unit care required for neonates with cleft lip/cleft palate can vary depending on the fetal airway status and any other abnormalities.

Neonates with cleft lip/cleft palate typically have early feeding difficulties and should be evaluated by a feeding specialist or therapist shortly after birth to decrease the risk of malnutrition and dehydration. For a neonate to extract milk from a nipple (human or artificial), two physiologic actions must occur: 1) the oral cavity needs to create a seal around the nipple so that negative pressure can be generated to create suction, and 2) there needs to be compression of the nipple.[47] The orofacial structural abnormalities with cleft lip/cleft palate can make it difficult for the neonate to create a seal or suction for milk extraction. Multiple cleft-specific bottles and feeding systems are available in the United States that allow milk extraction by compression of the nipple without suction. Education on the use of these systems and practice with supervision are of utmost importance for these children and their caregivers. Whether these children will be successful with direct breastfeeding as a means of nutrition depends on the size and type of defect(s), with reports indicating that those with isolated cleft lip are most successful.[48] Caregivers should be educated on the benefits of breast-milk feeding and supported by lactation specialists should they desire to place the child directly to breast.

Before surgical management, there are presurgical options for management of cleft lip/cleft palate, which are often referred to as presurgical infant orthopedic treatment.[49] Presurgical infant orthopedic treatment may be offered in the first few weeks of life and include lip taping and nasoalveolar molding. These treatments are intended to decrease cleft deformity and to improve surgical outcomes of the cleft lip and nasal repair.[50] There are differing opinions and study results regarding the efficacy of these modalities, and there is no guideline consensus on the use of presurgical infant orthopedic treatment across craniofacial centers in the United States.[51–54]

The first surgical intervention is often repair of the cleft lip, which typically occurs at 3–6 months of age. The multiple different surgical techniques depend on a unilateral or a bilateral defect. Repair of the cleft palate typically occurs at 9–18 months of life and should occur before significant speech development. It is common for children to need revision surgeries for oronasal fistulas or velopharyngeal insufficiency, which can interfere with speech if not corrected.[55]

Throughout early childhood until early adulthood, patients with repaired cleft lip/cleft palate continue to require ongoing multidisciplinary care with speech language pathology, pediatric dentistry, craniofacial surgery, orthodontics, and orthognathic surgery.[49] As these patients mature, they often need surgical, dental, and orthodontic treatment for maxillary hypoplasia and cosmesis.[56] Patients may also elect for scar revision and cleft rhinoplasty to reshape nares once skeletal maturity has been reached.

PROGNOSIS

The prognosis of cleft lip/cleft palate depends on the cleft severity, coinciding genetic syndromes, and

additional anomalies. Those with isolated, unilateral cleft lip will have a significantly different outcome compared with those with a bilateral cleft lip/cleft palate with a genetic abnormality. In addition, there are different outcomes of interest to families when discussing overall prognosis, including aesthetic appearance after the surgical procedure and middle ear dysfunction.

Surgical outcomes are difficult to measure for cleft lip/cleft palate because current evaluation methods have not been found to accurately depict patient satisfaction.[57] Studies assessing the superiority of one surgical technique over another are limited. In addition, in a four-part series titled *The Eurocleft Study,* the authors stated that when considering satisfaction with cleft care, "[the study] raised many more questions than it has answered."[58] The lack of a reliable method of evaluation or standardized grading after cleft lip/cleft palate repair is an additional challenge when discussing aesthetic prognosis.[59]

Hearing loss is an additional, well-known complication of cleft palate. Conductive hearing loss is most common because of middle ear problems such as eustachian tube dysfunction. Therapies to improve hearing are important to decrease delays in speech and language development.[60] These children often require tympanostomy tube placement (often multiple placements) by otolaryngologists for their chronic middle ear effusions, which may be coordinated with cleft lip or palate repair. The eustachian tube is opened by the tensor veli palatini muscles, which allow equilibrium of the middle ear. In cleft palate, the aponeurosis of the tensor veli palatini abnormally attaches along the bony cleft edges rather than the hard palate, decreasing the ability of the eustachian tube to open.[61] Surgically repairing the cleft palate will resolve eustachian tube dysfunction in approximately 50% of patients, with resolution for most patients occurring by 5 years of age.[61] Therapies to improve hearing are vital to decrease delays in speech and language development.

PSYCHOSOCIAL ASPECTS

The effects of cleft lip/cleft palate extend beyond the antenatal diagnosis and subsequent infantile surgical repair, with cleft lip/cleft palate influencing, at minimum, a portion of early psychosocial development. From a young age, children develop their sense of self through a complex composition of factors, including parental influence, peer interaction, and self-perception.[62]

The presence of a cleft lip/cleft palate can influence parenting methods in regard to discipline, academic expectations, and social independence. Parents of children with cleft lip/cleft palate may try to protect their children because of their diagnosis.[63] Regarding communication, children with cleft lip exhibit "at risk/delayed development" in the expressive language domain compared with 36-month-old children without cleft lip/cleft palate.[64] These findings are also supported by 4-year-old children with cleft palate demonstrating severe language delays, placing them at high risk for reading deficits and pervasive developmental disorders.[65] These difficulties in communication extend across all domains of social interaction, including an increased incidence of teasing at an early age, extending into adolescence.[62,63] One study showed that parents of children with cleft lip/cleft palate have substantially increased levels of psychological stress compared with parents of children without clefts.[66] Studies on children with repaired cleft lip/cleft palate report lower self-esteem secondary to self-perception of facial appearance (and teasing related to facial appearance), as well as increased symptoms of depression and anxiety.[62,67] With rates of adolescent depression increasing from 8.1% in 2009 to 15.8% in 2019 and anxiety and depression twice as prevalent in those with cleft lip/cleft palate, increased attention should be dedicated to further describing the effect of cleft lip/cleft palate on psychosocial disorders in this specific population, along with the development of targeted interventions to reduce risk.[63,68,69]

CONCLUSION

Orofacial clefts represent a complex congenital anomaly with genetic, environmental, and developmental determinants. Advances in imaging and genetic evaluation have improved prenatal detection and counseling, allowing early detection and care planning. Although considerable progress has been made, cleft lip/cleft palate continues to pose medical, developmental, and psychosocial challenges that require multidisciplinary, coordinated, long-term management. Continued research into the molecular mechanisms and environmental factors contributing to cleft lip/cleft palate will be essential to improve prevention, diagnosis, and outcomes for affected families.

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