Medscape

Pediatric Cleft Lip and Palate

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Overview

Practice Essentials

Orofacial clefts—including cleft lip (CL), cleft lip and palate (CLP), and cleft palate (CP) alone, as well as median, lateral (transversal), and oblique facial clefts—are among the most common congenital anomalies.[1] The incidence of orofacial cleft is approximately 1 in every 500-550 births. The prevalence varies by ethnicity, country, and socioeconomic status. Nonsyndromic CLP, the largest subgroup of craniofacial anomalies, occurs in 1.5-2.5 cases per 1000 live births. In the United States, 20 infants are born with an orofacial cleft on an average day (~7500 annually).

Children who have an orofacial cleft require several surgical procedures and multidisciplinary treatment and care; the conservative estimated lifetime medical cost for each child with an orofacial cleft is $100,000, amounting to $750 million for all children with orofacial cleft born each year in the United States.[2] In addition, these children and their families often experience serious psychological problems.[3, 4]

With rapidly advancing knowledge in medical genetics and with new DNA diagnostic technologies, more cleft lip and palate anomalies are diagnosed antenatally and more orofacial clefts identified as syndromic. Although the basic rate of clefting (1:500 to 1:550) has not changed since Fogh-Andersen performed his pioneering 1942 genetic study distinguishing two basic categories of orofacial clefts—namely, CL with or without CP (CL/P) and CP alone[5] —these clefts can now be more accurately classified.

The correct diagnosis of a cleft anomaly is fundamental for treatment, for further genetic and etiopathologic studies, and for preventive measures correctly targeting the category of preventable orofacial clefts.

Most individuals with CL, CP, or CLP, as well as many individuals with other craniofacial anomalies, require the coordinated care of providers in many fields of medicine (including otolaryngology) and dentistry, along with that of providers in speech pathology, audiology, genetics, nursing, mental health, and social medicine (see Treatment).

No single treatment concept has been identified, especially for a CLP. The timing of the individual procedures varies in different centers and with different specialists.

For patient education resources, see the Children's Health Center.

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Pathophysiology

Embryology

In facial morphogenesis, neural crest cells migrate into the facial region, where they form the skeletal and connective tissue and all dental tissues except the enamel. Vascular endothelium and muscle are of mesodermal origin.[6]

The upper lip is derived from medial nasal and maxillary processes. Failure of merging between the medial nasal and maxillary processes at 5 weeks' gestation, on one or both sides, results in CL. CL usually occurs at the junction between the central and lateral parts of the upper lip on either side. The cleft may affect only the upper lip, or it may extend more deeply into the maxilla and the primary palate. (Cleft of the primary palate includes CL and cleft of the alveolus.) If the fusion of palatal shelves is impaired also, the CL is accompanied by CP, forming the CLP abnormality.

CP is a partial or total lack of fusion of palatal shelves. It can occur in the following ways:

- Defective growth of palatal shelves
- Failure of the shelves to attain a horizontal position
- Lack of contact between shelves
- Rupture after fusion of shelves

The secondary palate develops from the right and left palatal processes. Fusion of palatal shelves begins at 8 weeks' gestation and continues usually until 12 weeks' gestation. One hypothesis is that a threshold is noted beyond which delayed movement of palatal shelves does not allow closure to take place, and this results in a CP.

Classification

The group of orofacial cleft anomalies is heterogeneous. It comprises typical orofacial clefts (eg, CL, CLP, and CP) and atypical clefts (eg, median, transversal, oblique, and other Tessier types of facial clefts).[7, 8] Typical and atypical clefts can both occur as an isolated anomaly, as part of a sequence of a primary defect, or as a multiple congenital anomaly (MCA). In an MCA, the cleft anomaly could be part of a known monogenic syndrome, part of a chromosomal aberration, part of an association, or part of a complex of MCA of unknown etiology (see the image below).


Classification of orofacial clefts.

The varying physical characteristics of CL, CP, and CLP, as well as further issues in classification, are discussed in greater detail in Presentation.

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Etiology

Most orofacial clefts, like most common congenital anomalies, are caused by the interaction between genetic and environmental factors (see the image below).
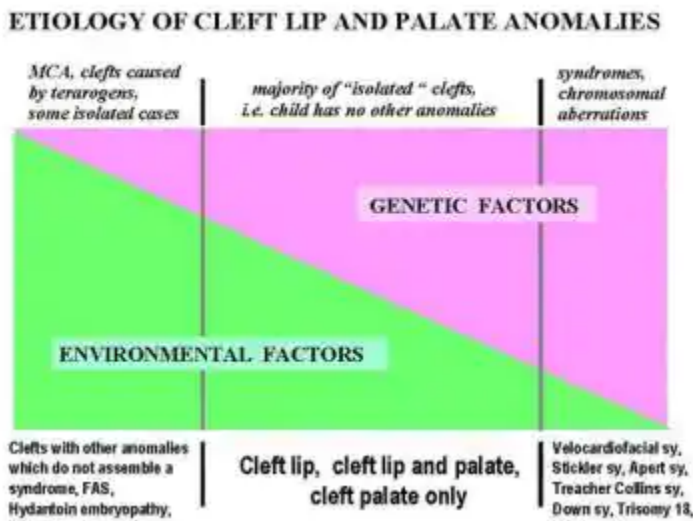
Rubella embryopathy, ...   Trisomy 13,....

Etiology of cleft lip and palate anomalies.

In those instances, genetic factors create a susceptibility for clefts. When environmental factors (ie, triggers) interact with a genetically susceptible genotype, a cleft develops during an early stage of development.

The proportion of environmental and genetic factors varies with the sex of the individual affected with cleft. In CL and CP, it also varies with the severity and the unilaterality or bilaterality of the cleft anomaly; the highest proportion of genetic factors are in the subgroup of females with a bilateral cleft, and the smallest proportion is in the subgroup of males with a unilateral cleft.

Thus, the classic multifactorial threshold (MFT) model of liability (see the first image below) can be applied to CL/P as the multifactorial model of liability with four different thresholds (see the second image below).

Distribution of the liability for cleft lip and palate
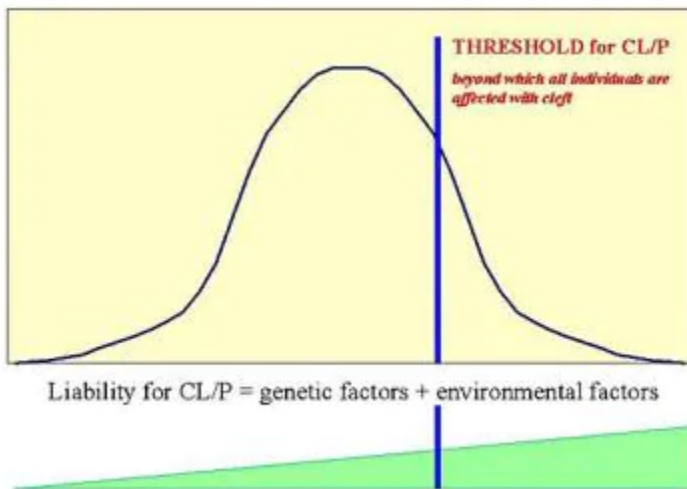
Multifactorial threshold model for the distribution of liability for cleft lip and palate.

Four-threshold model of the liability for cleft lip and palate
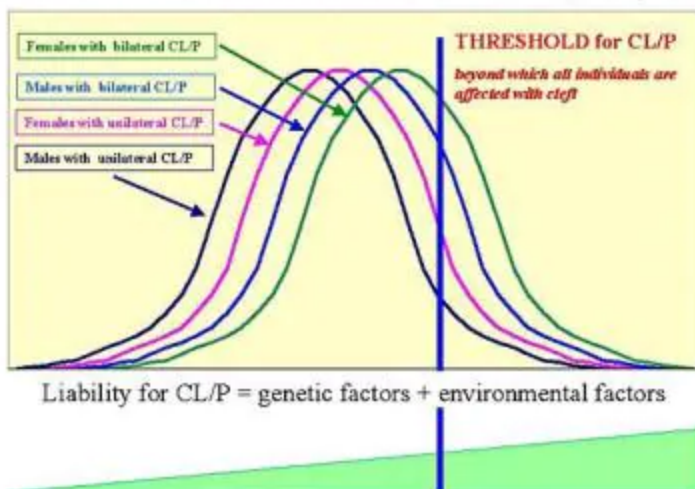
Four-threshold multifactorial threshold model of the liability for cleft lip and palate.

This model can facilitate understanding of differences in values of risk of recurrence as well as differences in prevention approaches between different subgroups of clefts.[9]

Theoretically, the subgroup of clefts closest to the population average should have the highest population prevalence, the

lowest value of heritability, and thus the lowest risk of recurrence. This was confirmed in a large, population-based study of whites with clefts (see the image below).[9]

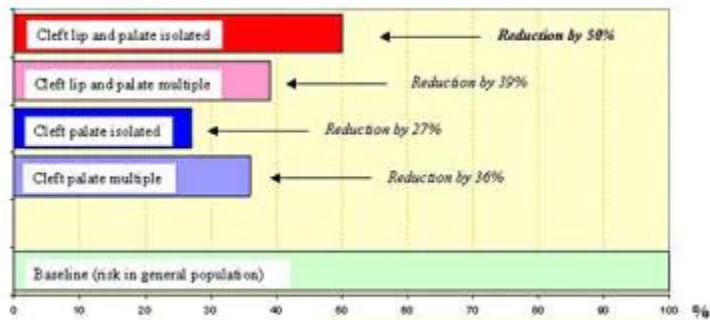Women who used multivitamins containing 0.4mg or more folic acid periconceptionally had 27-50% reduction in risk for child with orofacial cleft.

Decreased occurrence of orofacial clefts.

The value of heritability expresses a ratio of genetic and nongenetic factors. Heritability is equal to 1 for conditions completely controlled by genetic factors and equal to 0 for conditions completely controlled by environmental factors.

A higher proportion of environmental factors indicates a lower risk of recurrence and also gives a better chance to act in prevention, because the only etiologic factors that can be changed are environmental factors. Thus, the subgroup whose average prevalence is closest to the population average represents males affected with a unilateral CL/P. This subgroup is most common among orofacial clefts; the risk of recurrence for siblings and for offspring of an individual with cleft is the lowest, the value of heritability is the lowest, and efficacy of primary prevention is the highest (see Treatment, Prevention).

A cleft develops when embryonic parts called processes (which are programmed to grow, move, and join with each other to form an individual part of the embryo) do not reach each other in time and an open space (cleft) between them persists. In the normal situation, the processes grow into an open space by means of cellular migration and multiplication, touch each other, and fuse together.

In general, any factor that could prevent the processes from reaching each other—for instance, by slowing down migration or multiplication of neural crest cells, by stopping tissue growth and development for a time, or by killing some cells that are already in that location—would cause a persistence of a cleft. Also, the epithelium that covers the mesenchyme may not undergo programmed cell death, so that fusion of processes cannot take place.[6]

DNA studies

Considerable interest has developed in the identification of genes that contribute to the etiology of orofacial clefting. Advances in modern molecular biology, newer methods of genome manipulation, and availability of complete genome sequences led to an understanding of the roles of particular genes that are associated with embryonic development of the orofacial complex.[10]

The first candidate gene was transforming growth factor-α (TGFA), which showed an association with nonsyndromic CLP in a white population.[11] Lidral et al investigated five different genes (TGFA, BCL3, DLX2, MSX1, TGFB3) in a largely white population from Iowa.[12, 13] They found a significant linkage disequilibrium between CL/P and both MSX1 and TGFB3 and between CP and MSX1. The TGFB3 gene was identified as a strong candidate for clefting in humans based on both the mouse model[14] and the linkage disequilibrium studies.[15, 13, 16]

Other candidate genes that show an association with nonsyndromic CLP include D4S192, RARA, MTHFR, RFC1, GABRB3, PVRL1, and IRF6.

MSX1 was found to be a strong candidate gene involved in orofacial clefts and dental anomalies. Analysis of the MSX1 sequence in a multiplex Dutch family showed that a nonsense mutation (Ser104stop) in exon 1 segregated with the phenotype of nonsyndromic cleft lip and palate.[17] Some have proposed that cleft palate in MSX1 knock-out mice is due to insufficiency of the palatal mesenchyme.[18]

Zucchero et al reported that variants of IRF6 may be responsible for 12% of nonsyndromic cleft lip and palate, suggesting that this gene would play a substantial role in the causation of orofacial clefts.[19] A meta-analysis of all-genome scans of

subjects with nonsyndromic cleft lip and palate, including Filipino, Chinese, Indian, and Colombian families, found a significant evidence of linkage to the region that contains interferon regulatory factor 6 (IRF6).[20]

Also, gene-gene interactions have been examined. A complex interplay of several genes, each making a small contribution to the overall risk, may lead to formation of clefts. Jugessur et al reported a strong effect of the TGFA variant among children homozygous for the MSX1 A4 allele (9 CA repeats).[21]

Evaluation of gene-environment interactions is still in a preliminary stage. Studies of the role of smoking in TGFA and MSX1 as covariates suggested that these loci might be susceptible to detrimental effects of maternal smoking.[16, 22] Folate-metabolizing enzymes such as methylenetetrahydrofolate reductase (MTHFR), which is a key player in etiology of neural tube defects, and RFC1 are considered candidate genes on the basis of data that suggest that folic acid supplementation can reduce incidence of nonsyndromic cleft lip and palate.[23]

More than 30 potential candidate loci and candidate genes throughout the human genome have been identified as strong susceptibility genes for orofacial clefts. The MSX (4p16.1), TGFA (2p13), TGFB1 (19q13.1), TGFB2 (1q41), TGFB3 (14q24), RARA (17q12), and MTHFR (1p36.3) genes are among the strongest candidates.[20, 24, 25]

The TGFB3 gene was identified as a strong candidate for clefting in humans based on a mouse model. Generally, palatogenesis in mice parallels that of humans and shows that comparable genes are involved.[26] Kaartinen demonstrated that mice lacking the TGFB3 peptide exhibit cleft palate.[14] In addition, the exogenous TGFB3 peptide can induce palatal fusion in chicken embryos, although the cleft palate is a normal feature in chickens.[27]

In humans, association studies between the TGFB3 gene and nonsyndromic CL/P showed conflicting results. Lidral reported failure to observe an association of a new allelic variant of TGFB3 with nonsyndromic CL/P in a case-control study of the Philippines' population.[12] Another study by Tanabe analyzed DNA samples from 43 Japanese patients and compared results with those from 73 control subjects with respect to four candidate genes, including TGFB3.[28] No significant differences in variants of TGFB3 between case and control populations were observed.

On the other hand, subsequent case-control association studies, family-based studies, and genome scans supported a role of TGFB3 in cleft development. Beaty examined markers in five candidate genes in 269 case-parent trios ascertained through a child with nonsyndromic orofacial clefts;[16] 85% of the probands in the study were white. Markers at two of the five candidate genes (TGFB3 and MSX1) showed consistent evidence of linkage and disequilibrium due to linkage.

Similarly, Vieira attempted to detect transmission distortion of MSX1 and TGFB3 in 217 South American children from their respective mothers.[29] A joint analysis of MSX1 and TGFB3 suggested a possible interaction between these two genes, increasing cleft susceptibility. These results suggest that MSX1 and TGFB3 mutations make a contribution to clefts in South American populations.

In a study of the Korean population, Kim reported that the G allele at the SfaN1 polymorphism of TGFB3 is associated with an increased risk of nonsyndromic CL/P. The population study consisted of 28 patients with nonsyndromic CL with or without CP and 41 healthy controls.[30]

In 2004, Marazita performed a meta-analysis of 13 genome scans of 388 extended multiplex families with nonsyndromic CL/P.[20] The families came from seven diverse populations including 2551 genotyped individuals. The meta-analysis revealed multiple genes in 6 chromosomal regions including the region containing TGFB3 (14q24).

In the Japanese population, blood samples from 20 families with nonsyndromic CL/P were analyzed by using TGFB3 CA repeat polymorphic marker. On the basis of the results of the study, the investigators concluded that either the TGFB3 gene itself or an adjacent DNA sequence may contribute to the development of cleft lip and palate.[31]

A study by Ichikawa et al investigated the relationship between nonsyndromic CL/P and seven candidate genes (TGFB3, DLX3, PAX9, CLPTM1, TBX10, PVRL1, TBX22) in a Japanese population.[32] The sample consisted of 112 patients with their parents and 192 controls. Both population based case-control analysis and family based transmission disequilibrium test (TDT) were used.

The results showed significant associations of single nucleotide polymorphisms (SNPs) in TGFB3 and nonsyndromic CL/P, especially IVS+5321(rs2300607).[32] Although IVS-1572 (rs2268625) alone did not show a significant difference between cases and controls, the haplotype "A/A" for rs2300607- rs2268625 showed significant association. The author concluded that the results demonstrated positive association of TGFB3 with nonsyndromic CL/P in Japanese patients.

A study by Bu et al found evidence of an association between nonsyndromic CLP and SNPs in FOXF2 (6p25.3).[33]

Several micromanifestations of orofacial clefts have been studied,[34, 35] and additional candidate genes associated with these minimal, clinically less significant anomalies have been suggested.[34, 36]

Associations of specific candidate genes with nonsyndromic CL/P have not been found consistent across different populations. This may suggest that multiplicative effects of several candidate genes or gene-environmental interactions are

noted in different populations.

The identification of factors that contribute to the etiology of nonsyndromic CL/P is important for prevention, treatment planning, and education. With an increasing number of couples who seek genetic counseling as a part of their family planning, the knowledge of how specific genes contribute to formation of nonsyndromic CL/P has gained an increased importance.

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Epidemiology

Reported data on the frequency of orofacial clefts vary according to the investigator and the country. In general, all typical orofacial cleft types combined occur in white populations with a frequency of 1 per 500-550 live births. Although the total combined frequency of CL, CLP, and CP is often used in statistics, combining the two etiologically different groups (ie, CL/P and CP alone) represents a misclassification bias similar to that of combining clefts with other congenital malformations.

The sex ratio in patients with clefts varies. In whites, cleft lip and cleft lip and palate occur significantly more often in males, and cleft palate occurs significantly more often in females. In CL/P, the sex ratio correlates with the severity and laterality of the cleft. A large study of 8952 orofacial clefts in whites found the male-to-female sex ratio to be 1.5-1.59:1 for CL, 1.98-2.07:1 for CLP, and 0.72-0.74:1 for CP.[9]

The prevalence of clefts varies considerably in different racial groups. The lowest rate is for blacks. A high prevalence of CL/P was found for the Japanese population, and the highest prevalence was found for the North American Indian populations.

In contrast, no remarkable variation among races was found in isolated CP. In particular, its prevalence did not significantly vary between black and white infants or between infants of Japanese and European origin in Hawaii. Leck considered that such findings may reflect a higher etiologic heterogeneity of CP than of CL/P. Methods of ascertainment and classification criteria undoubtedly influence prevalence figures.[7]

In a large population-based study of 4433 children born with orofacial cleft (ascertained from 2,509,881 California births), the birth prevalence of nonsyndromic CL/P was 0.77 per 1000 births (CL, 0.29/1000; CP, 0.48/1000), and the prevalence of nonsyndromic CP was 0.31 per 1000 births (see the image below).[37]

Prevalence of orofacial clefts (Tolarova and Cervenka, 1998).

In that study, the risk of CL/P was slightly lower among the offspring of non-US-born Chinese women compared to US-born Chinese women and slightly higher among non-US-born Filipinos relative to their US-born counterparts. For CP, lower prevalences were observed among blacks and Hispanics than among whites. The risk of CP was higher among non-US-born Filipinos compared to US-born Filipinos. These prevalence variations may reflect differences in both environmental and genetic factors affecting risk for development of orofacial cleft.

Risk of recurrence

Genetic factors (ie, genes participating in the etiology of nonsyndromic orofacial clefts) are passed to the next generation, thus creating an increased risk for such anomaly in offspring. The risk of recurrence also differs with respect to proportion of genetic and nongenetic factors. In CL/P, the hypothetical four-threshold model (see Etiology) closely corresponds with

differences in the risk of recurrence.

From a clinical point of view, the following two factors are most important in evaluating the risk of recurrence for CL/P:

- Sex of the individuals (ie, patient and individual at risk)
- Severity of the effect in the patient (eg, unilateral vs bilateral)
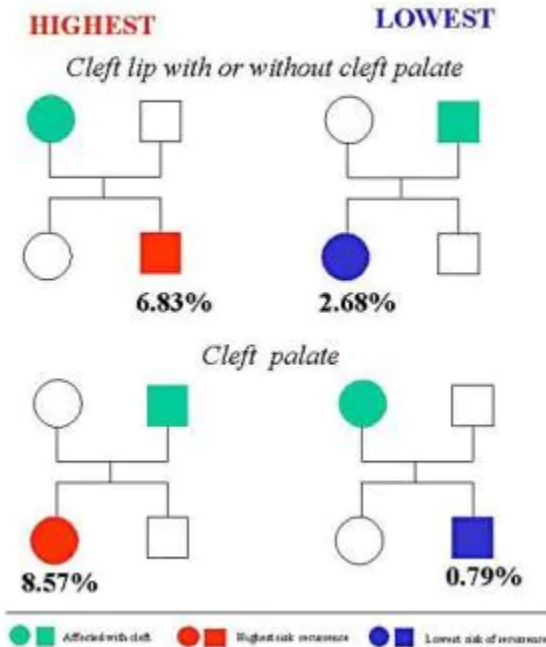
The lowest recurrence risk for CL/P is for the subcategory of male patients with unilateral cleft (see the first image below) and, within this category, for sisters of males with a unilateral cleft and for daughters of fathers with a unilateral CL/P (see the second image below). The highest risk of recurrence of CL/P is for the subcategory of female patients affected with a bilateral CL/P.

RECURRENCE RISK FOR CL±P *(Cleft lip with or without cleft palate)*

Type of cleft and sex of proband	RISK IN SIBS (%)			RISK IN CHILDREN (%)		
	brother	sister	total	son	daughter	Total
MALE-unilateral	2.25	1.35	1.84	4.91	2.27	3.60
MALE-bilateral	4.17	4.41	4.29	11.54	4.88	8.60
FEMALE-unilateral	5.26	3.13	4.29	4.55	3.05	3.80
FEMALE-bilateral	15.78	7.14	12.12	17.24	7.69	12.73
TOTAL	3.91	2.67	3.34	6.41	3.11	4.82

Recurrence risk in cleft lip with or without cleft palate.

Highest and lowest risk of recurrence of cleft lip with or without cleft palate.

The risk of recurrence for CP seems to be influenced only by sex. The risk is highest for daughters of fathers affected with a CP and lowest for sons of mothers affected with a CP (see the image below).

RECURRENCE RISK FOR CP *(Cleft palate only)*

Sex of proband	RISK IN SIBS (%)			RISK IN CHILDREN (%)		
	brother	sister	total	son	daughter	Total
MALE	1.69	1.68	1.69	2.94	8.57	5.80
FEMALE	2.70	2.25	2.48	0.79	2.86	1.73
TOTAL	2.21	1.96	2.09	1.55	5.14	3.25

Recurrence risk in cleft palate.

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Presentation

Physical Examination

Cleft lip with or without cleft palate

Cleft lip (CL) can occur either unilaterally (on the left or right) or bilaterally. The line of cleft always starts on the lateral part of the upper lip and continues through the philtrum to the alveolus between the lateral incisor and the canine tooth, following the line of the sutura incisiva up to the foramen incisivum. The clefting anterior to the incisive foramen (ie, lip and alveolus) is also defined as a cleft primary palate.

CL may occur with a wide range of severity, from a notch located on the left or right side of the lip to the most severe form, bilateral CL and alveolus that separates the philtrum of the upper lip and premaxilla from the rest of the maxillary arch (see the image below).

Examples of cleft lip.

The mildest form is a microform and is a subtler expression of the cleft lip with or without cleft palate (CL/P) phenotype; it can typically involve small defects such as a notch located on the lip, also called forme fruste[38] or congenital healed CL,[39] and alveolar arch or asymmetrical drooping of the nostril.[40] Most often, these CL microforms occur unilaterally. Microform of CL is a rarely reported birth defect that occurs in 6 cases per 1,000,000 live births.[39]

The phrase "possible carriers" was used to search in families afflicted with orofacial clefts.[40] The investigation was carried out in 153 families of probands with nonsyndromic CL/P. In possible carriers (individuals in between two affected individuals; for example, a child and mother's mother are affected with a cleft, so the mother is a possible carrier), there was nearly always some microform with a higher incidence in all relatives of the subject; the asymmetrical drooping of the nose was the most frequent microform. The microforms may be used as a prognostic criterion.

Family prognosis is generally worse if any microform has been found in near relatives of the patient. In a family without CL/P, the incidence of a microform may increase the risk for clefting, but the actual probability is low. However, in a case of consanguineous marriage, the cleft microforms found in both partners should serve as a warning signal. The incidence of

microforms in a certain population group (or in a certain area) must be taken into account in studies concerning the epidemiology in order to prevent erroneous interpretation of the findings.[40]

An important contribution to the classification of CL has been identifying and defining CL subphenotypes.

Marazita presented evidence that subepithelial (occult) defects of the superior orbicularis oris (OO) muscle represent the mildest form of the lip portion of CL/P.[41] This review provided descriptive histology of OO muscles from cadavers, assessed the rate of OO defects in unaffected relatives of individuals with CL/P via ultrasonography (US), and compared with controls and sequence BMP4 in non-CL/P individuals with OO defects. Non-CL/P relatives of individuals with overt CL/P had a significantly higher frequency of OO defects than controls with no family history of CL/P.

A pattern of disorganized OO muscle fibers was noted in those individuals with OO discontinuities diagnosed via US.[41] Sequencing of BMP4 found a significant increase in potentially damaging mutations in individuals with OO defects versus controls. This is significant support for the hypothesis that subepithelial OO muscle defects are a mild manifestation of the lip portion of the CL/P phenotype.

Suzuki et al also used ultrasonography to detect subtle defects of the OO muscle (subepithelial defects).[42] Histologic studies showed disorganization of muscle fibers and excess connective tissue in comparison with normal OO muscles. The BMP4 mutation frequency for overt CL/P cases alone was not significantly greater than for controls, but the frequency for microform plus OO muscle cases was significantly greater than for controls. Furthermore, BMP4 mutation frequency was significantly lower in overt CL/P cases than in microform plus OO muscle cases.

These results suggested that amino acid alteration in BMP4 resulted in delayed lip closure (resulting in the appearance of a healed scar) or that actual healing of the cleft occurred by an unknown mechanism. BMP4 has a role in microform and subepithelial clefting that is consistent with the speculation that a genetic pathway may be involved in both wound healing and CL/P.

Another study employed US to compare the frequency of discontinuities in the OO muscle in 525 unaffected relatives of individuals with non-CL/P vs 257 unaffected controls.[43] OO muscle discontinuities were observed in 10% of the non-CL/P relatives, compared with 5.8% of the controls—a statistically significant increase. Male relatives had a higher rate of discontinuities than male controls did (12% vs 3.2%). Female relatives also had a higher rate of discontinuities than female controls did, but the increase was not statistically significant (8.9% vs 7.4%).

These data confirm the hypothesis that subepithelial OO muscle defects are a mild manifestation of the CL phenotype. Identification of subepithelial OO muscle defects may be important in a clinical setting as a means of providing more accurate recurrence risk estimates to relatives in cleft families. Furthermore, the expansion of the non-CL/P phenotypic spectrum should improve the power of genetic studies.

When CL continues from the foramen incisivum further through the sutura palatina in the middle of the palate, a cleft lip and palate (CLP), either unilateral or bilateral, is present (see the image below). A wide range of severity may be observed. The cleft line may be interrupted by soft (skin or mucosa) bridges, hard (bone) bridges, or both, corresponding to a diagnosis of an incomplete cleft. This occurs in unilateral and bilateral CLP.

Examples of cleft lip and palate.

Cleft palate

Cleft palate (CP; see the images below) is etiologically and embryologically different from CL/P.

Examples of cleft palate.

Submucous cleft palate.

Several subtypes of CP can be diagnosed on the basis of severity. The uvula is the place where the minimal form of clefting of the palate is observed. (However, a relatively high prevalence of this anomaly in the general population suggests that a certain proportion may represent the very far end of a normal variability.) A more severe form is a cleft of the soft palate. A complete CP constitutes a cleft of the hard palate, soft palate, and cleft uvula. The clefting posterior to the incisive foramen is defined as a cleft of secondary palate (see the image below).


Examples of cleft palate.

In a significant proportion of patients, the cleft of the hard palate is covered by mucosa and continues through the soft palate, forming a so-called submucous CP. A submucous CP may occur in the hard palate only and continue to the open cleft of the soft palate, or it may occur as a submucous cleft of the soft palate with or without a notch into the hard palate. Careful clinical examination may reveal a blue triangle in continuation of the cleft of the soft palate, which represents a cleft of the bone palate underneath mucosa (see the image below).
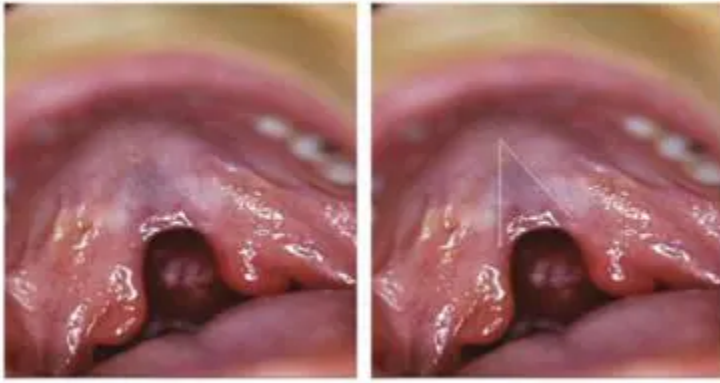
Submucous cleft palate.

The palate cleft may take two distinguishable forms: a V shape, which is most common in isolated clefts, or a U shape, which is most common in Robin sequence (see Pierre Robin Malformation) and in syndromic clefts.

The CP posterior to the incisive foramen is defined as the cleft of the secondary palate. CL and cleft of the palate anterior to the incisive foramen (unilateral or bilateral) is defined as the cleft of primary palate (thus, in bilateral CL, premaxilla is separated from lateral palatal segments). The bifid uvula is a sign that adenoidectomy may result in hypernasal speech if a complete adenoidectomy is done.
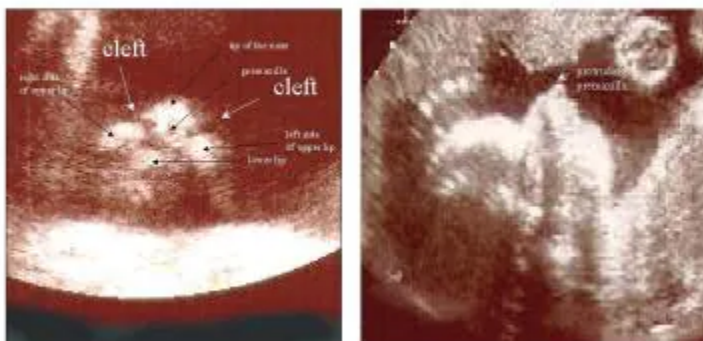
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Workup

Ultrasonography

Cleft lip (CL) can be easily diagnosed by performing ultrasonography (US) in the second trimester of pregnancy when the position of the fetal face is located correctly (see the images below).[44]

Bilateral cleft lip on ultrasound.

Courtesy of Dr. F. Golda, Prague (xxkk@xkgm.xmt.ct)

Median cleft lip on ultrasound.

Usually, diagnosing a cleft palate (CP) with US is not possible; however, an experienced physician or technician may catch an atypical movement of the fetal tongue in a lateral view. In the case of a large CP, the tongue moves up into an open space (cleft) in the roof of the oral cavity. Three-dimensional (3D) imaging has been introduced to antenatal US for diagnosis of cleft anomalies and appears to be promising for recognizing a CP in a fetus.

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Treatment

Approach Considerations

Most individuals with cleft lip (CL), cleft palate (CP), or cleft lip and palate (CLP), as well as many individuals with other craniofacial anomalies, require the coordinated care of providers in many fields of medicine (including otolaryngology) and dentistry, along with that of providers in speech pathology, audiology, genetics, nursing, mental health, and social medicine.

Treatment of orofacial cleft anomalies requires years of specialized care and is costly. The average lifetime medical cost for treatment of one individual affected with CLP is $100,000.[2] Although successful treatment of the cosmetic and functional aspects of orofacial cleft anomalies is now possible, it is still challenging, lengthy, costly, and dependent on the skills and experience of a medical team. This especially applies to surgical, dental, and speech therapies.

Because otitis media with effusion is very common among children with CP, involvement of an otolaryngologist in the multidisciplinary treatment plan is very important. The otolaryngologist performs placement of ventilation tubes in conjunction with the CP repair.[45] If a concurrent CL is present, the ventilation tubes are placed during that repair. Many of these children see otolaryngologists well beyond the time they see many of the other specialists because some children continue to have eustachian tube dysfunction after their palates are closed.

A team for the multidisciplinary treatment of a child with an orofacial cleft includes the following specialists:

- Pediatrician
- Nurse practitioner
- Plastic surgeon
- Pediatric dentist
- Otolaryngologist
- Geneticist
- Genetic counselor
- Speech pathologist
- Orthodontist [46]
- Maxillofacial surgeon
- Social worker
- Psychologist [4]

No single treatment concept has been identified, especially for a CLP. The timing of the individual procedures varies in different centers and with different specialists.

The following is the most common treatment protocol currently used in most cleft treatment centers:

- Newborn - Diagnostic examination, general counseling of parents, feeding instructions, palatal obturator (if necessary); genetic evaluation and specification of diagnosis; empiric risk of recurrence of cleft calculated; recommendation of a protocol for the prevention of a cleft recurrence in the family
- Age 3 months - Repair of CL (and placement of ventilation tubes)
- Age 6 months - Presurgical orthodontics, if necessary; first speech evaluation
- Age 9 months - Speech therapy begins

- Age 9-12 months - Repair of CP (placement of ventilation tubes if not done at the time of CL repair)
- Age 1-7 years - Orthodontic treatment
- Age 7-8 years - Alveolar bone graft
- Older than 8 years - Orthodontic treatment continues

Other surgical procedures can be performed in patients with severe clefts as necessary (see Surgical Therapy).

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Medical Therapy

Neonatal care

When a neonate with a cleft is born, a pediatrician has three major concerns:

- Risk of aspiration because of communication between oral and nasal cavities
- Airway obstruction (in addition to sequelae of aspiration, especially in Pierre Robin sequence, where the CP is combined with micrognathia and the tongue has a normal size)
- Difficulties with feeding of a child with a cleft and nasal regurgitation

These three factors are influenced by the presence of other major or minor anomalies that may, in association with a cleft, represent one of 300 known cleft syndromes.[6] Therefore, a neonate with an orofacial cleft should be seen by a medical geneticist as soon as possible.

As with any other medical condition, each case is different. A child with a severe cleft may do very well, whereas a child with a much less severe condition may experience many problems. An individual approach is necessary; however, several major rules apply to every neonate born with a cleft.

A pediatrician or neonatologist is usually the first person to take care of a neonate born with a cleft and the first to talk to the parents. As soon as possible, each baby born with orofacial cleft should be referred to the cleft palate or craniofacial center, where each specialist evaluates the baby, delineates the best management options and treatment plan, and continuously revises individual procedures and treatment during follow-up visits.

Feeding of infant with cleft

The vast majority of children with cleft lip and palate anomalies are born with a normal birth weight. However, because of feeding and other difficulties mentioned above, the most common problem the pediatrician has to deal with is insufficient weight gain. One of the pediatrician's main responsibilities is to closely monitor the infant's weight. Pediatricians may supervise mothers themselves or may refer them to a nutritionist, feeding specialist, experienced nurse practitioner, or other specialist.

Most children born with CLP are unable to be breastfed. Those with CP cannot produce the negative pressure necessary for suction. Mothers of children with a unilateral CL may succeed with breastfeeding when the child is positioned so that the cleft in the lip is obstructed by the mother's breast.

No single right or correct method of feeding has been identified. Parents, working together with the healthcare provider, should choose the method that is best for their infant. Most infants can complete a feeding in 18-30 minutes. If more than 45 minutes is required, the infant may be working too hard and may be burning calories that should be used for weight gain. An infant who nurses or bottle feeds every 3-4 hours tends to gain weight better than an infant who feeds frequently (feedings < 2 hours apart) for short periods.

Helpful hints for a parent breastfeeding an infant with a cleft are as follows:

- In a case of an isolated CL, the infant typically does not experience feeding problems beyond learning how to "latch on" to the nipple at the beginning of the feeding; infants with CP must squeeze the milk out of the nipple by compressing the nipple between the tongue and whatever portion of the palate that remains
- Massaging the breast and applying hot packs on the breast 20 minutes before nursing usually helps
- The mother should apply pressure to the areola with her fingers to help the engorged nipple protrude; she should hold the infant in a semiupright, straddle, or football position; she should support the breast by holding it between her thumb and middle finger, making sure that the infant's lower lip is turned out and the tongue is under the nipple
- If the infant cannot hold onto the nipple any more, the mother can collect the remaining milk using an electrical or manual breast pump or by squeezing the breast with both hands and can finish the feeding with collected milk in a bottle
- The mother should increase her fluid intake (eg, by drinking larger quantities of water)

Hints for feeding breast milk with a bottle are as follows:

- Particularly for infants with bilateral CLP, breastfeeding is not possible
- The mother can use a breast pump (an electric pump ensures the highest level of success); then, she can feed the baby with a bottle (see below)

Hints for feeding milk formula with a bottle are as follows:

- The most appropriate milk formula should be selected by a pediatrician or feeding specialist
- Various nipples and bottles are made specifically for infants with clefts; the goal is to find a nipple and bottle that make feeding easy for the infant and still allow ample opportunity to suck
- A soft nipple is generally better than a hard nipple (some can be softened by boiling)
- Use a crosscut nipple to prevent choking; any nipple can be crosscut manually by using a single-edged razor blade; the crosscut is on the tongue side
- The bottle should be squeezed and released, not continually squeezed
- The nipple is angled to a side of the mouth, away from the cleft

Other recommendations include the following:

- More upright or seated positions prevent the milk from leaking to the nose and causing the infant to choke
- Advise the mother to stop feeding and allow the infant to cough or sneeze for a few seconds when nasal regurgitation occurs; a palatal obturator may be used

Gaining weight and preventing aspiration and ear infections are the most important parts of caring for neonates with a cleft during their first days and weeks of life.

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Surgical Therapy

Undoubtedly, closure of the CL is the first major procedure that tremendously changes children's future development and ability to thrive. Variations occur in timing of the first lip surgery; however, the most usual time occurs at approximately age 3 months.

Pediatricians used to strictly follow a rule of "three 10s" as a necessary requirement for identifying the child's status as suitable for surgery (ie, 10 lb [4.5 kg], 10 g/dL of hemoglobin, and age 10 weeks). Although pediatricians are presently much more flexible, and some surgeons may well justify a neonatal lip closure, considering the rule of three 10s is still very useful.

Anatomic differences predispose children with CLP and those with isolated CP to ear infections. Therefore, ventilation tubes are placed to ventilate the middle ear and prevent hearing loss secondary to otitis media with effusion.

In multidisciplinary teams with significant participation of an otolaryngologist, the tubes are placed at the initial surgery and at the second surgery routinely. The hearing is tested after the first placement when ears are clear with tubes. If no cleft surgery is planned early, placing the tubes early[47] (eg, by age 6 months) and monitoring hearing with repeated testing is recommended.

Complications include eardrum perforation and otorrhea, particularly in patients with open secondary palates in which closure is planned for later.

For preventive reasons, ear tubes are usually placed when the child is still under general anesthesia for cleft repair.

Detailed surgical treatment is described elsewhere (see Craniofacial, Bilateral Cleft Lip Repair, Craniofacial, Bilateral Cleft Nasal Repair, Craniofacial, Unilateral Cleft Nasal Repair, Craniofacial, Unilateral Cleft Lip Repair). Pediatricians may find it useful to inform parents of the kinds of procedures that a child with cleft may undergo.

The most common surgical procedures for a child with a CLP anomaly are as follows:

- Repair of the CL
- Repair of the CP
- Revision of the CL
- Closure and bone grafting of the alveolar cleft
- Closure of palatal fistulae
- Palatal lengthening
- Pharyngeal flap
- Pharyngoplasty
- Columellar lengthening

- CL rhinoplasty and septoplasty
- Lip scar revision
- LeFort I maxillary osteotomy

Maxillary distraction osteogenesis is increasingly being used as an alternative to conventional orthognathic surgery for correction of maxillary hypoplasia in CLP patients.[48, 49]

Orthodontic treatment is highly specialized and varies from case to case. The two stages of orthodontic treatment of a child with CLP are as follows:

- Surgery-related orthodontics - Early management (from birth until the time of surgical closure of the palate); orthodontics related to alveolar bone graft; permanent dentition management
- Cleft-related orthodontics (not related to surgical treatments)

There has been considerable enthusiasm for employing presurgical infant orthopedics (PSIO) in CLP patients to improve surgical outcomes with minimal intervention.[50] Esenlik et al reviewed the literature on nasoalveolar molding (NAM) with an eye to both benefits and limitations.[51] Their review suggested that NAM does not alter skeletal facial growth but found evidence of benefits to patients, caregivers, surgeons, and society, including the following:

- Documented reduction in the severity of the cleft deformity before surgery and, as a consequence, improved surgical outcomes
- Reduced burden of care on caregivers
- Reduction in the need for revision surgery
- Consequent reduced overall cost of care to patient and society

There is growing interest in the application of robotics to cleft surgery. Initial studies showed this to be feasible; however, economic challenges remain, and optimal approaches are yet to be defined.[52]

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Complications

Hypertrophic scarring is a frequent postoperative complication of surgical treatment of cleft lip with or without cleft palate (CL/P), often necessitating multiple lip revision operations throughout childhood in an effort to improve aesthetics and function.[53] Dysregulated, exaggerated inflammation appears to contrubute significantly to scar formation. Current therapies for hypertrophic scarring after CL/P surgery are not especially effective, but the use of specialized proresolving mediators of inflammation to accelerate wound healing may afford new therapeutic opportunities for managing this complication.

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Prevention

Research on the association between orofacial clefts and folic acid consumption strongly suggested that a certain proportion of these serious anomalies can be prevented by periconceptional supplementation of folic acid and multivitamins. The preventive approach is assumed to be especially successful in those situations where environmental factors represent a substantial part of the etiologic background.

Primary prevention (ie, prevention of a birth defect before it develops in the embryo or fetus) is attempted for prevention of recurrences in at-risk families to which a previous baby with the anomaly has been born; it is also applicable in the general population for prevention of occurrences.

Decades after initial experimental animal studies indicated that vitamin deficiency in a mother could cause congenital malformations in the offspring,[54, 55, 56] formiminoglutamic acid excretion testing for defective folate metabolism was found to be positive more often in women pregnant with a child with a neural tube defect (NTD) or another congenital abnormality than in control subjects.[57] Furthermore, periconceptional supplementation with multivitamins[58] or folic acid[59] was found to have a role in the prevention of NTDs.

Nonetheless, prevention of congenital anomalies seemed impossible to realize as the ultimate goal of teratology[60] until a randomized, controlled, double-blind, multicenter trial sponsored by the British Medical Research Council (MRC) showed a 72% decrease in the recurrence of NTDs when women ingested 4 mg/day of folic acid from the day of randomization before conception and for 12 weeks thereafter.[61, 62]

However, prophylactic multivitamin therapy, including folic acid, was first used to prevent CLP anomaly in future offspring of women whose first child had CL/P.[63, 64, 65]

On the basis of these study results, Burian (of the Czechoslovak Academy of Sciences in Prague) initiated a study in which women who had given birth to a child with an orofacial cleft began taking the multivitamin supplement preparation Spofavit (vitamins A, B1, B2, B6, C, D3, and E; nicotinamide; and calcium pathothenicum) either immediately after a subsequent pregnancy was confirmed or periconceptionally when pregnancy had been planned.[66]

Although Burian's observations were mainly empirical, a prospective trial of periconceptional multivitamin and high folic acid supplementation was conducted in women at risk for giving birth to a child with CL/P.

In a nonrandomized prospective interventional study from the Czech Republic, including 221 pregnancies in women at risk for a child with CL/P, a dramatic reduction of cleft recurrences was found after periconceptional supplementation with Spofavit and high-dose folic acid (10 mg/day).[67, 23] Supplementation began at least 2 months before planned conception and continued for at least 3 months thereafter. A comparison group, comprising 1901 women at risk for giving birth to a child with CL/P, received no supplementation and gave birth within the same period as the study group.

In the supplemented group, three of 214 informative pregnancies resulted in neonates with CL/P, a 65.4% decrease from the expected value (see the image below).[23, 67] Subset analysis by proband sex, severity of CL/P, and both variables showed the highest supplementation efficacy in probands with unilateral cleft (82.6% decrease from the expected value).
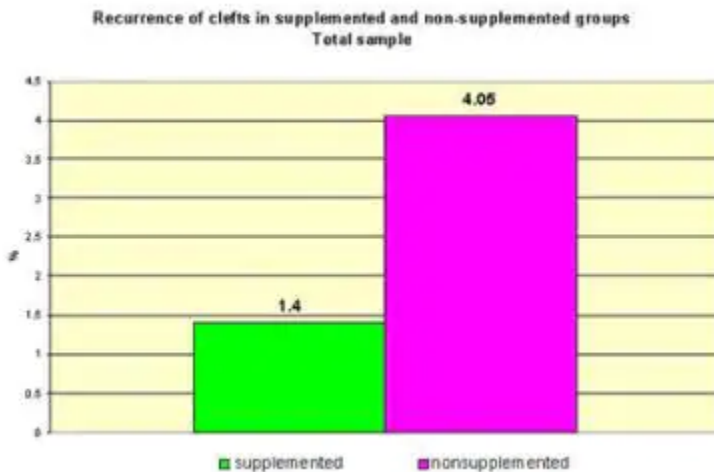
Recurrence of clefts in supplemented and nonsupplemented groups.

No efficacy was observed for female probands with bilateral CL/P. Generally, the efficacy was higher for subgroups with unilateral clefts than for those with bilateral clefts and for male than for female probands (see the image below).

Table 5: Prevention of CL±P by periconceptional vitamin (with particularly high folic acid) supplementation[1]

Proband	Nonsupplemented (without/with cleft)	Supplemented (without/with cleft)	Efficacy	
			Expected occurrence	Decreased by (%)
CL±P (1)	1,824/77	211/3	8.67	65.4
Male with CL±P (2)	1,149/42	129/1	4.58	78.2
Female with CL±P (3)	675/35	82/2	4.14	51.7
Unilateral CL±P (4)	1,511/55	163/1	5.76	82.6
Bilateral CL±P (5)	313/22	48/2	3.29	39.2

[1] Fisher's exact test was used for all results. (1) P=0.030579; (2) P=0.063989; (3) P=0.227924; (4) P=0.0203802; (5) P=0.3734264

Prevention of cleft lip and palate by periconceptional vitamin (with particularly high folic acid) supplementation.

Similarly, a large population-based case control study of fetuses and live-born infants in the 1987-1989 cohort of births in California reported that periconceptional use of multivitamins, which usually contain 0.4 mg or more of folic acid, reduced the occurrence of CL/P by approximately 27-50% (see the image below).[68] In this study, 734 mothers with an infant with an orofacial cleft and 734 control mothers with an infant without a birth defect were evaluated.

Recurrence of clefts in supplemented and non-supplemented groups.
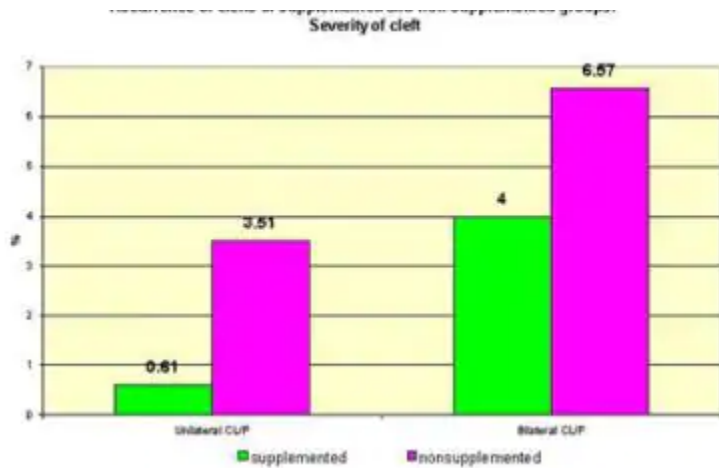
Recurrence of clefts in supplemented and nonsupplemented groups, severity of cleft.

In contrast, the study completed by Hayes did not support a protective association between the periconceptional folic acid supplementation and the risk of oral cleft.[69]

However, the most interesting results supporting high-dose folic acid in the prevention of nonsyndromic clefts were those of Czeizel et al in the Hungarian Case-Control Surveillance of Congenital Anomalies.[70] This randomized double-blind, controlled trial of periconceptional supplementation with a multivitamin including a low "physiologic" dose of folic acid (0.8 mg/day) showed no preventive effect on the first occurrence of isolated CL/P or CP alone; however, the general evaluation of congenital anomalies indicated a reduction of nonsyndromic clefts after the use of high-dose folic acid (3-9 mg/day) in the early postconception period.

A subsequent article by Czeizel discussed these two controversial findings and suggested a "dose-dependent effect" of folic acid in the prevention of orofacial clefts.[71]

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