

# The Causes of Clefting

Clefts of the lip and palate have been documented as far back as the thirteenth century, and they most certainly existed earlier. Clefts can be caused by a number of factors that affect the mother early in the first trimester of pregnancy. These factors include infections and toxicity; poor diet; hormonal imbalance; and genetic interferences. Some of the causes may be due to excessive amounts of cortisone, insulin, vitamin A, aspirin, and a diet deficient in folic acid. Some believe that in very rare instances pressure against the upper jaw by the embryo's knee or the mandible or tongue may cause clefting.

Facial clefts are among the most common congenital malformations in humans. Most geneticists believe that genetic and environmental factors, that is, those things that the mother might have eaten or not have eaten or may have been subjected to, such as measles or other diseases including high fever, can result in a cleft of the lip and/or palate. However, in any individual case a wide variety of causative agents and metabolic factors can be responsible. Good maternal and prenatal health care is essential to increase the possibility that the child will be free of birth defects.

Approximately 7% of live-born children in the United States are affected by birth defects involving the head and face. With a current rate of 3,250,000 live births per year, this means that 227,500 American babies are born every year with either major or minor birth defects of the head and face. The most common of these defects is the cleft lip and/or palate, which affects approximately 1 in 750 births or 4,300 newborns in the U.S. each year. Recent studies show an increasing incidence, particularly over the last century.

Cleft lip with or without cleft palate and cleft palate without cleft lip rank as the third and fifth most frequent congenital malformations in the United States. An isolated cleft of the palate is seen less frequently and has an incidence of 0.4 per 1,000 live births (1 in 2,500 live births). Clefts of the lip with or without a cleft of the palate affect more males (and occur in 1:1,000 live births), while clefts of the palate only affect more females (and occur in 1:2,500 live births). Left-sided clefts (70% of unilateral clefts) are more common than bilateral clefts of the lip and palate, and the right-sided clefts are the least common.

The incidence of clefts of the lip and/or palate varies by racial and ethnic group. The highest incidence occurs among Native Americans (approximately 1 in 278 live births). Among whites of European extraction, approximately 1 in 750 live births will have a cleft lip or palate. Among African-Americans, it is much lower, occurring in approximately 1 in every 3,330 births.

No single factor can be found to be the cause of all facial-palatal clefts. Most can be classified either as an isolated birth defect presumed to be *multifactorial* (meaning with multiple genetic and environmental factors combined) or as part of a genetic *syndrome* (meaning two or more birth defects with a specific natural history and expected course of progression).

Genetic syndromes involving clefts of the lip and/or palate can be considered part of a single gene disorder (autosomal-recessive, autosomal-dominant, or sex-linked), the result of a *teratogenic agent* (anything that interferes with development, such as chemical substances that enter the mother's blood stream and then the fetus's) or event (for example, one induced by hemorrhage, medication, or drug), or one aspect of a chromosomal disorder.

Genetic and environmental factors affect the development and function of humans starting from the time of fertilization and continuing through the prenatal and postnatal periods and throughout life. The critical period during which genetic and environmental events can adversely affect lip and palate development is the sixth through ninth weeks of pregnancy.

For quite some time, most cases of cleft lip and/or palate have been considered to be examples of multifactorial inheritance. Only 3% of cases were previously thought to be of a different cause (syndromic, single gene, or chromosomal). Recently, a number of investigators have found that a significant number of their patients with clefts have syndromic conditions (meaning more than one malformation) that are associated with other anomalies. Specifically, 44% to 64% of the patients with oral-facial clefting are found to in fact have associated anomalies. In 1970, when only 3% of cases were felt to be syndromic, only about fifty clefting syndromes were well described. Today, clefting is known to occur in more than 250 syndromes, including Pierre Robin syndrome, Stickler syndrome, de Lange's syndrome, Marfan syndrome, Gorlin syndrome, and some craniosynostosis syndromes.

Much has also been learned about the ill effects of teratogenic agents. A number of agents previously thought to be of high risk (such as antihistamines that were once used to combat nausea and vomiting during pregnancy) have not been substantiated when

subjected to scientific scrutiny, while a number of agents have been clearly identified as being associated with clefting (eg, the fetal hydantoin, fetal alcohol, and fetal trimethadione syndromes). It is imperative that women in their reproductive years be aware of and heed the advice of health-care professionals with access to teratogen information systems. Women must become aware of any medications or drugs they are using or chemicals to which they may be exposed. Because the early critical period of potential cleft formation is at a time before many women are aware that they are pregnant, true prevention will finally depend on an atmosphere conducive to more aggressive preconception health care and counseling. The latest advances in *microcytogenetics* (very small-cell genetics) have helped to better identify a number of chromosome anomalies (abnormal development) associated with clefting syndromes.

The chances of having a child with a cleft lip or palate will vary from one family to another depending on a number of factors. For those individuals where the clefting represents an isolated birth defect and has a multifactorial basis, the risk depends on the number of affected individuals in the family: in general, the risk increases with the number of affected relatives (see Table). For other families, the occurrence and recurrence depends on the specific genetic diagnosis and its natural history and mode of inheritance. Because these hereditary factors are variable and complicated, those with clefting in the family should seek evaluation and counseling from a qualified clinical geneticist. Such evaluation can help identify specific potential medical problems associated with one syndrome or another as well as prevent undue anxiety about the risk of recurrence of clefts in future births.

For couples contemplating or expecting parenthood, many choices based on genetic considerations are available. If either has a suspected family history

for a genetic condition or has had a child or family member with a birth defect, such as oral-facial clefting, a diagnostic evaluation by a clinical geneticist and genetic counselling are strongly recommended. Prenatal testing using the techniques of chorionic villus sampling, amniocentesis, and ultrasound are able to reveal more and more of these conditions (although not all birth defects can be diagnosed).

For more information and referral sources, contact the National Society of Genetic Counselors, 233 Canterbury Dr., Wallingford, PA 19086. You can also contact your local chapter of the March of Dimes.

Studies indicate that about a third of children born with oral-facial clefts have a family history of clefting. In the United States and Western Europe, there is a family history of clefting in approximately 40% of cases, leaving approximately 60% of cases without any known familial occurrence. There is a greater chance of having a child with a cleft if the mother or father, or other siblings (ie, first-degree relatives) have had a cleft. There is less risk of clefting if only the grandparents, aunts, uncles, nieces, or nephews (ie, second-degree relatives) have had a cleft, and even less risk if only first cousins (ie, third-degree relatives) have had a cleft.

### The Risk of Giving Birth to a Child with a Cleft\*

Number of affected parents	Number of affected siblings	Cleft lip with or without cleft palate	Isolated cleft palate
–	–	0.12%	0.05%
–	1	4%–5%	2%–3%
1	–	2%	1.7%
1	1	13%–14%	14%–17%
2	–	13%–14%	14%–17%
–	2	13%–14%	14%–17%
2	1	20%–25%	25%–50%
2	2	15%–50%	50%

\*From David DJ, Henriksson TG, Cooker RD. *Craniofacial Deformities*. Australian Cranio-Maxillo Facial Foundation, 226 Melbourne St, North Adelaide, South Australia 5006.