Controversies of Cleft Palate Repair: A Systematic Review of Literature

Thesis

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Cleft lip and palate (CLP) are common congenital deformities which represent a heterogeneous group of disorders affecting the lips and oral cavity and are generally divided into two groups: cleft lip with or without palate (CL/P) and isolated cleft palate (CP). These disorders are present in about 1.7 per 1000 live births, with ethnic and geographic variations. Cleft lip and palate affects speech, hearing, appearance and psychology of the affected child, which can lead to lifelong unfavorable outcomes for health and social integration [(1)].

Cleft palate affects almost every function of the human face except vision. Nowadays, a child born with CLP should not be considered as unfortunate, because surgical repair of these defects has to an extent reached a satisfactory level [(2)].

Typically, children with CLP need multidisciplinary care which starts from birth to adulthood. Care for children born with CLP generally includes many disciplines such as nursing, plastic surgery, maxillofacial surgery, speech therapy, otolaryngology, audiology, orthodontics, dentistry, psychology, genetics, and counseling. This care has tended to be fragmented leading to variations in management, which continue to cause controversy [(3)].

When assessing a child with CLP, certain things should not be over looked as: oro-nasal fistulae (ONF), inability to project upper lip symmetrically, deviation of the nasal septum towards the non clefted side, speech production and maxillofacial growth retardation. All of these problems indicate failure to achieve goals of repair [(4)].

The goals of CP repair are best achieved when surgeons with extensive training and experience in all phases of care are actively involved in the planning and treatment of children with CP. Surgical treatment must be based on the best available clinical research to avoid unfruitful, biased treatment schemes and to optimize outcomes of treatment [(5)].

The ideal surgical approach for management of CP deformities continues to be a source of controversy. Different treatment approaches and various techniques have evolved and described over the past years in a quest to balance speech development with facial growth, esthetic considerations as well as the social needs of a child with CLP [(6)].

Le Monnier, a French dentist, was the first to report a successful CP repair in Paris in 1766 [(5)]. The von Langenbeck palatoplasty described by Bernard von Langenbeck in the mid-1800s is the oldest procedure still in use today [(7)]. Most of the techniques proposed through the past years will be revised in this review.

With respect to the timing of surgical repair, most centers around the world now undertake the first surgery once feeding patterns have been established and birth weight has regained. The foremost difference in timing protocol in major centers is found in the sequence in which lip and palate elements are operated upon [(8,9)]. There is an ongoing debate on the appropriate time of hard palate closure. It is believed that early closure may have an adverse effect on facial growth [(10)]. Whereas late closure (after the second or third year) can have negative influence on speech [(11)]. The timing and sequencing of cleft lip and palate repair is controversial.

A lack of agreement exists regarding the timing and specific techniques used during each stage of cleft reconstruction [12].

Complications of CP may occur at any stage during the procedure. It may be as an intra-operative, immediate post-operative or delayed post-operative complications. Suggestions on how to prevent and manage these complications will be discussed in this review [2].

Revisiting the available literature to critically analyze the various timing and sequence protocols as well as surgical techniques of repair and their modifications are valuable assets for improvement of the quality of primary CP repair. In addition; this may offer a solution to the ongoing debate regarding the choice of the method of repair used, the timing, and the staging of primary repair of CP.

"The history of man for the nine months preceding his birth would, probably, be far more interesting and contain events of greater moment than all the three score and ten years that follow it".

Samuel Taylor Coleridge, 1800

❖ Nature of the defect caused by cleft palate:

➢ Embryology

In order to comprehend the goals of lip and palate repair from an anatomic perspective, the cleft surgeon must have knowledge and appreciation for the failure of embryogenesis that results in the formation of a cleft. During fetal development, various prominences fuse and continue at critical points to create and form the lip, nose, and palate. Any disturbance in the normal process of the fetal development during this period results in congenital anomalies [(3)].

Neural crest cells, which delaminate from the neural folds, contribute to and migrate through mesenchymal tissue into the developing craniofacial region where they participate in formation of the frontonasal prominence, the paired maxillary and mandibular processes, which all together surround the primitive oral cavity. This occurs by the fourth week of human embryonic development. The nasal placodes (ectodermal thickenings) formed by the end of the fourth week of embryogenesis divides the lower portion of the frontonasal prominence into paired medial and lateral nasal processes [(1)]. The so called "Palatogenesis" begins towards the end of the fifth week intrauterine and continues throughout till the twelfth week (Figure 1) [(4)].

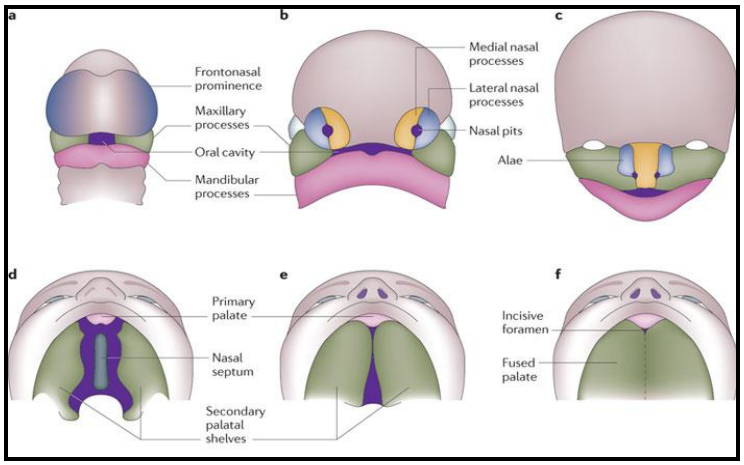


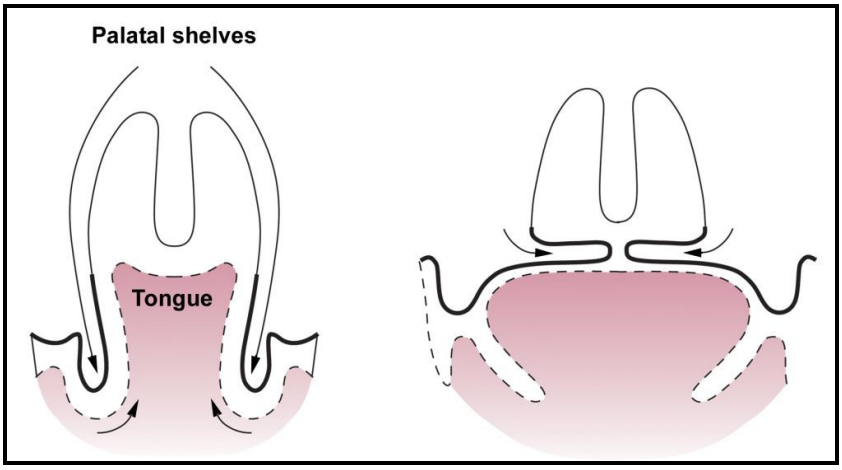
Figure (1): Development of the face and palate [(3)]

At approximately six weeks of human embryonic development the base of the nose, nostrils, and upper lip are formed by fusion of the median nasal prominence with the lateral nasal prominences and maxillary prominences. Confluence of these anterior components results in what is called the primary palate. Failure of this mechanism, leads to formation of clefts of the lips and/or maxilla [(3)]. Later during growth, the primary palate becomes the premaxilla (that part of the maxilla which houses the incisor teeth). This part is exactly situated anterior to the incisive foramen in the upper jaw and represents only a small portion of the adult hard palate [(4)]. Immediately before these processes are completed, the lateral nasal process has a peak of cell division that renders it vulnerable to teratogenic insults, and any growth disturbance at this critical time may lead to failure of the fusion mechanism [(1)].

The first sign of obvious development of the secondary palate happens within the sixth week of embryogenesis when outgrowth from the maxillary processes of the paired palatal shelves, initially grow vertically down on either side of the developing tongue (Figure 2-a) [(1)]. The

secondary palate extends posterior to the incisive foramen and is derived from the fusion of the lateral palatine processes [4].

By the seventh week of embryonic development, the palatal shelves shift from the vertical position and become horizontally positioned above the tongue, coming into contact, fusing together and forming a midline epithelial seam which subsequently degenerates allowing mesenchymal continuity across the palate (Figure 2-b). After that, the palatal mesenchyme differentiates into a bony element that correlates with the position of the hard palate and a muscular element that correlates with the position of the soft palate. In addition to fusing in the midline, the secondary palate fuses anteriorly with the primary palate and superiorly with the nasal septum [1].



a) **b)**

Figure (2): Formation of the secondary palate [1].

By the tenth week of embryogenesis these fusion processes are complete. Development of the secondary palate thus divides the oro-nasal space into oro and nasal cavities, allowing the function of mastication and

respiration to take place simultaneously. The lip and primary palate have different developmental origins from the secondary palate; therefore clefts of these areas can be subdivided into CL/P and isolated CP, in which the lip is not affected. This subdivision confirmed by the finding that, under most conditions CL/P and isolated CP do not segregate in the same family[(1)].

A unilateral cleft palate occurs when one palatal shelf of one side fails to fuse with the other components. However, a bilateral cleft palate occurs due to failure of fusion of both palatal shelves with each other and with the midline septum. When programmed cell death (apoptosis) takes place at the edges of the palatal shelves, this is when fusion occurs. Ossification occurs shortly after fusion of the primary palate to the secondary palate [(3)]. This ossification forms the hard palate. Clefts of the primary palate occur anterior to the incisive foramen, whereas, cleft of the secondary palate occur posterior to it [(4)].

If at any point throughout the development, failure of fusion should occur in any of the previously mentioned components, a cleft of the primary and/or secondary palates will be formed. Based on the degree of failure of fusion, clefts may be either complete or incomplete [(3)].

A submucous palatal cleft becomes evident when imperfect union of the muscle occurs across the velum (soft palate) beneath intact mucosal surface. Abnormal musculature anatomy may be associated with abnormal Velopharyngeal function (Velopharyngeal insufficiency (VPI)). This type of cleft results in hypernasality of speech [(4)].

➢ Epidemiology:

The overall incidence of orofacial clefts, which are the most common major congenital craniofacial abnormality, are present in approximately 1 in 700 live births. However, the incidence varies according to ethnic background, geography and the nature of the cleft itself. In the context of CLP, significant differences in the prevalence of clefts exist when specific ethnic/racial populations are examined. Therefore, the incidence in African American populations is approximately 0.3 per 1000, in Caucasian populations 1.0 per 1000, and in Asian populations 2.1 per 1000 [(9)]. Concluding that the birth prevalence in African Americans is less common than the total population, but the Asian population tends to have a higher prevalence [(3)].

According to international data collected from 57 registries for years 1993-98 which suggest a variation in birth prevalence of CLP of 3.4-22.9 per 10,000 births. Moreover, a more pronounced variation for isolated CP, with prevalence of 1.3-25.3 per 10,000 births. Variations in methods of ascertainment might have a larger effect on isolated CP than on CL/P because CP is less manifested. Parts of Latin America and Asia (china, Japan) showed high rates of CL/P nevertheless, Israel, South Africa, and southern Europe showed low rates. Rates of isolated CP were high in parts of northern Europe and Canada and low in parts of Latin America and South Africa [(1)].

However, the incidence of isolated CP is racially homogeneous at approximately 1 per 2000 live births. Never the less, unilateral cleft lip and palate (UCLP) commonly occurs nine times more than bilateral cleft lip and palate (BCLP), and occur on the left side twice as frequent as it

occurs on the right side. The ratio of left:right:bilateral clefts is 6:3:1. Cleft lip and palate predominantly affects males with a ratio of (M:F 2:1) whereas females are rather more commonly affected by isolated CP [(9)].

Bilateral cleft lip and palate are most often associated with clefting of both the primary and secondary palates. In the majority of cases, UCLP is shown to be an isolated nonsyndromic congenital defect that is not associated with any other major congenital anomalies [(3,4)]. Interestingly, it has been shown that affected women with CL/P have a higher frequency of affected children than men with CL/P [(4)].

Nevertheless, CLP and isolated CP may be often associated with other major congenital anomalies. The proportion of individuals with additional birth anomalies varies significantly between studies but, generally, further defects appear to be more frequent for individuals with isolated CP than for those with CLP [(1)]. In Europe, a study [(10)] of almost 4000 individuals with isolated CP, 55% of cases were isolated, 18% were reported to be in association with other congenital anomalies, and 27% were noted as a part of known syndromes. Another study of almost more than 5000 individuals with CL/P, 71% of cases were isolated and 29% were seen to be associated with other congenital anomalies [(11)].

- **Genetics and Etiology:**

More than a hundred Mendelian disorders are related in a way or another with CL/P (thus defining syndromic CL/P, or CP) [(4)]. Cleft lip and palate are thought to be of a multifactorial etiology with a number of potential contributing factors. Even though inheritance may play an integral role, but it is not considered a single-gene disease. These potential contributing factors may include chemical exposures, radiation, maternal

hypoxia and hyperthermia, teratogenic drugs, nutritional deficiencies, physical obstruction, or genetic influences [3]. Teratogenic drugs include steroids, antiepileptic drugs (phenytoin), and diazepam. Phenytoin was found to encourage CL, on the contrary 6-aminonicothinamide (a drug used to reduces cardiovascular oxidative injury following ischemia/reperfusion) was found to induce formation of CP. Infectious diseases such as rubella and toxoplasmosis when occur during the first trimester, are also thought to be associated with clefting [4].

One prevailing theory relates the process of CLP as a threshold in which a group of factors come together to raise the individual above a threshold at which the time of mechanism of fusion fails [3].

Recently, it has been shown that multiple genes have been responsible in the etiology of clefting. Some include the *MSX*, *LHX*, *goosecoid*, and *DLX* genes. Additional disturbances in growth factors or their receptors results in the failure of fusion which include fibroblast growth factor, transforming growth factor-β, platelet-derived growth factor, and epidermal growth factor [12].

By comparing isolated CP to other types of clefts, it has been shown that isolated CP has a much greater proportion of patients with an associated syndrome or sequence [13]. Some of the more common syndromes seen associated with isolated CP include Stickler's, Van der Woude's or DiGeorge syndromes [3].

There are over 350 known syndromes associated with oral clefts [14]. Some syndromes are associated with chromosomal disorders (Trisomy 13, Trisomy 18, Turner and Down syndromes) or monogenic syndromes (Meckel, Van Der Woude, Apert, Treacher Collins, and Pierre Robin

syndrome) [15]. The significant majority of the syndromic cases are due to Pierre Robin sequence (25% of syndromic clefts) and velo-cardio-facial syndrome (15%). The Pierre Robin sequence is associated with the majority of Stickler syndrome [16]. Therefore, an early identification and diagnosis is important, as functional issues may arise early and continue throughout life. Making a definitive diagnosis and providing genetic counseling is of prime importance; this could only be achieved through long-term genetic follow up [3].

According to a longitudinal population based study done in Norway, in 2008, which demonstrated that the relative risk of recurrence of an isolated CP in first degree relatives does not appear to be linked to the anatomical severity of the deformity [9, 17].

Moreover, according to another study done in the same year, the relative risk of recurrence of cleft in first degree relatives was 32% for any CL and 56% for isolated CP, which in return indicates that genetics contribute more to isolated CP rather than its contribution to CL. There was a low (three-fold) crossover risk between the incidence of CL and isolated CP in families, which indicates that genes as MSX-1 and IRF-6 may be participating in all forms of oral clefting [9,18].

With respect to non-syndromic clefts, unaffected parents having one child with CL/P will have 4% risk of conceiving a second affected child, while this risk increases up to 9% with having two affected children. In cases which one of the parents has a CL/P, the risk of conceiving an affected child is 4%, which increases to 17% for a second child to be affected. A total of 35% of CLP patients and 54% of isolated CP patients were shown to be associated with another congenital anomaly, although less than 3% of these cases result from a single gene

disorder[3,9,19]. Inheritance may be chromosomal, Mendelian or sporadic (Table 1)[9].

Table (1): Genetic associations with orofacial clefting [9]

Mode of inheritance	**CLP**	**CP**
Chromosomal	Trisomy 13 or 21	
Single gene	Van der Woude (Chromosome 1, AD)	Treacher Collins Syndrome (Chromosome 5, AD)
	EEC (ectrodactyly ectodermal hyperplasia and CL/P) Syndrome (Chromosome 3, AD)	Stickler Syndrome (Chromosome 12, AD)
		Velocardiofacial Syndrome (Chromosome 22, AD)
		Opitz G/BBB Syndrome (AD)
Sporadic		Pierre Robin Sequence

The chances of a cleft to recur within a family depends on several factors, including family history, severity of the clefting, gender, degree of relationship to the affected individual, and the association of a syndrome. It is complicated to predict the patterns of inheritance of families who have a history of CLP. A skilled geneticist/dysmorphologist is best prepared to make these determinations and predictions based on pedigree analysis and genetic tests. The characteristics of any hereditary influence will have an effect on the presence of a cleft [3].

❖ Classifications and Anatomy:

➢ Classification of cleft palate:

Various Classification schemes have been devised in the last 70 years, but few have received widespread clinical acceptance. The typical classification system used clinically to describe standard CLP is based on careful anatomic description of the cleft [(20)]. Clefts can be either unilateral or bilateral; microform, incomplete, or complete, and may involve the lip, nose, primary palate, and/or secondary palates (Figure 3). Also, there is a submucous cleft where the palatine muscle fails to fuse at the midline, but this is not considered an actual cleft [(15,20)]. Clefts have extremely variable presentations; each individual needs a custom-tailored repair in order to achieve the best symmetry and balance needed [(21)].

Cleft may either be non-syndromic or syndromic. Nonsyndromic clefts may be isolated anomalies or may be associated with other anomalies resulting from a single developmental abnormality or primary malformation, while syndromic clefts are associated with malformation involving other developmental regions [(22)]. However these terms are not descriptive of the original cleft.

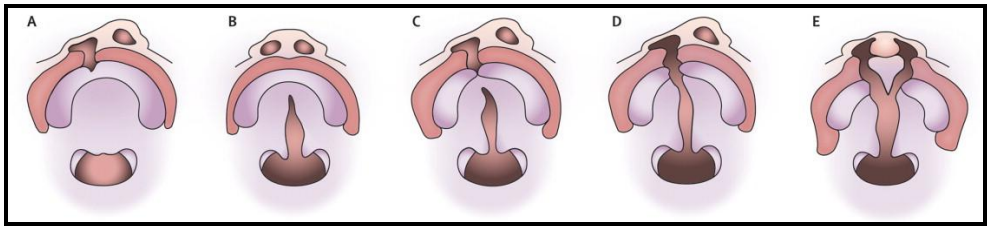


Figure (3): Non-syndromic orofacial clefts (A) Cleft lip and primary palate. (B) Cleft palate. (C) Incomplete unilateral cleft lip and palate. (D) Complete cleft lip and palate. (E) Complete bilateral cleft lip and palate [(1)].

- **Davis and Ritchie classification :**

In 1922 this classification was established based upon "operative" anatomic findings and concluded that each subgroup is further subdivided into the extent of the cleft (1/2, 1/3,...).

1. Group I: Clefts anterior to the alveolus (unilateral, median, or bilateral CL)
2. Group II: Post-alveolar clefts (CP alone, soft palate alone, soft palate and hard palate, or submucous cleft) [20,21].

- **Veau classification**:

Classification system proposed in 1931[15,20,21] and is also based upon anatomic findings still has some popularity today which is illustrated in four groups (Figure 4):

1. Group I (A) Clefts of the soft palate alone.
2. Group II (B) Clefts involving the hard and soft palates (not extending anterior to the incisive foramen).
3. Group III (C) Complete unilateral and palate (CUCLP).
4. Group IV (D) Complete bilateral cleft lip and palate (CBCLP) .

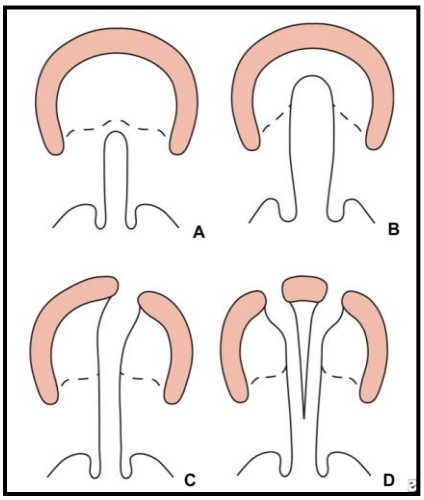


Figure (4): Veau classification.
(A) Clefts of the soft palate alone.
(B) Clefts involving the hard and soft palates (not extending anterior to the incisive foramen). (C)Complete unilateral cleft lip and palate. (D)Complete bilateral cleft lip and palate [20].