CHAPTER II

LITERATURE REVIEW

The non-syndromic cleft is a major congenital defect throughout the world (Figure 1) with an incidence of 1:700 live births.[17] In general, Asian and Amerindian populations present the highest incidence, often at 2:1,000 or higher, Caucasian populations are intermediate at 1.2-1.6:1,000, and African-derived populations have the lowest at 0.4:1,000. Among Asians, the risk for oral clefts is highest among Far East Asians, e.g., Japanese, Chinese and Koreans.[1] In Thai populations during 1989-91, the prevalence was 1.62:1,000 live births.[18] The types of cleft vary between sexes. Males have higher rates of cleft lip and palate (1:0.76), females have higher rates of isolated cleft palate (2.88:1), and overall, clefts occurr in males more than in females (2:1).[19] Unilateral clefts of both primary and secondary palates are found to occur over three times more frequently than bilateral clefts. The left side is affected more than the right.[20]

2.1 Embryology

Embryologically, the primary and secondary palates give rise to the nose, lips, and palate . The primary palate (which eventually forms the lips and nose) begins to form during the fifth week of gestation. The frontonasal process, a central and anterior area of mesenchymal tissue anterior to the brain, develops two thickened areas along its lateral edges, referred to as the nasal placodes; these placodes invaginate to form two nasal pits (that eventually form the nostrils). The ridges of tissue that form on

either side of the nasal pits are known as the medial and lateral nasal prominences. Over the next 2 weeks of gestation the two maxillary prominences, which are inferior and lateral to the nasal pits, migrate medially and fuse with the medial nasal prominences to form the primary palate.[21] Normal fusion of the primary palate is complete by the sixth week of gestation. The structures that develop from the primary palate include the nose, lip, prolabium (central upper lip), and premaxilla. These structures are anterior to the incisive foramen (Figure 2).

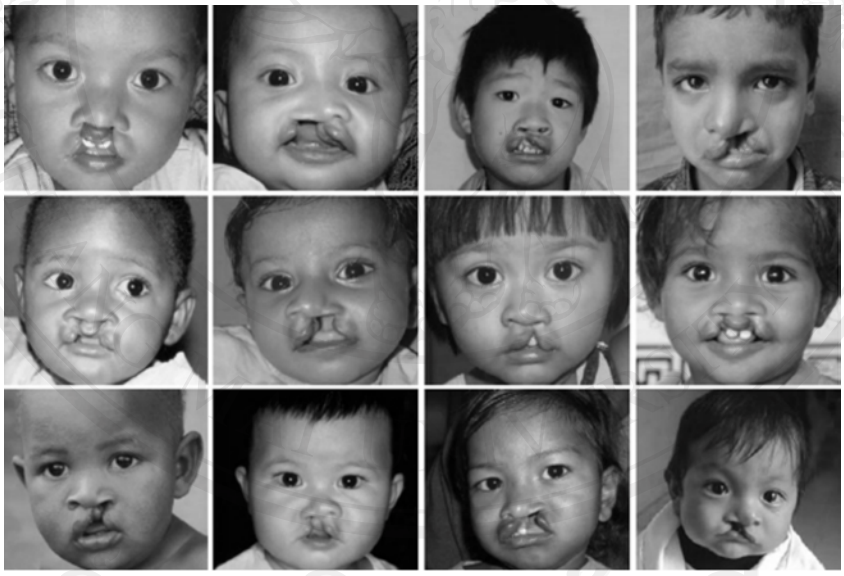

Figure 1 Children with cleft lip and palate (copy from blog.wink-web.com.s37079.gridserver.com)

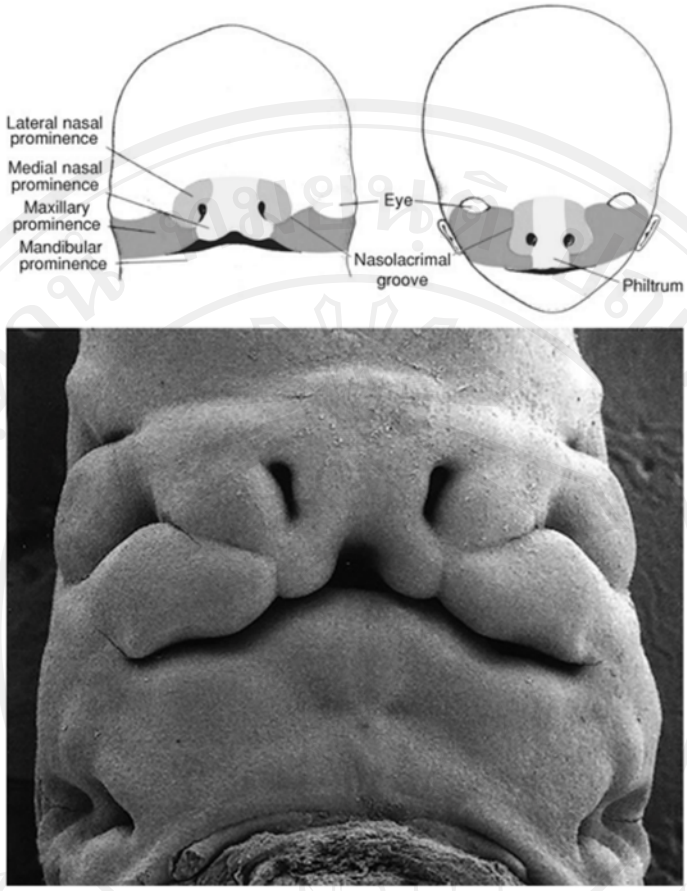

Figure 2 Facial development in the embryo. The medial and lateral nasal prominences join to form the nasal pit; the medial nasal prominence and the maxillary prominence fuse to form the primary palate. The nasal tip, columella, and philtrum are derived from the medial nasal prominence; the lateral upper lip forms from the maxillary prominence (adapted from van Aalst, 2008).[22]

Development of the secondary palate begins during the sixth week of gestation. At this time, the maxillary prominences form two shelf-like outgrowths, the palatine shelves. These shelves initially grow downward on each side of the tongue; during the seventh week of gestation, they ascend, growing horizontally above the tongue, and eventually fuse to form the secondary palate.[21] Fusion begins at the

incisive foramen and proceeds posteriorly toward the uvula. Normally, the shelves fuse in the midline to form the bony hard palate; the hard palate fuses to the vomer of the nasal septum at the ninth week of gestation. Palatal fusion continues posteriorly, with full formation of the secondary palate by the twelfth week of gestation. The secondary palate (posterior to the incisive foramen) includes both the hard the soft palate.

There are many classifications of clefts available; however, one commonly used was first described by Veau in 1931.[22] This classification simply divides the defects into four subgroups (Figure 3). Class I is an isolated soft palate cleft; Class II is a hard/soft cleft palate; Class III is an unilateral cleft lip and palate; and Class IV is a bilateral cleft lip and palate. This system does not include a class for cleft lip with incomplete cleft palate.

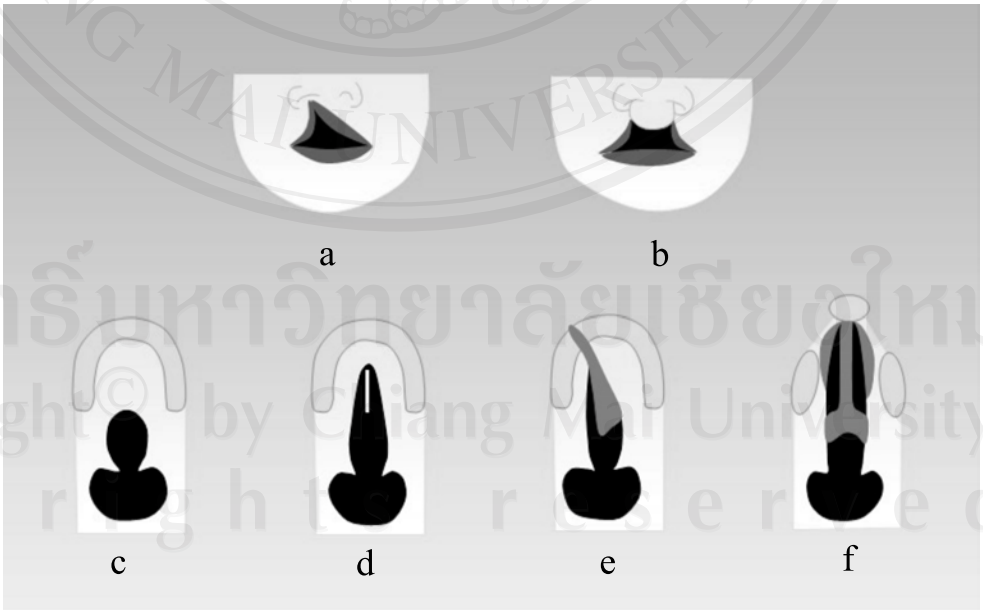

Figure 3. Non-syndromic orofacial clefts. Unilateral cleft lip (a). Bilateral cleft lip (b). Isolated soft palate cleft (c). Isolated hard and soft palate cleft (d). Unilateral cleft lip and palate (e). Bilateral cleft lip and palate (f).

2.2 Genetic and environmental causes of clefting

The etiology of clefts is complex and unknown, but includes genetic and environmental factors.[23] The genes involved in clefting are becoming increasingly understood. Genetic predisposition for the development of palatal defects, along with environmental hazards, can disrupt normal embryogenesis. Multiple chromosomal abnormalities have been shown to cause clefts, including chromosomes 1, 2, 4, 6, 11, 14, 17 and 19. Multiple environmental factors have also been noted to cause clefts, including alcohol use, cigarette smoking (two-fold increase), folate acid deficiency (and a host of potential other nutritional factors) and steroid use (three-fold increase) by the mother during pregnancy. Other environmental factors that predispose to cleft palate formation include hypoxia and high doses of retinoids (vitamin A). The process of anterior to posterior palatine fusion takes approximately one week longer in female fetuses than in male fetuses; this added time allows for longer teratogenic exposure, and may explain the increased incidence of isolated cleft palates in girls.

The problems associated with patients with clefts are feeding, speech, hearing, and psychological problems, dental irregularities, and impaired growth of the midface. The best treatment should ensure a good esthetic and functional outcome when these patients are adults. The patients should be able to speak and eat without problems and have an invisible scar and no growth disturbance.[24] These aims of treatment can be achieved by having an interdisciplinary team comprising speech

therapists, orthodontists, specialist nurses, surgeons, psychologists, geneticists and pediatricians.[25]

The surgical procedures in patients with cleft lip and palate are very important during the first year of life. In the usual treatment sequence,[26] the cleft lip is repaired within three months of age, whereas a cleft palate is repaired between 18 and 24 months of age (Table 1).

In Thailand, the Orthodontic Foundation recommends the use of presurgical orthopaedic plates after birth, but before lip closure, which is carried out between three to four months of age. The palatal cleft is often repaired later, at nine to twelve months of age (Table 2).

Table 1 Usual treatment sequence

Age	Management
3 months	Lip adhesion
10 months	Definitive lip surgery (Rotation advancement)
18 to 24 months	Hard and soft palate closure (von Langenbeck technique with vomer flap)
5 to 7 years	Orthodontic expansion (Quad helix)
6 to 8 years	Superior based pharyngeal flap, if necessary
7 to 9 years	Bone graft (Iliac crest)
8 years or later	Protraction face mask (if necessary)
Varies	Maxillary surgical advancement (Lefort I osteotomy or distraction osteogenesis)
Varies	Lip and nose revision

Surgical repairs in cleft lip and palate patients, especially during the first year of life, are fundamental steps of the whole treatment. Two major protocols of lip and

palate closure are usually accessible, i.e., one-stage closure and two-stage closure. All soft tissue cleft structures are repaired in one surgical session for the one-stage approach while the two-stage approach is separated into two procedures: lip repair and then palate repair.

Table 2 Guideline for treatment in patients with cleft lip and palate

Age	Management
0-3 months	Presurgical orthopaedic plate
3 months	Repair of the cleft lip, nasal floor and nose repair
4-9 months	Oral care, speech assessment
9-12 months	Repair of palate
1-4 years	Oral care, secondary repair of lip and palate
4-5 years	VPI, secondary repair of nose
5-8 years	Orthodontic preparation for bone grafting
8-11 years	Orthodontic treatment for bone grafting
11-12 years	Definitive orthodontics
12-15 years	Orthodontic treatment with temporary prosthesis
>15 years	Orthognathic surgery, corrective dentistry

2.3 One-stage closure of cleft lip and palate

One-stage closure, or “simultaneous repair,” is based on repair within the first year. It is infrequently performed in cleft centers worldwide, despite more than 40 years having passed since it was introduced by Davies in 1966.[6] The concept of “one-stage closure,” or “simultaneous repair,” involves early repair of the entire cleft within the first 12 months, preferably between six and 12 months, of life. According to this concept, cleft lip, palate and alveolus are repaired in one surgical session to obtain the best functional and developmental results.

2.4 Two-stage closure of cleft lip and palate

In two-stage closure, the lip and palate repairs are performed separately. The lip repair is managed at a mean age of three months before the palate repair. Dorf and Curtin[27] divided the two-stage repair into two subgroups, determined by the timing of palate repair: early and late palatal closure. Twelve months of age was used as an arbitrary dividing point between early and late palatal closure.

Early palatal closure refers to simultaneous or separate repair of the hard and soft palate at the mean age of three to 12 months, when patients begin to learn to speak. An apparent advantage of early palatal closure is that it avoids disturbances of normal development of speech in early life,[28] produces less oronasal fistulization, less velopharyngeal incompetence, and less need for secondary operations for speech.[29] Nevertheless, a criticism of this approach is the possibility of causing substantial disturbances in maxillary growth.

In 1968, Schweckendiek[30] advocated a two-stage palate repair with early closure of the soft palate. The hard palate was left open with the rationale that this would allow normal development of the maxilla. The oronasal fistula was occluded by prostheses until the hard palate was closed at 15 years of age. This procedure offered soft palate closure for speech but delayed hard palate closure to avoid early subperiosteal dissection and to reduce scarring of the palate.[31] In theory, late hard palate repair should be less damaging than early hard palate repair because of the effects of scar tissue on maxillary growth. Friede and Enemark[32] found that patients who had hard palate repair at 104 months had less retrusion of the maxilla and better jaw relation than did patients who had such repair at three months. In overview, the

fundamental advantage of this technique is to avoid scarring of the hard palate, which affects growth of the maxilla, but disadvantages are problems of articulation.[33]

2.5 One-stage closure and two-stage closure of cleft lip and palate

The comparison of the outcomes between one-stage and two-stage closure of cleft lip and palate are still controversial (Table 3). Some studies have revealed a growth aberration.[7-9, 34] Simultaneous closure in rabbits resulted in inhibition of anterior-posterior and transverse maxillary growth.[7] Some significant changes were also found in mandibular length and nasal deflection. All subjects developed anterior crossbite and functional shifts to the cleft side. Simultaneous lip and palate repair resulted in more severe craniofacial and maxillary growth aberrations than did lip repair or palate repair performed separately.[8-9, 34] It is noteworthy that these studies were experimental and their results cannot be adapted to the clinical setting. However, many of these studies[11, 35-37] demonstrated that simultaneous repair of cleft lip and palate before 12 months of age provided better speech, hearing, and maxillofacial growth. Deng *et al.*[11] stated that simultaneous repair of lip and palate in infancy is safe and reliable. Acceptable or excellent lip appearance and speech function was obtained in this operation. In 1996, Honigmann[10] published a preliminary report on one-stage closure in patients with clefts during the first year of life. One-stage repair includes the anatomical reconstruction of the soft palate, hard palate closure in two layers, and alveoloplasty with bone grafting and lip repair. Honigmann[10] observed that growth problems have not been seen in the primary dentition period. Although Fudalej, *et al.*[(38)] reported that a retruded maxilla and mandible were presented as decreased SNA and SNB angles (Figure 4); the maxilla

rotated anteriorly while the mandible rotated posteriorly. The craniofacial structures, as seen on postero-anterior cephalograms, of subjects following a one-stage simultaneous repair are symmetrical. Corbo, *et al.*[13] and Savaci, *et al.*[5] compared cephalograms of patients who underwent either simultaneous repair or two-stage operation with those of patients without clefts. Although the groups with clefts revealed a retruded maxilla and mandible with backward rotation of the palatal plane, no significant differences were observed between them. De Mey, *et al.*[12] reported that the anterior midfacial morphology of patients with clefts at 10 years of age was not different after one-stage and two-stage palatal closure. One-stage closure resulted in less downward inclination of the maxillary plane to the anterior cranial base than did two-stage closure. Several other studies also shared personal opinions and details supporting this surgical protocol.[36-37] Nevertheless, long-term follow-up, especially regarding craniofacial growth, is still limited.

Table 3 Comparison of outcomes of one-stage and two-stage treatnents.

Authors, year	Subjects	Evaluation	Controls	Results
Bardach, et al.,1988	Beagles	Lateral ceph.	Normal	One-stage: more severe craniofacial growth aberrations
Bardach, et al., 1993	Beagles	Lateral ceph.	Normal	One-stage: more detrimental of maxillary growth
Bardach, et al.,1994	Beagles	Lateral ceph.	Normal	Two-stage: less severe maxillofacial aberration
Honigmann, et al., 1996	UCLP & BCLP		-	One-stage: growth problems have not been seen in the primary dentition period
Deng, et al.,	UCLP &		-	One-stage: acceptable and or

2002	BCLP			excellent lip appearance and speech function
Savaci, et al., 2005	UCLP	Lateral ceph.	Normal	Maxillomandibular retrognathism in cleft groups at 7th year and one-stage = two-stage
Corbo, et al.,2005	UCLP	Lateral ceph.	Normal	One-stage = two-stage at 7 and 12 years of age, maxillomandibular are retrusive, palatoversion of upper incisors
Fudalej, et al., 2005	UCLP	Dental models	Normal	One-stage: prevents a serious constriction of the maxillary dental arch (intermolar width, interpremolor width and arch length)
De Mey, et al., 2006	UCLP	Lateral ceph.	-	One-stage = two-stage in antero-posterior midfacial morphology at 10 years of age
Fudalej, et al., 2007	UCLP	Lateral ceph.	Normal	One-stage = two-stage, maxillomandibular retrognathism in cleft groups at 10th year and 81% have adequate overjet
Fudalej, et al., 2007	UCLP	Postero-anteror ceph.	Normal	Lateroorbitale, Lateronasale,Zygion and Condylion landmark showed asymmetry
Fudalej, et al., 2009	UCLP	Dental models	13 cleft centers	One-stage: Dental arch relationship was comparable with the results of the centers

				with the best outcome
Fudalej, et al., 2009	UCLP	Dental models	-	Dental arch relationship was similar in both groups

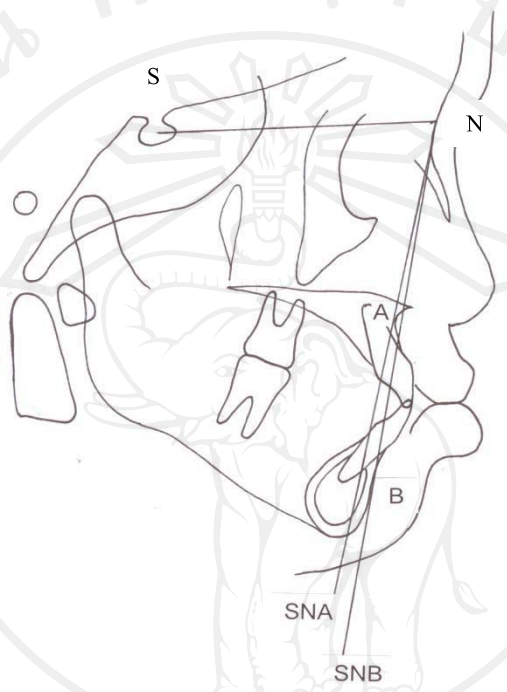

Figure 4 SNA and SNB angles

2.6 Timing of hard palate closure

The optimal time for hard palate closure in patients with cleft lip and palate remains controversial. The controversy is focused on early palatoplasty to improve speech development versus delayed palatal closure to minimize disturbance of facial growth.[4, 39-41] Friede and Enemark[32] indicated that delayed hard palate closure resulted in more growth, possibly because interference with maxillary growth was postponed to a later age, when less growth remained. Liao, *et al.*[42] reported that late hard palate repair has a smaller adverse effect on the growth of the maxilla than does

early hard palate repair. This timing primarily affects the anteroposterior development of the maxillary dento-alveolus and is attributed to the development being undisturbed before closure of the hard palate. A comprehensive review by Rohrich *et al.*[4] recommended a two-stage palate repair, with soft palate repair at three to six months of age and hard palate repair at 15 to 18 months of age. The investigators previously referred to in this paragraph advocated delayed hard palate closure. Friede *et al.*[43] still questioned whether it was necessary to delay repair until the age of nine years rather than five years, because similar and satisfactory maxillary growth was found in two samples in which patients underwent surgery at different ages. Ross[44] concluded that variation in the timing and technique of hard palate repair within the first decade of life did not affect growth appreciably. He also emphasized the importance of palatal closure for psychological reasons and speech development. Noverraz, *et al.*[39] suggested that early hard palate closure results in no significant differences in dental arch relationships in the four stages of dental development: deciduous dentition, early mixed dentition, late mixed dentition and permanent dentition.

The majority of practitioners, however, repairs both hard and soft palates simultaneously between nine and 12 months of age, finding a compromise between the benefits of early repair for speech outcomes and delayed repair for growth outcomes.

In relation to the effects of maxillary growth after lip repair, lip repair is the most important factor in the restraint of maxillary growth in patients with complete unilateral clefts of lip, alveolus and palate. The height and projection of the upper lip are reduced following lip repair.[2] Shi *et al.*[45] reported that lip repair (Millard-rotation-advancement technique) had inhibitory effects on anteroposterior growth of the

maxilla. The nasal septum deviated to the cleft side. da Silva Filho *et al.*[46] reported that the effect after lip repair consisted of reduction of the premaxillary anterior projection and lingual tipping of the upper incisors. However, comparative studies concerning different methods of lip repair in patients with a unilateral cleft have shown no differences in maxillary growth.[44]

Patients with an isolated cleft palate, which is related to the inherent growth limitation of the congenital anomaly, may have midfacial hypoplasia.[47] The growth disturbance is more pronounced in patients with clefts of both the primary and secondary palates (lip and palate) than with of the secondary palate alone. Palatal repair inhibits forward displacement of the basal maxilla and anteroposterior development of the maxillary dento-alveolus. Palatal repair has no effects on the growth of the mandible.[48]