DENTAL ARCH RELATIONSHIPS IN NON-SYNDROMIC UNILATERAL CLEFT LIP AND PALATE (UCLP) CHILDREN OF PAKISTAN

by

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LIST OF ABBREVIATIONS

CLP	Cleft lip and palate
BCLP	Bilateral cleft lip and palate
CL	Cleft lip only
CP	Cleft palate only
CS	Cleft side
EUROCRAN	European Collaboration on Craniofacial Anomalies index/yardstick
GOSLON	Great Ormond Street, London and Oslo, Norway
HB	Huddart/Bodenham scoring system
MHB	Modified Huddart/Bodenham scoring system
NAM	Nasoalveolar molding
NCS	Non-cleft side
OFC	Orofacial clefts
PSIO	Pre-surgical infant orthopaedics
TBCLP	Total bilateral cleft lip and palate
TUCLP	Total unilateral cleft lip and palate
UCLP	Unilateral cleft lip and palate
VL	Von Langenbeck technique
VY	Veau Wardill Kilners' pushback technique

HUBUNGAN GERBANG GIGI DALAM BUKAN-SINDROMIK BERAT SEBELAH BIBIR DAN LELANGIT REKAH (UCLP) ANAK-ANAK PAKISTAN

ABSTRAK

Di peringkat global, satu daripada setiap 700 kelahiran dipengaruhi oleh sumbing bibir dan lelangit. Setiap kadar kelahiran, ia adalah salah satu kongenital anomali kelahiran orofacial yang paling biasa. Kajian lepas menunjukkan bahawa sumbing bibir dan lelangit dipengaruhi pelbagai faktor, tetapi genetik dan faktor alam sekitar memainkan peranan yang penting dan telah dikaji secara meluas secara individu dan bersama. Penglibatan pelbagai pihak adalah penting untuk memastikan pengurusan rawatan sumbing bibir dan lelangit berkesan. Pembedahan utama membaikpulih fungsi dan struktur. Pelbagai kaedah telah direka dan diamalkan dalam merawat sumbing bibir dan lelangit walaubagaimanapun tiada satu kaedah yang dipilih menjadi kaedah utama dalam rawatan tersebut.

Hasil rawatan kaedah pembedahan utama perlu dinilai dari factor kongenital dan postnatal. Kesan pembedahan ke atas pertumbuhan dan hubungkait antara faktor-faktor yang telah dinyatakan haruslah di audit. Dentoalveolar telah digunakan secara meluas untuk menilai hasil rawatan. Pelbagai indek telah direka berdasarkan darjah pertumbuhan yang berbeza.

Terdapat kekurangan yang teruk apa-apa pengetahuan hasil rawatan dan peranan protokol yang berlainan di kalangan penduduk Pakistan. Matlamat kami adalah untuk menentukan taburan baik / tidak baik daripada hasil rawatan yang menggunakan GOSLON Yardstick, sistem Huddart yang diubah suai / Bodenham, dan EUROCRAN kayu pengukur. Untuk menilai hubungkait antara faktor rawatan kongenital dan selepas bersalin terhadap hasil rawatan berdasarkan indeks yang dinyatakan.

101 pasangan kanak-kanak Pakistan yang menghidapi unilateral sumbing bibir dan lelangit dengan junlah usia min 8.05 ± 0.79 dinilai menggunakan GOSLON, MHB dan ukuran EUROCRAN. Min skor indeks GOSLON adalah 3.04 ± 1.25. Skor min EUROCRAN berdasarkan penggredan gigi adalah 2.72 ± 0.76, manakala, berdasarkan morfologi permukaan lelangit, skor min adalah 2.20 ± 0.73. Skor min MHB, berdasarkan 5 kumpulan adalah 2.85 ± 1.30.

Dengan bantuan pangkalan data yang baru ditubuhkan, kumpulan rawatan sumbing boleh meningkatkan dan mewujudkan sensitif berdasarkan teknik yang terkini. Min skor GOSLON bagi penduduk Pakistan menemukan satu hasil rawatan perantaraan dan boleh dibandingkan dengan kajian populasi Asia yang lain seperti Malaysia dan Jepun. Berdasarkan sistem pemarkahan Huddart diubahsuai / Bodenham, pesakit Pakistan mempunyai hasil rawatan dari baik kepada lemah. Keputusan kajian adalah lebih sensitif dilihat dari segi darjah pertumbuhan yang songsang. Menurut indeks EUROCRAN, berdasarkan penggredan pergigian, pesakit Pakistan mempunyai frekuensi yang lebih tinggi dari hasil rawatan yang lemah dan ini adalah lebih teruk berbanding dengan penduduk Eropah. Menurut indeks EUROCRAN, berdasarkan morfologi permukaan lelangit, jumlah pesakit unilateral bibir dan lelangit dari Pakistan mempunyai hasil yang lebih teruk berbanding dengan kajian sebelumnya.

DENTAL ARCH RELATIONSHIPS IN NON-SYNDROMIC UNILATERAL CLEFT LIP AND PALATE (UCLP) CHILDREN OF PAKISTAN

ABSTRACT

Globally, one out of every 700 live-births are affected by cleft lip and palate (CLP). By occurrence rate, it is one of the most common congenital orofacial birth anomaly. Literature indicates that CLP has a multifactorial origin, but genetics and environmental factors play a vital role and have been extensively studied individually and in conjunction. A multidisciplinary involvement is absolute to successfully manage and treat CLP. Primary surgical repairs are required to restore function and structure. Numerous designs for repair of CLP have been devised and practiced but the superiority of outcome following a single surgery over the rest has not been established.

It is necessary to assess the treatment outcomes of these primary surgical repairs under the influence of congenital and post-natal factors. Audit can be performed to assess their effect on growth along with association of these confounding factors. Dentoalveolar relationships have been extensively used to assess the treatment outcome. Many indices have been developed which are based on different planes of growth.

There is a severe lack of any literature of the treatment outcome and the role of different protocols in Pakistani population. Present study aims to determine the distribution of favourable/unfavourable treatment outcome by using GOSLON Yardstick, Modified Huddart/Bodenham system (MHB), and EUROCRAN yardstick, and to evaluate the association of the congenital and post-natal treatment factors on the treatment outcome based on these indices.

101 model pairs of Pakistani children having total unilateral cleft lip and palate with a mean age of 8.05 ± 0.79 were assessed using GOSLON, MHB and EUROCRAN yardsticks. The mean score for GOSLON index is 3.04 ± 1.25.The mean score of EUROCRAN based on dental grading is 2.72 ± 0.76, whereas, based on the palatal surface morphology, the mean score is 2.20 ± 0.73. The mean score of MHB, based on 5 groups, is 2.85 ± 1.30.

With the help of present established database, teams providing cleft care can improve and establish protocols based on recent advanced techniques. Mean GOSLON scores, of Pakistani population unravel an intermediate treatment outcome and are comparable with other Asian population studies like Malaysia and Japan. According to Modified Huddart/Bodenham scoring system, Pakistani patients have a fair to poor treatment outcome. The results were more sensitive considering transverse planar growth. According to EUROCRAN index, based on dental grading, Pakistani patients have a higher frequency of poor treatment outcome, which was worse in comparison to the European populations. Based on palatal surface morphology, Pakistani TUCLP patients have the worse outcome in comparison to previous studies.

CHAPTER 1

INTRODUCTION

1.1 Background of study

Cleft lip and palate (CLP) is defined as "non-fusion of the upper lip and/or the roof of the mouth (hard and/or soft palate) which appears as a gap in the affected structures" (Erverdi and Motro, 2015). One child in every 700 live-births suffers from CLP, that makes it one of the most commonly occurring congenital orofacial birth defects (Murray, 1995). According to a recent epidemiological survey in Pakistan, one child in every 523 suffers from it with a preponderance to males (Elahi *et al.*, 2004). However, to the best of my knowledge no reported evidence till date was found on Pakistani population for treatment outcome of any type of cleft case.

Previous studies indicate that CLP has a multifactorial origin (Jones, 1993; Bernheim *et al.*, 2006; Dixon *et al.*, 2011). Patients suffering from CLP can be congenitally syndromic or non-syndromic depending on the number of other associated health problems (Saal, 2002). A patient is considered syndromic if he/she suffers from one major or three minor health problems in addition of CLP. Other than the syndromes, common health problems associated with the non-syndromic CLP children are dental anomalies (Cassolato *et al.*, 2009; Wu *et al.*, 2011), aesthetic issues (Sinko *et al.*, 2005), hearing difficulties (Yang and McPherson, 2007), speech problems (Shprintzen, 2008), and psycho-social behavioural issues (Broder, 2001; Sinko *et al.*, 2005). Treatment of CLP involves a multidisciplinary approach for a favourable treatment outcome.

Treatment objectives involve primary surgical repair of lip and palate to restore occlusion, function, and aesthetics. Numerous surgical repair techniques have been devised to perform cleft repair, but the best has not been identified till date (Mølsted *et al.*, 1992). Confounding factors other than technique also include, timing of repair (Rohrich *et al.*, 1996), surgical skill, favourable growth pattern and many other factors which have not been identified.

To improve the treatment outcomes of these surgical cleft repairs one should identify the role of the reparative surgeries, their confounding factors and the association between the two. To audit the treatment outcome of CLP many indices have been designed based on different scales of measurement. The most commonly used scale of measurement to assess treatment outcome of CLP is the dentoalveolar relationships.

One of the method to evaluate the dentoalveolar relationships is by assessing the dental casts of the patient. Since 1972, many researchers have tried to develop an audit tool which is suitable to measure the treatment outcome of the patient on which primary surgeries have been performed (Huddart and Bodenham, 1972). However, these indices came into wide use in 1987, when Great Ormond Street, London and Oslo, Norway (GOSLON) index was developed (Mars *et al.*, 1987). After which researches started to notice the importance of an audit tool which can be used to assess the treatment outcome and determine the benefits, advantages and disadvantages of the numerous surgical procedures which were in practice.

However, GOSLON index had its own pros and cons. It selected reference dental models to represent different groupings of unilateral cleft lip and palate (UCLP) patients depending on the complexity of orthodontic treatment need. Prior training and calibration was required to grade dental models reliably. After a decade, an issue regarding the age of patient was raised (Atack *et al.*, 1997a). A new index for young children was developed to eliminate the possibilities of "contamination" of patient treatment outcome till the age of ten, for example, alveolar bone grafting and/or orthodontic treatment, etcetera (Atack *et al.*, 1997a). However, both of these indices were subjective in nature, and did not readily support true statistical evaluation. Both considered growth in an anteroposterior plane heavily, then transverse and vertical, respectively in that order. This led to the modification of the originally advised Huddart/Bodenham scoring system in 1997 (Heidbuchel and Kuijpers-Jagtman, 1997).

Through modification in the scoring system it was considered that all types of clefts at all ages can be measured (Heidbuchel and Kuijpers-Jagtman, 1997; Mossey *et al.*, 2003), which came to be known as Modified Huddart/Bodenham scoring system (MHB). However, the index weighed the treatment outcome in transverse plane as heavily as anteroposterior. EUROCRAN index was devised recently which grades dental models in two modules. A dental scoring which grades the models for assessing anteroposterior and vertical growth, and a palatal scoring to assess the transverse growth (Fudalej *et al.*, 2011; Patel, 2011).

1.2 Statement of the problem

Evidence based practice has revolutionized every field of health care. With an increase in epidemiological surveys, outcome effects of the treatment provided are being evaluated which has led to the selection of an appropriate technique, development of up to date protocols, and possible prevention of environmental factors that can effect treatment outcome. On the other hand, under developed countries like Pakistan continue to provide treatment on traditionally established protocols.

In Pakistan, one in every 523 live-births suffers from some form of clefting. Yet only one epidemiological study has been conducted for the population of Pakistan and that also with the collaboration of foreign agencies (Elahi *et al.*, 2004). CLP prevalence varies among different racial and ethnic groups (Croen *et al.*, 1998). Treatment outcome of any form of CLP in Pakistani population has never been documented. There is scarcity of knowledge of the treatment outcome in Pakistani population. There is no database available to compare with other ethnicities, or alternatively, to longitudinally assess the treatment progress within the population.

1.3 Justification/Rationale of study

By determining the treatment outcome using indices based on dentoalveolar relationships, we intend to formulate a database, which will allow comparison of Pakistani with others. It will also act as a baseline for future comparative studies to document any negative or positive influence of treatment amongst the target population.

This will facilitate health care providers to plan a treatment, justify the modifications in surgeries, and to better understand the growth outcome of Pakistani population. It will reduce the treatment cost by timely planning of early intervention rather than delayed corrective procedures. Health care providers will be able to discuss the general trends of outcome with patients' family. They will try to moderate parent expectations, improve motivation of patient/parents and reduce the burden of care by timely informed consent. Most importantly, this study will raise awareness among Pakistani health care professionals to document and practice higher standards of protocols available and help reduce CLP care burden at a social level.

CHAPTER 2

LITERATURE REVIEW

2.1 Embryology of cleft lip and palate (CLP)

2.1.1 Formation of upper lip

During 6th to 7th week of embryonic development, maxillary prominences increase in size, as illustrated in Figure 2.1 A. These prominences also migrate medially, compressing the mesial nasal prominences in a mesial direction, eventually resulting in fusion of both mesial nasal prominences, as illustrated in Figure 2.1 B (Magreni and May, 2015).

2.1.2 Formation of intermaxillary segment

The fusion of mesial nasal prominences occur at a deeper level, extending horizontally, leading to the formation of intermaxillary segment. This comprises of philtrum of lip, upper jaw containing the four incisors and the primary palate as illustrated in Figure 2.2 (Magreni and May, 2015).

2.1.3 Formation of secondary palate

At the same time, the secondary palate is mainly formed by the two shelf-like outgrowths of the maxillary prominences. During 6th week, the horizontal palatine shelves are directed obliquely downwards on either side of the tongue, as illustrated in Figure 2.3.

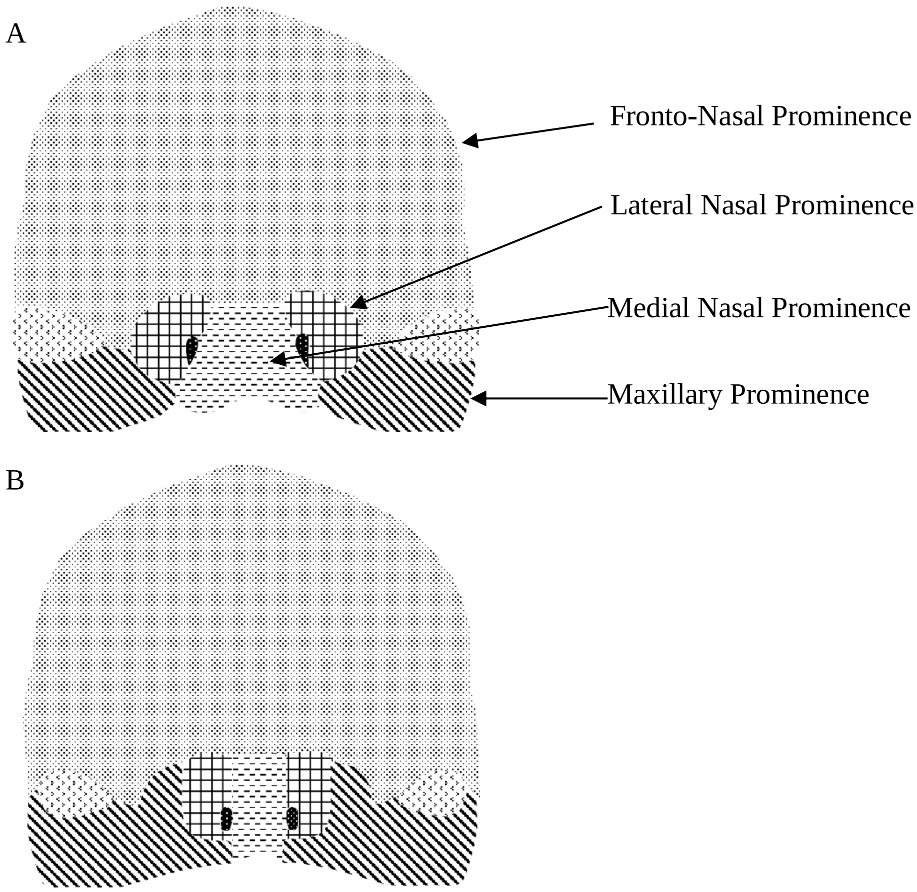

Figure 2.1: Frontal view of face A. 7th week of development. B. 10th week of development.

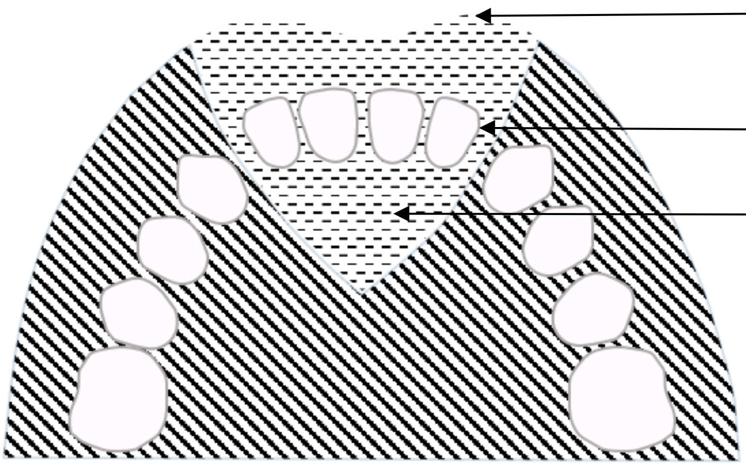

Figure 2.2: Ventral view of intermaxillary segment.

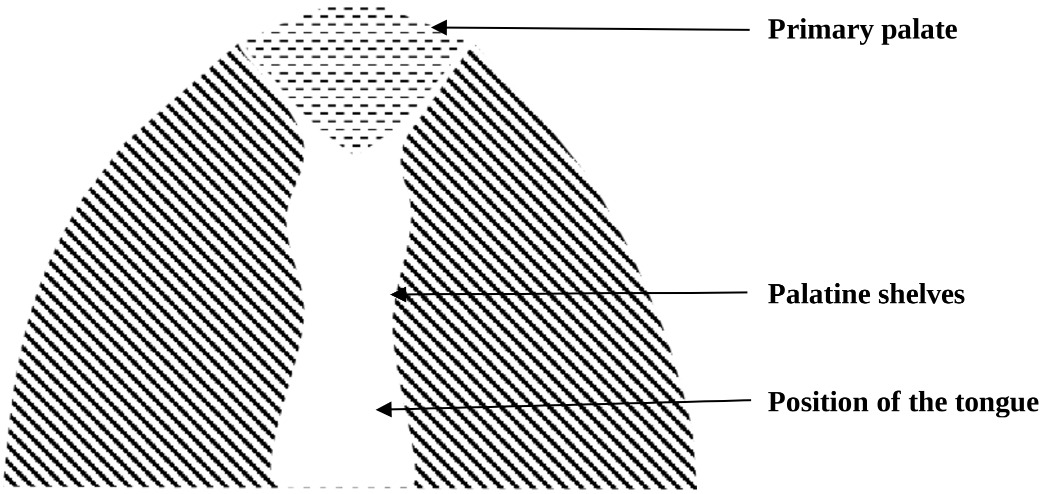

Figure 2.3: Ventral view of the palatine shelves at 6th week.

In the 7th week, the palatine shelves attain a horizontal position above the tongue and by the end of 10th week, start to fuse together to form secondary palate, as illustrated in Figure 2.4 (Magreni and May, 2015). Fusion of palatine shelves anteriorly results in the formation of incisive foramen. Incisive foramen is an embryological landmark demarcating the primary and the secondary palate.

2.1.4 Formation of cleft lip and palate

Failure of fusion of mesial nasal processes creates a gap or a split termed as cleft, which can extend from the lip up to the primary palate. Whereas, failure of fusion of maxillary prominences also results in the formation of a cleft involving secondary palate. This phenomenon of cleft formation can occur in isolation or simultaneously i.e., involving lip, primary and secondary palate. For example, when failure is in isolation it will be termed as "isolated cleft lip" (CL) or "isolated cleft palate" (CP). Whereas, in latter case "total cleft lip and palate" is formed. When the failure of fusion is on one side it is termed as "unilateral" but if both sides are involved then the resulting cleft will be termed as "bilateral" (Bernheim *et al.*, 2006).

2.1.5 Classification of cleft lip and palate

Early Veau classification was based on the increase in severity of the cleft and was classified into four groups (Schwartz *et al.*, 1993). First group having a cleft of the soft palate, 2nd having a cleft of the secondary palate, 3rd having a cleft involving the primary and secondary palate thereby resulting in the total unilateral cleft lip and palate (TUCLP) and the last group having total bilateral cleft lip and palate (TBCLP).

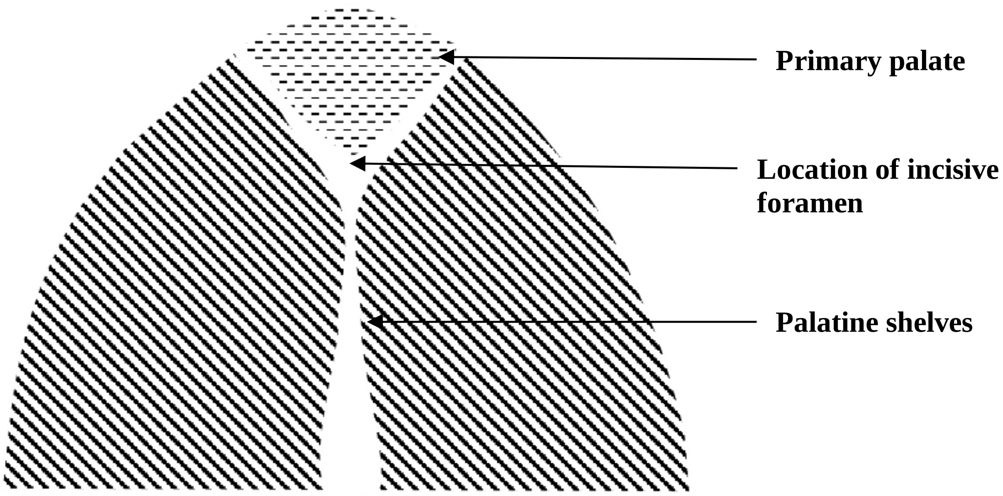

Figure 2.4: Ventral view of the palatine shelves at 7th week forming the secondary palate.

Later, Kernahan and Stark classified clefts based on the consideration of the incisive foramen as the reference point (Kernahan and Stark, 1958). First group having all the clefts of lip and primary palate up to the incisive foramen, second having clefts of the secondary palate consisting of the soft and hard palate and last group having combinations of both former groups (Tan and Henry, 1985).

Kriens proposed LAHSHAL classification which utilized the letters L, A, H, and S to represent lip, alveolus, hard palate, and soft palate, respectively. It is a palindromic system representing both sides. To explain, suppose we classify a case having “aHS” where the upper-case letters represent total cleft of the hard and soft palate whereas lower-case letter represents partial cleft of alveolus. It gives an easy and comprehensive description of the defect (Kriens, 1989).

Numerous other classifications have been proposed but their use has been limited depending upon different facets of the complex management protocols designed for CLP. For example, conventional surgeons widely consider that the incisive foramen based classification provides sufficient description of the anomaly for planning the treatment. Contemporarily, epidemiologists rely on a rather more objective classification to record the minute details for each case specifically, which would allow them to derive biologically and statistically sound results. Currently, the classification based on the incisive foramen is accepted and is being used globally (Dugas, 2010). Origin and location of the incisive foramen is illustrated in Figure 2.4. The classification based on incisive foramen will be used in the latter text to allow comparative research as it has been widely documented in the literature.

Orofacial clefts (OFC) are also classified into syndromic or non-syndromic, on the basis of association with other major or minor developmental abnormalities. The importance of this classification has been previously expressed, to facilitate in finding the etiology, devising management plan, and counselling regarding recurrence risks (Saal, 2002).

2.2 Epidemiology of CLP

2.2.1 Incidence rates

According to literature, CLP has been extensively documented as one of the most commonly occurring hereditary orofacial birth defects (Murray, 1995). Contemporarily, it has also been deemed as the most common non-syndromic cranio-facial defect (Cardoso *et al.*, 2013). It has been documented as the second most common general birth defect (Strong and Buckmiller, 2001; Thong *et al.*, 2005).

An overall incidence of 1.43:1000 of OFC to live births , has been broadly reported in literature (Stanier and Moore, 2004; Dixon *et al.*, 2011). However, significant heterogeneity among different ethnicities have been computed (Freni and Zapisek, 1991; Schutte and Murray, 1999). An overall incidence ratio of approximately 1.30:1000 among Asian population has been published (Cooper *et al.*, 2006). Regarding non-syndromic clefts 1.41:1000 in Japanese, 1.21:1000 in Chinese and 1.25:1000 in other Asian populations have been documented (Cooper *et al.*, 2006; Alam *et al.*, 2008).

A ratio of 2.1 to 1000 has been recently reported in African native population (Akintububo *et al.*, 2014). A ratio of approximately 1.06 to 1000 has been documented in a 30-year epidemiological study conducted in Iran (Kianifar *et al.*, 2015). From previous studies an estimate of 0.98:1000 has been made in Indian population (Kharbanda *et al.*, 2014). A range of 0.34-2.29:1000 would be safe to represent more than 30 surveys conducted on the variety of Caucasian populations (Freni and Zapisek, 1991; Schutte and Murray, 1999; Mossey *et al.*, 2009).

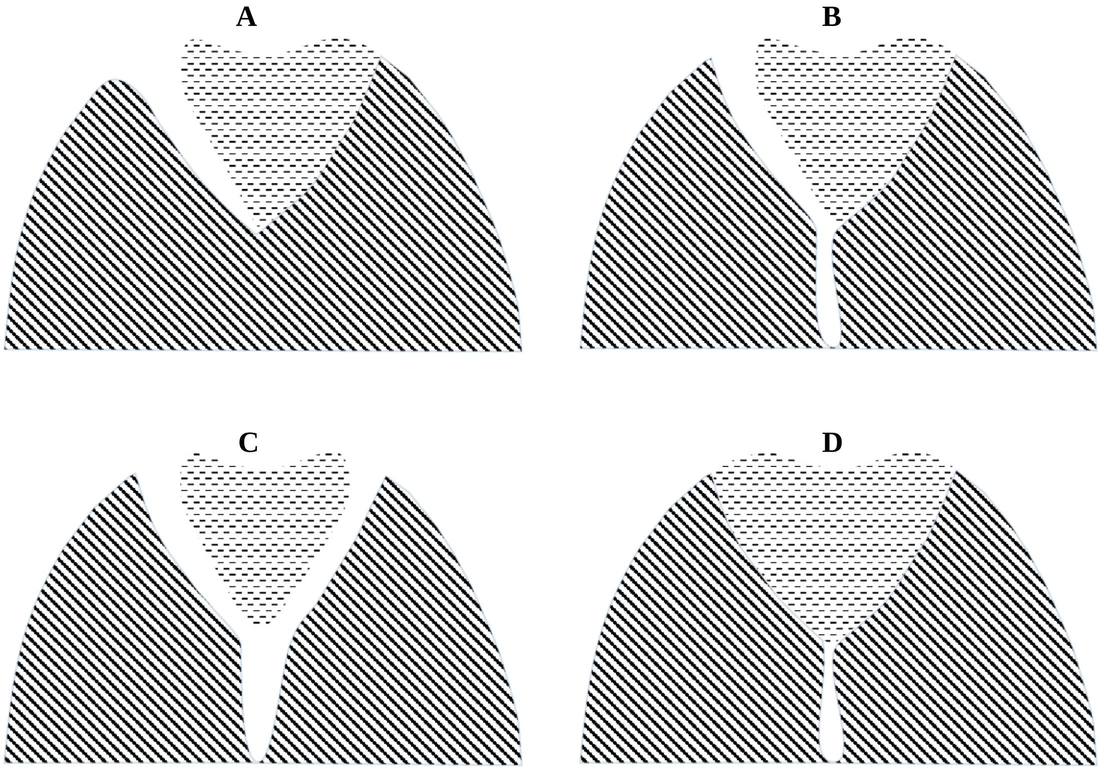

Figure 2.5: Classification system based on embryology.

A. Cleft lip only (CL) **B.** Total unilateral CLP (TUCLP) **C.** Total bilateral CLP (TBCLP) **D.** Cleft palate only (CP).

B.

Figure Legend: According to Internationally accepted classification (Millard Jr, 1976),

Group 1: Clefts of anterior palate(primary palate)
(lip and alveolous) (right and/or left)

Group 2: Clefts of anterior and posterior (primary and secondary palate)
(lip, alveolous and hard palate) (right and/or left)

Group 3: Cleft of posterior palate (secondary palate)
(hard palate and soft palate) (right and/or left)

Further subdivision were based on being “total” or “partial”

Overall 1.91:1000 was reported in an unprecedented epidemiological study in Pakistan. 42% cases of CL, 24% of CP and 34% cases of combined CLP were reported. Male preponderance was noted among CL and CLP cases, whereas females were commonly affected by CP (Elahi *et al.*, 2004).

Unilateral cleft lip has been often associated with cleft palate in 45-68% of the cases (Kirschner and LaRossa, 2000). There is two-fold probability of unilateral cleft lip extending to the palate (UCLP) to occur on the left side , and UCLP is nine times more common than bilateral cleft lip and palate (BCLP) (Habib, 1978; Kirschner and LaRossa, 2000; Kajii *et al.*, 2013).

2.2.2 Gender differences

Although the specific aetiology of the sexual disparities among cleft patients is unknown, but literature reveals a large difference in occurrence rate among different genders. Some studies reveal that 60-80% of the newborns with CLP are males (Drillien *et al.*, 1966; Nguyen and Sullivan, 1993; Kirschner and LaRossa, 2000; Strong and Buckmiller, 2001; Stanier and Moore, 2004). Moreover, males are also found to have more severe defects of CLP as compared to females (Cooper *et al.*, 1979). On the contrary, females are found to have a rather frequent occurrence of CP (Nguyen and Sullivan, 1993; Kirschner and LaRossa, 2000; Strong and Buckmiller, 2001; Stanier and Moore, 2004). The effect of late embryonic fusion of maxillary prominences have been associated with increased risk of being exposed to teratogens leading to cleft formation (Burdi and Faist, 1967). Male preponderance has also been associated with more severe or total CLP defects in other studies (Converse *et al.*, 1997). Among Japanese population the sexual disparities were less pronounced (Fujino *et al.*, 1963). Female preponderance in CP has also been found (Fraser and Calnan, 1961). Whereas, CP extending to the incisive foramen has been found more common in females (Converse *et al.*, 1997).

To comprehend CLP epidemiology, extensive studies involving massive geographical areas and a large sample size are required like the study conducted in Iran (Kianifar *et al.*, 2015). Overall incidence rates have been established among different races based on hospital records, statistical calculations, and surveys with a lack of structural classification. The influence of, exclusion of still births, syndromic clefts, different types of clefts, and abortions can greatly under predict the incidence reported in literature (Dugas, 2010).

2.3 Aetiology of CLP

2.3.1 Genetic Factors

Overall, OFC have been linked with 200-400 genetic syndromes (Wong and Hagg, 2004; Arosarena, 2007). However, non-syndromic clefts are more common and their genetic aetiology has been attributed to a single-gene locus mutation at one time or involving multiple sites (Jones, 1993; Strong and Buckmiller, 2001).

To measure the genetic influence and strength of hereditary involvement on occurrence of clefts, concordance rates are assessed. A range of 40-60% in monozygotic twins was quoted in previous studies (Jones, 1993; Nguyen and Sullivan, 1993; Marazita and Mooney, 2004) and 5% in dizygotic twins (Murray, 2002). A 100% concordance rate is essential to declare genetic mutation as the sole cause of OFC (Murray, 2002).

Various studies have been published in literature in quest of finding a genetic linkage. Various loci have been suggested to influence the occurrence of clefts. The findings have been briefly summarized in Table 2.1. CLP has been commonly associated with an autosomal dominant disorder known as Van der Woude syndrome (Kirschner and LaRossa, 2000). Interferon Regulatory Factor 6 gene has been strongly linked to this syndrome and CP (Zuchero *et al.*, 2004).

Chromosome 22q11.2 deletion has been notoriously associated with many syndrome. Namely, velo-cardio-facial syndrome (Sphrintzen syndrome), Digeorge syndrome, conotruncal anomaly face syndrome are among the most common (Shprintzen, 2008).

2.3.2 Environmental Factors

Environmental factors, lifestyle, health conditions, and socioeconomic background have been extensively documented as having a significant role in increasing or decreasing the risk of occurrence of clefts. Potential factors imparting effect on OFC have been briefly tabulated in Table 2.2. The rationale of finding these associations may not help in diagnosis or treatment of CLP, but it can greatly assist in planning pregnancies (Chen *et al.*, 2007; Mossey *et al.*, 2007). Hypothetically, planning pregnancies would include habitual modification, avoidance of unplanned pregnancies, diet counselling, genetic counselling, etc. Numerous gene-environment interactions regarding cleft lip and palate have also been explored by scientists. Interaction of smoking with *RARA*, *TGFA*, *MSX1*, *TGFB3*, *P450*, *GST*, and *EPHX1*, contemporaneously interaction of alcohol consumption with *TGFA*, *MSX1*, and *TGFB3* has been extensively researched (Maestri *et al.*, 1997; Romitti *et al.*, 1999; Hartsfield *et al.*, 2001; Mitchell *et al.*, 2001; van Rooij *et al.*, 2001; Haque *et al.*, 2015a).

Table 2.1: Summary of gene linkage/association studies. Adapted from (Murray, 2002)

Gene	Locus	Linkage	References
SKI/MTHFR	1p36	Positive	(Shaw *et al.*, 1998; Mills *et al.*, 1999; Passos-Bueno and Steman, 1999; Shaw *et al.*, 1999; Blanton *et al.*, 2000; Wyszynski and Diehl, 2000; Martinelli *et al.*, 2001a; Martinelli *et al.*, 2001b; Vieira *et al.*, 2005; Chevrier *et al.*, 2007)
TGFB2	1q41	Negative	(Lidral *et al.*, 1997; Tanabe *et al.*, 2000)
TGFA	2p13	Negative	(Ardinger *et al.*, 1989; Chenevix-Trench *et al.*, 1992; Holder *et al.*, 1992; Vintiner *et al.*, 1992; Field *et al.*, 1993; Shiang *et al.*, 1993; Feng *et al.*, 1994; Jara *et al.*, 1995; Lidral *et al.*, 1997; Maestri *et al.*, 1997; Mitchell, 1997; Pezzetti *et al.*, 1998; Christensen *et al.*, 1999; Machida *et al.*, 1999; Tanabe *et al.*, 2000; Zeiger *et al.*, 2005; Vieira, 2006)
MSX1	4p16	Positive	(Lidral *et al.*, 1997; Lidral *et al.*, 1998; Beaty *et al.*, 2001; Beaty *et al.*, 2002)
	4q31	Both	(Mitchell *et al.*, 1995)
	6p23	Both	(Scapoli *et al.*, 1997; Pezzetti *et al.*, 1998)
PVRL1	11q23	Negative	(Sözen *et al.*, 2001)
TGFB3	14q24	Negative	(Lidral *et al.*, 1997; Lidral *et al.*, 1998; Tanabe *et al.*, 2000; Beaty *et al.*, 2001; Beaty *et al.*, 2002)
GABRB3	15q11	Negative	(Tanabe *et al.*, 2000; Scapoli *et al.*, 2002)
RARA	17q21	Both	(Chenevix-Trench *et al.*, 1992; Shaw *et al.*, 1993)
BCL3	19q13	Both	(Shaw *et al.*, 1993; Stein *et al.*, 1995)
IRF6	1q32.3q41	Positive	(Zuchero *et al.*, 2004)
TBX1	22q11.2	Both	(Shprintzen, 2008)

Table 2.2: A summary of lifestyle and environmental risks of OFC.

Agent	Comments	Selected references
Anticonvulsant drugs like, Diazepam, Phenytoin, Phenobarbital	A ten-fold increased risk of OFC has been associated with the use of Phenytoin.	(Dravet *et al.*, 1992; Abrishamchian *et al.*, 1994; Shaw *et al.*, 1995)
Corticosteroids	An estimated increased risk up to three-folds has been documented.	(Park-Wyllie *et al.*, 2000)
Benzodiazepines	A possible risk has been associated in two studies.	(Safra and Oakley, 1975; Saxén and Saxén, 1975)
Isotretinoin	Positive teratogenic effects on pregnant females and mice were detected.	(Willhite *et al.*, 1985; Jones, 1993)
Sickness	Infections during pregnancy like influenza, rubella, and common cold were significantly high among mothers of affected cases.	(Natsume *et al.*, 2000)
Smoking	According to various studies and meta-analyses, an occurrence risk of 2-20% has been associated. Although the negative effects of public smoking, pollution, and passive smoking have not been attributed.	(Warkany and Nelson, 1940; Johnston and Millicovsky, 1985; Lammer *et al.*, 1985; Khoury *et al.*, 1987; Van den Eeden *et al.*, 1990; Rothman *et al.*, 1995; Shaw *et al.*, 1996; Beaty *et al.*, 1997; Croen *et al.*, 1998; Mitchell *et al.*, 2003; Little *et al.*, 2004; Tamura *et al.*, 2005; Honein *et al.*, 2007)
Alcohol	Depending upon consumption, high quantities of routine consumption during pregnancies have been associated with a higher risk of cleft occurrence. Moreover, prenatal ethanol exposure has been known to cause lysis of neural crest cells, which could result in gene alteration or mutation.	(Gordon and Shy, 1981; Kotch and Sulik, 1992; Cartwright and Smith, 1995; Rothman *et al.*, 1995; Munger *et al.*, 1996; Croen *et al.*, 1998; Shaw and Lammer, 1999; Shaw *et al.*, 2003)
Multivitamin	Multivitamin supplementation has shown 25% reduction in occurrence risk of clefts.	(Tolarova, 1982; Tolarova and Harris, 1995; Shaw *et al.*, 1999; Johnson and Little, 2008)

Table 2.2 (Continued)

Agent	Comments	Selected references
Folic Acid	Folic acid supplementation during initial four months of pregnancy was found to have a protective effect against OFC and in another study, high doses of maternal folic acid supplementation have shown increased occurrence risk as compared to low doses.	(Tolarova, 1982; Johnston and Millicovsky, 1985; Tolarova and Harris, 1995; Czeizel *et al.*, 1996; Jacobsson and Granström, 1997; Ulrich *et al.*, 1999; Schubert *et al.*, 2002)
Socioeconomic status	A feeble association of low-income to increased occurrence risk has been discussed in few studies.	(Sivaloganathan, 1972; Moosey and Little, 2002; Elahi *et al.*, 2004)
Exposure to organic solvents	Parental exposure due to occupation or environment has been associated with an inconsistent risk.	(Gordon and Shy, 1981; Garcia, 1998; Lorente *et al.*, 2000; Shaw *et al.*, 2003)
Vitamin B6 deficiency	In Asian populations, where polished rice is staple food, increased risk of OFC has been documented.	(Munger *et al.*, 2004)
Zinc	A deficiency of zinc is proved to cause CP. Low plasma concentrations of zinc increase the risk of OFC.	(Warkany and Nelson, 1940; Krapels *et al.*, 2004; Tamura *et al.*, 2005)
Riboflavin	CP was formed in subjects with riboflavin induced deficiency.	(Strean and Peer, 1956)
Vitamin A	High levels of vitamin A consumption were found to have increased teratogenic effects.	(Rothman *et al.*, 1995; Mitchell *et al.*, 2003)

2.4 Impact of CLP on patients

Unfortunately, numerous problems have been associated with non-syndromic cleft lip and palate patients. Associated health problems include, feeding problems (Clarren *et al.*, 1987; Jones, 1993), hearing defects (Yang and McPherson, 2007), speech problems (velo-pharyngeal dysfunction) (Al Omari and Al-Omari, 2004; Salyer *et al.*, 2006), aesthetic problems (Ross and MacNamera, 1994; Sinko *et al.*, 2005), poor cognitive functioning and social skills (Broder, 2001; Eiserman, 2001), paediatric and orthodontic complications (Devlin, 1998) and a wide list of dental anomalies (Cassolato *et al.*, 2009; Wu *et al.*, 2011).

Most commonly occurring dental anomaly is congenitally missing maxillary lateral incisor of the cleft side (Wu *et al.*, 2011). Crossbite and class III malocclusion have also been documented as the most commonly associated dental anomalies (Paradowska-Stolarz and Kawala, 2014). Other dental anomalies associated with CLP are, supernumerary teeth, peg laterals, impacted teeth, retained deciduous dentition, etcetera (Cassolato *et al.*, 2009; Wu *et al.*, 2011; Haque and Alam, 2015).

2.5 Treatment of CLP

Management of CLP has immensely evolved over the past century. Multidisciplinary approaches and new techniques for management of CLP have been introduced, discussed and modified. Age plays an important role while planning treatment of CLP. A flow chart of chronological management of CLP patients is presented in Figure 2.6.

2.5.1 Pre-surgical infant orthopaedics

Many intraoral devices have been introduced to facilitate feeding and controlling naso-labio-maxillary growth. Clinical trials to assess the use of these devices suggested no significant effect of pre-surgical infant orthopaedic (PSIO) devices but naso-alveolar molding (NAM) was not studied in these trials (Grayson and Garfinkle, 2014). However, significant clinical improvements with use of PSIO have also been attributed in literature (Koshikawa-Matsuno *et al.*, 2014). In 2014, potential advantages and disadvantages of PSIO including NAM were comprehensively discussed in heated point/counterpoint articles (Grayson and Garfinkle, 2014; Hathaway and Long, 2014). Treatment outcomes of as many as 16 inter-centre studies were assessed and comparatively favourable results were found among centres where non-PSIO treatments were performed (Vig and Mercado, 2015).

2.5.2 Cleft lip repair

Lip repair (cheiloplasty) aims to approximate the abnormal attachments in corrected location with minimal scarring. Clinical anatomy of a cleft lip differs from a healthy lip as, the circular perioral fibers of the musculature (orbicularis oris) are obliquely attached to the caudal nasal septum instead of encircling the oral orifice in continuity (Anastassov and Joos, 2001; Haque and Alam, 2014a). Numerous techniques have been devised for the primary lip repair as shown in Figure 2.7.

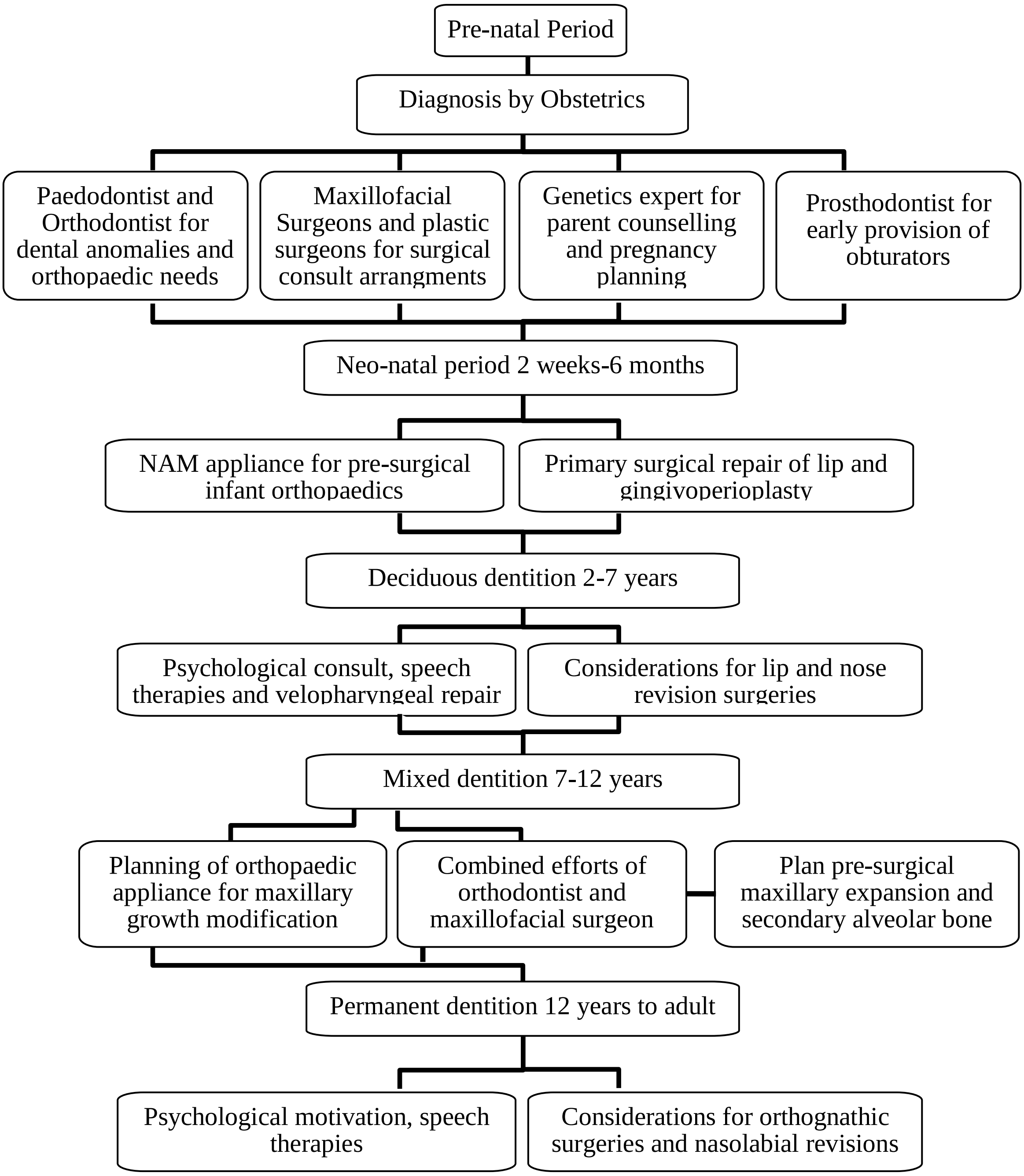

Figure 2.6: Chronological flow diagram of orofacial cleft management.

2.5.2.1 Tennison-Randall Technique (Tennison, 1952; Randall, 1959)

A triangular flap was initially designed for cleft lip repair by Tennison, which was later modified by Randall, to improve its reproducibility with ease and precision. This technique is still in use by some surgeons, and it produces predictable results (Arosarena, 2007).

2.5.2.2 Millard rotation advancement technique

It is one of the most popular techniques being used for cleft lip repair (Millard Jr, 1961). It has been modified several times by surgeons belonging different school of thoughts (Millard Jr, 1961). Advantages and disadvantages of Millard technique are numerous (Kirschner and LaRossa, 2000; Arosarena, 2007). Millard attempted to preserve cupid's bow, philtral dimple, and improve nose prominence (Millard Jr, 1976).

2.5.3 Cleft palate repair

Palatal repair (palatoplasty) aims to create a physical barrier between oral and nasal cavities. Surgical repair of soft and hard palate is performed generally around 6-9 months of age. Two most important factors in determining surgical outcome are timing of surgery and technique of palatoplasty used (Kirschner and LaRossa, 2000; Lilja *et al.*, 2006). However, delayed palatal closure has been linked with poor speech outcomes, though it remains debateable. Many surgical techniques have been devised to repair palate using one-stage or two-stage techniques (Haque and Alam, 2014b). One-stage technique involves approximating the soft and hard palate simultaneously in a single appointment. Whereas, in two-stage technique both are dealt with in separate appointments. Statistically, no significant difference of surgical outcome has been documented between one-stage and two-stage technique. Figure 2.8 shows major different techniques available for palatoplasty.

2.5.3.1 Von Langenbeck technique

In 1861, Von Langenbeck (VL) introduced two-flap uranoplasty (palatoplasty), which is still practiced (Arosarena, 2007). Simplicity of design and the smaller dissection involved has led to its frequent use over the past century (Vig and Mercado, 2015). Main drawback of this procedure was the poor speech outcome, and minimal increase in length of soft palate (Dreyer and Trier, 1984).

2.5.3.2 Veau-Wardill-Kilners' pushback palatoplasty

Recognizing the drawbacks of Von Langenbeck technique, efforts were made to design a technique which could address the issue of speech problems and short palatal length. To achieve sufficient palatal lengthening, one of the most commonly used technique was Veau-Wardill-Kilners' (VY) pushback palatoplasty (Kirschner and LaRossa, 2000). Because of the large scar area left intentionally for secondary healing there is increased risk of a palatal fistula formation which has led to its limited use (Krause *et al.*, 1976).

2.5.4 Alveolar process repair

Primary and secondary alveolar bone grafting have been used to augment the defected area with a bone graft from various sources. Usually alveolar bone grafts are required to facilitate eruption process of permanent dentition, reduce nasal asymmetry, contouring arch and implant site preparation (Kajii *et al.*, 2009; Dugas, 2010). The idea of primary alveolar bone grafts has been abandoned since the gold standard set by secondary alveolar bone replacement (Boyne and Sands, 1972; Meazzini *et al.*, 2008).