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THREE-DIMENSIONAL ANALYSIS OF MORPHOLOGICAL CHANGES IN THE FACE AND MAXILLA OF PATIENTS WITH UNILATERAL COMPLETE CLEFT LIP AND PALATE AFTER PRESURGICAL NASOALVEOLAR MOLDING TREATMENT

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I. BEYAN

Bu tez çalışmasının kendi çalışmam olduğunu, tezin planlanmasından yazımına kadar bütün aşamalarda etik dışı davranışımın olmadığını, bu tezdeki bütün bilgileri akademik ve etik kurallar içinde elde ettiğimi, bu tez çalışmasıyla elde edilmeyen bütün bilgi ve yorumlara kaynak gösterdiğimi ve bu kaynakları da kaynaklar listesine aldığımı, yine bu tezin çalışılması ve yazımı sırasında patent ve telif haklarını ihlal edici bir davranışımın olmadığı beyan ederim.

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II. CONTENTS

IV. ABBREVIATIONS

1- CLP: Cleft Lip and Palate

2- CLO: Cleft Lip Only

3- UCLP: Unilateral Cleft Lip and Palate

4- CPO: Cleft Palate Only

5- IO: Infant Orthopedics

6- NSCLP: Non Syndromic Cleft Lip and Palate.

7- No: Number

8- 2D: Two Dimensional

9- 3D: Three Dimentional

10- 3D RF: Three Dimensional Reverse Face

11- RA: Retinoid Acid

12- Ocs: Orofacial Clefts

13- NAM: Naso-Alveolar Molding

14- SLOB: Same Lingual Opposite Buccal

15- LDI: Laser Doppler Imaging

16- STL: Stereolihtograph Format

17- SFS: Shape from Shading

18- VRML: Virtual Reality Machine Language

19- CAD/CAM: Computer Aided Design / Computer Aided Manufacturing

20- GA: Gestational Age

21- ABW: Alar Base Width

22- CoW: Columella Width

23- CNW: Width of the Clefted Nostril

24- NCNW: Width of the Non Clefted Nostril

25- CoL: Columella Length

26- I: Incisal Point Where Big Segment Dislocation is Measured

27- C, C': The point Where Alveolar Crest and Lateral Sulcus are Intersecting

28- Q, Q': The point Where Gingival Groove and Palatal Sulcus are Intersecting

29- L: The Most Mesial Point of Small Segment on Alveolar Crest

30- G: The Most Mesial Point of Big Segment on Alveolar Crest

31- BSD: Big Segment Dislocation
32- SSD: Small Segment Dislocation
33- ACW: Anterior Cleft Width
34- PCW: Posterior Cleft Width
35- Min: Minimum
36- Max: Maximum
37- ICC: Intraclass Correlation Coefficient
38- Fig: Figure
39- CBCT: Cone Beam Computed Tomography

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1. SUMMARY

The aim of this study is to evaluate the three-dimensional (3D) changes occurring in the maxilla in terms of cleft width and dislocation of the segments and in the face in terms of nostril and columella width, height and length, of patients with Unilateral Complete Cleft Lip and Palate (UCLP) after receiving presurgical Nasoalveolar Molding (NAM).

Twenty four pairs of digital models (for each idividual, one before and one after NAM) of non syndromic newborn infants were selected from the Department of Orthodontics of Marmara University. All infants were within one month of age when NAM was started.

Intraoral and extraoral landmarks were used to evaluate 3D changes in the maxilla, and nose, to quantify nostril and columella width, height and length.

The results showed a statistically significant increase in the values of the columella length measurement and in the alar base width. On the other hand, statistically significant decrease observed in the values of columella width, of posterior alveolar width, as well as in the linear measurements that demonstrate the dislocation of the big and small segment of the maxilla.

Key words: nasoalveolar molding, unilateral cleft lip and palate, maxillary and facial morphological changes, 3D analysis.

2. ÖZET

Cerrahi Öncesi Uygulananan Nazoalveoler Molding Tedavisinin Unilateral Tam Dudak Damak Yarıklı Hastalarda, Yüz ve Maksillada Meydana Getirdiği Morfolojik Değisikliklerin Üç Boyutlu Olarak İncelenmesi

Bu çalışmanın amacı; unilateral tam dudak damak yarıklı hastalarda cerrahi öncesi uygulanan nazoalveoler düzeltim (NAM) sonrası maksillada yarık segmentlerinin genişliği ve segmentlerin dislokasyonunu ve yüzde burun delikleri ve kolumella genişligi, yüksekliği ve uzunluğunda oluşan değişimleri üç boyutlu (3D) olarak gözlemlemektir.

Çalışma sonuçları Marmara Üniversitesi Ortodonti Anabilim Dalı Bebek Kliniği arşivinden sendromu olmayan yirmi dört çift yenidoğana ait dijital model (her birey için, bir NAM öncesi ve bir NAM sonrası) seçildi. Nazoalveoler düzeltim başladığında bütün infantlar ilk aylarının içindeydi.

Burun delikleri ve kolumellanın genişliği, yüksekliği ve uzunluğunun hesaplanmasında, maksilla ve burundaki değişimin 3 boyutlu olarak değerlendirilmesinde intraoral ve ekstraoral noktalar kullanılmıştır.

Çalışma sonuçları kolumella uzunluğu ve burun tabanı genişliği değerlerinde istatistiksel olarak anlamlı bir artış göstermiştir. Diğer taraftan, kolumella genişliği, ve posterior alveol genişliği değerlerinde istatistiksel olarak anlamlı bir azalma gözlemlenmiştir. Aynı şekilde maksillanın büyük ve küçük segmentlerindeki dislokasyonu gösteren çizgisel ölçümlerde de düşüş gözlenmiştir.

Anahtar sözcükler: nazoalveolar şekillendirme, tek taraflı dudak damak yarığı, maksilla ve yüz morfolojisinde değişim, 3D analizleri

3. INTRODUCTION AND AIMS

The treatment of Cleft Lip and Palate (CLP) is a long, difficult and detailed process, to which different departments of medicine and dentistry contribute in an integrating manner (78). A successful treatment for CLP infants demands accurate diagnostic methodology, detailed treatment plan and multi-disciplinary approach.

Although these craniofacial defects are common, the exact etiology remains still unclear. These defects have a multi-factorial background with an active interaction between genetic and environmental factors (223).

Cleft lip and palate among the other types of orofacial clefts is the most complicated to be treated. The location, the width and the severity of the cleft lip and palate has an impact on speech, facial appearance, dental relationships, and craniofacial growth, hearing, social and psychological problems.

The most desirable improvements in appearance for the patients with CLP and their relatives are in the area of lip and nose. Especially, the uncorrected nasal deformity has been unacceptable and patients with this condition have been ridiculed, which has generated major psychosocial impact on the patients and the parents (195). Individuals with cleft lip and palate present significantly more dental anomalies, even outside the cleft area, than do individuals without clefts.

The management of cleft patients has evolved dramatically in recent years. In children born with a CLP, presurgical infant orthopedics (PSIO) is performed during infancy mainly in order to facilitate feeding, to reduce the cleft width, to actively mold and reposition the deformed nasal cartilages and alveolar processes and to lengthen the deficient columella in the neonatal period, prior to the primary lip and nasal surgery.

During the early infant stage, the cartilage remains soft and pliable, probably because of the estrogen and hyaluronic acid. In 1993 Grayson and Cutting (66) introduced the most popularized system of PSIO, the Nasoalveolar Molding (NAM) The presurgical Nasoalveolar Molding process takes advantage of malleability of immature cartilage and its ability to maintain permanent correction of its form.

A survey showed a wide diversity in models of care and national policies as well as clinical practices in Europe (199). Of the 201 centers that registered, the survey showed 194 different protocols being followed for only unilateral clefts. In 1993 Grayson and Cutting (66) introduced Nasoalveolar Molding (NAM). However its effectiveness is still not well documented and is a controversial subject between proponents and opponents (29, 161).

The principal objectives of treatment for individuals with clefts are to improve feeding, hearing, speech, facial appearance and reducing the negative social and psychological impact to these individuals. Success of these goals is maximizing the chances of children with cleft growing up and developing normally to their social and physical environment.

Often in the past, children born with CLP received inadequate care due to diagnostic errors, inadequate or ill-timed procedures as well as failure to identify the full spectrum of problems associated with it (24).

For decades dental casts, X-rays and photographs were used for analyzing and documenting CLP patients. The transfer and exchange of these documents for communication and information are very important between the physicians. The time spent during transfer, the low resilience to natural damage, the lack of space for storage are major disadvantages of plaster models. These disadvantages lead the scientific community to create digitized study and analysis models.

The purpose of this study is to evaluate the Three-Dimensional (3D) changes occurring in the Maxilla in terms of cleft width and dislocation of the segments and in the Face in terms of nostril and columella width, height and length, of patients with Unilateral Complete Cleft Lip and Palate (UCLP) after receiving Presurgical

Nasoalveolar Molding (PNAM) treatment in the Department of Orthodontics of Marmara University.

4. LITERATURE REVIEW

4.1. Cleft Lip and Palate

4.1.1 Historical Perspective of Cleft Lip and Palate

The earliest historical signs of cleft lip and palate reveal horror and utter disbelief. In ancient times even in medieval ages, many congenital deformities, including the cleft lip and palate, were considered to be evidence of the presence of an evil spirit in the affected child (36).

Facial deformities were most condemned and the infants were "removed from the tribe or cultural unit and left to die in the surrounding wilderness", a practice that still prevails today in certain African tribes. In Sparta, the unfortunate newborns were abandoned on Mount Tagete in an area known as ‘’Kaiadas’’, while in Rome they were drowned in the Tiber River or thrown off the Tarpeian rock. The noted philosopher Plato, justified it in one of his dialogues in the Republic, explaining that it was a means of removing evil omens and preserving the soundness of the race. George Dorrance discussed the case of a mummy that had been reported in 1929 by Smith and Dawson in their work Egyptian Mummies published in London. Thus Egyptians knew about the deformity. In the ancient Mediterranean civilizations these children were said to possess supernatural powers (155).

Fabricius ab Aquapendente (1537-1619) was the first to suggest that in the development of the human foetus the upper lip only coalesces along the middle line at a very late stage (54). The most convincing explanation of the origin of the facial cleft in this period was furnished by Philippe Frederick Blandin (1838-96), who suggested that it resulted from a failure of the premaxilla and the maxillary segments to unite (15).

In 1808 Meckel (126) published his theory that the lips were formed from five separate processes which eventually united, three for the upper lip and two for the lower lip.

William His (76) described that the embryological development of the mid-face resulted from the fusion of the five processes around the stomodeum, failure of any two of these parts to join would result in the formation of a different type of cleft, varying from unilateral and bilateral clefts to the rare cleft of the lower lip along the median line.

4.1.1.2 History of Lip Repair

Boo-Chai (1966) reported a case of successful closure of a cleft lip at approximately 390 A.D. in China, although the surgeon's name is not mentioned (108). The first well documented description of cleft lip and its surgical repair was from Yperman (1295-1351) a Flemish surgeon. He closed the freshened borders of the cleft lip with a triangular needle armed with a twisted wax suture, a common method of suture at the time. In order to approximate the internal and external wound edges, he reinforced the closure with a long needle passed through the lip some distance from the edges of the cleft, the needle was held in place by a wraparound ligature-of-eight thread (230).

In 1497 Hyeronimus Brunschwig, a military surgeon from Alsace after scarifying the margins of the cleft with scissors, applied a pinching clamp (Zwickhafft) or self-retaining clamp (Telphaffen), and then sutured the margins together with interrupted waxed stitches. The sutures and clamp were left in place for some time, after which the wound was covered with a mixture made of egg and pulverized eggshell (21).

Pierre Franco described the techniques of correction of both unilateral and bilateral cleft lips in Traite des Hernies very meticulously. He used dry sutures, pins and a triangular bandage. Franco in 1556 wrote: "... cleft lips are sometimes cleft without a cleft of the jaw or palate, sometimes the cleft is only slight, and at times the cleft is as long and as wide as the lip". In 1561 he wrote: "Those who have cleft palates are more difficult to cure, and they always speak through the nose. If the palate is only slightly cleft, and if it can be plugged with cotton, the patient will speak more clearly, or perhaps even as well as if there were no cleft, or better, a palate of silver or lead can be applied by some means and retained there" (56).

Most surgeons till the early 19th century were scarifying the margins of the cleft and suturing them together, employing various expedients to ensure good approximation of the edges.

In 1844 Mirault introduced the modern cross-flap technique of lip closure and since that time nearly every conceivable type of flap - triangular, rectangular, or curvilinear–has been tried. Mirault's technique remained popular and was advocated during the twentieth century (134).

About the time of repairing it was a subject of debate for many years. Hendrik van Roonhuysen of Amsterdam and James Cooke of Warwick felt that the operation should be carried out as soon as possible, when the patient was just three or four months of age as it is more dangerous to perform at an older age in contrast to Leclerc who noted in 1701 that their "continual crying would hinder the reunion (14).

4.1.1.3 Refinement of the Repair

Dieffenbach recommended that clefts of the hard palate could be closed by separating palatal mucosa from the bone. While he also recommended lateral relaxing osteotomies to close clefts of the secondary palate, he did not employ these until 1828. This technique is still employed in certain centers at the present time (49).

Werner H. Hagerdon of Magdeburg who had studied under von Langenbeck, introduced a further improvement in 1848 (68). He recommended interrupting the vertical repair with a quadrangular rather than a triangular flap. This modification offered obvious advantages, particularly in the case of bilateral clefts, for it made the repair easier and by exerting pressure on the premaxilla helped to correct its protrusion. Hagerdon operated two babies within a week of their birth and was the first surgeon to do a single-stage bilateral cleft lip repair. A century later, in 1949, Hagerdon's technique was modified by Arthur Baker Le Mesurier, after by C.W. Tennison in 1952 and finally from Peter Randall in 1959 (14).

Andrea Ranzi kept the faith that while a simple harelip could be corrected shortly after birth, operations on more complex deformities should be postponed for up to five years (172).

4.1.1.4 Cleft Lip and Palate in the Arts

Individuals born with cleft lip and/or palate are often stigmatized and face much psychosocial adversity. Representation of cleft has been made during ages in various art media including films, masks, advertisements and paintings.

Evidence of masks depicting cleft lips and other facial defects representing comedic characters in dances also have been found, such as Bondres Cungih, a ‘‘bucktoothed, hare-lipped crazy clown who will do anything to avoid working’’ (205).

Leonardo da Vinci (1452–1519) included in his sketches a realistic profile drawing presumably of a monk with features of a poorly surgically repaired bilateral cleft lip and palate. Albrecht Dürer’s (1471–1528) collection of profile drawings ‘‘Fifteen Constructed Heads’’ is another example of a poorly surgically repaired bilateral ceft lip and palate (169).

In the field of ceramics and pottery interesting is Tord Skoog’s discovery in 1969 of a Corinthian terra-cotta head (Archeological Museum, Corinth) dated back to the fourth century BC with labial and nasal anatomy characteristic of an unrepaired left cleft lip and palate. Indonesian Topeng dance uses clef mask drama to depict characters that may have been viewed as simple-minded unintelligent or comedic based solely on their facial characteristics (232).

Moreover, ceramical depictures of clefted people is found in the civilization of the Moche (100 to 700 AD) area of Trujillo, Peru. The major difference from the western point of view between the ceramic art produced during the Moche period and the later Korean, Indonesian and English works is the perceived acceptance of the cleft lip anomaly as a part of life and nature, rather than as punishment for sins or a source of social stigma (5).

4.1.2 Basic Information

4.1.2.1 Definition

Cleft lip and palate are birth defects that affect the upper lip and the roof of the mouth. A cleft is a gap in a body structure that results from incomplete closing of a specific structure during development. Some babies have only a cleft lip. However, many babies with cleft lip have a cleft palate as well (6).

- Cleft Lip is a congenital facial deformity of the lip, usually the upper lip, due to a mesodermal deficiency or to a failure of merging in one or more of the embryologic processes that form the lip. It is frequently associated with cleft tooth socket and cleft palate. Also called cheiloschisis, harelip (6).

- Cleft Palate is a congenital fissure in the roof of the mouth, resulting from incomplete fusion of the palate during embryonic development. It may involve only the uvula or extend through the entire palate. Also called palatoschisis (6).

4.1.2.2 Description

Cleft lip may be observed only as a small notching of the lip to a unilateral cleft lip revealing the unfused maxillary process with the intermaxillary segment of one side. Malformation of more severe consequences results in bilateral cleft lip where neither of the maxillary swellings has fused with the intermaxillary segment. Extremely severe cases of bilateral cleft lip display the philtrum and the entire undifferentiated intermaxillary segment, which would have developed into the primary palate.

Many cases of cleft lip present malformation of the primary palate and the anterior teeth. Rarely, the median nasal processes fail to fuse and proliferate, resulting in median cleft lip. Depending on the severity of the cleft lip and the structures associated with it, surgical repair is successful, although it may require several procedures.

Posterior (secondary) cleft palate results from failure of the lateral palatine processes to fuse in the midline with the intermaxillary segment, thereby permitting direct communication between the oral and nasal cavities. Unilateral cleft palate results when one palatal shelf does not fuse with the intermaxillary segment. When both shelves fail to fuse with each other and the median nasal septum, bilateral cleft palate results.

Anterior (primary) cleft palate is a consequence of fusion failure between the primary and secondary palatal processes. Clefts of both anterior and posterior palates result from failure of fusion between the primary palate, palatal shelves of the secondary palate, and the median nasal septum.

Varying degrees of clefting exist, the last described being most severe, and the least severe is observed simply as a bifid uvula. Factors producing cleft lip, with or without cleft palate, are distinctly different from factors producing cleft palate alone (75).

4.1.3 Incidence

Orofacial clefting including Cleft lip with or without palate is a major public health problem and the most common craniofacial anomaly affecting one in every 500–1000 births worldwide. Cleft lip only (CLO) and Cleft Lip and Palate (CLP) account for 65% of all head and neck anomalies (198). According to W.H.O every 600 newborn babies worldwide is born with a cleft lip and/or palate (220). In the United States, 20 infants are born with an orofacial cleft on an average day or aproximally 7500 every year.

Children who have an orofacial cleft require multidisciplinary treatment with several complicated surgical procedures. The estimated lifetime medical cost for each child with an orofacial cleft is $100.000 in the U.S. (34).

There are numerous epidemiological studies that describe the prevelance of these craniofacial anomalies (95, 179).

The nonsyndromic CLP varies from 70 to 80% of the total cleft population (185). The birth incidence varies geographically from 2.7:1000 in Native Americans to 0.79-3.74:1000 in Asian populations to 0.18-1.67:1000 in African populations, to 0.4:1000 in African Americans and finally, to 0.91-2.69:1000 in Caucasians. In a study conducted in Istanbul/Turkey the incidence of CLP was 1.51 per 1000 births (190). Finally in Greece the prevelance of CLP is 0.47/1000 and 0.34/1000 for CPO (149). Generally, the highest total incidence is among American Indians and Japanese, with the lowest total incidence among Africans (212). Left-sided clefts are more frequent among patients with Cleft lip only and Cleft lip and palate (74).

The geographical variation seems to be less important than the ethnic differences. CLO seems to be much less dependent on racial and ethnic differences than CLP. Moreover differences occured between the two sexes among the different racial and ethnical population (30, 142, 143, 144, 145, 212, 225, 226).

Table 1: Incidence of CPO-CLO-CLP according to gender and race

Characteristics	CPO	CLO	CLP
Race	—	—	—
Caucasians	0.87	0.38	0.75
Africans	0.46	0.26	0.42
Gender	—	—	—
Male	0.51	0.35	0.75
Female	0.59	0.32	0.50
Prevalance	0.6/1000	1/1000	1/1000

4.1.4 Etiology

In 2013 the aetiology of Orofacial Clefts is still uncertain and controversial. There is a general agreement that oro-craniofacial syndromes are a multifactorial phenomenon, a compilation between enviromental and genetic factors (141).

Cleft lip and palate is the result of disturbed fusion of the processes that form the face, caused by abnormal morphogenesis of the upper lip and primary palate either by misguided epithelial movement, or impromper epithelial-mesenchymal transformation (EMT), or disrupted apoptosis (86).

Cleft of the lip and/or palate occurs from a failure of fusion of the frontonasal prominence with the medial nasal process, or from the primary palate with the secondary palate or from the lateral palatine shelves with each other (148). Approximately 70% of all cases of CLP and 50% of cases of CPO are considered to be nonsyndromic (128).

The remaining cases are a compilation of a wide range of malformation syndromes, including over 500 Mendelian syndromes, as well as those arising secondary to chromosomal or teratogenic effects (196).

4.1.4.1 Genetic Factors

A variety of genes are involved in the development of lip and palate. These genes control some major signaling molecules (growth and transcription factors) that are responsible for formation of specific proteins which in turn control initiation, differentiation and morph-differentiation of the tissue of lip and palate. The studies in Clefts demonstrate that heritability for non syndromic is around 76% (98).

Monozygotic twins are ten-fold more likely to be concordant for a cleft compared to dizygotic twins (40% vs. 4.2%) indicating the underlying genetic base and finally clefting aggregates in families (61). The frequency of occurrence in a child with CLP if it has two parents with CLP is 15% and if it has only one parent with CLP the frequency decreases to 2%- 6% (38).

It has been estimated that between the third and the fourteenth gene any of these genes is involved and plays main aetologic factor in a single population. The total amount of genes involved in clefting may be bigger (193).

Among these genes and factors which are correlated with lip and palate are Transforming growth factor beta (TGFβ), Transforming growth factor alpha (TGFα), Msh homeobox (MASX1) and Paired box (Pax) genes (PAX2), Paired-like homeodomain transcription factor (pitx2), RARA, and finally p63 (193).

Morever, still there is 100% genetic linkange between these genes even though there is lack of investigations due to small numbers of families that are participating in the studies (104, 113, 144, 210).

4.14.2 Environmental Factors

Many environmental factors have been examined in epidemiologic studies as risk factors for oral clefts. The major of these factors are:

4.1.4.2.1 Maternal Smoking

Smoking causes specific mutation in TGFα, Poliovirus receptor-related 1 (herpes virus entry mediator C: nectin-1: CD111) known as (PVRL1) or Interferon regulatory factor 6 (IRF6) causing CLP (94).

Also tobacco smoking and consuming during the pregnancy period is related with various outcomes like: low birth weight, preterm weight (109).

4.1.4.2.2 Alcohol Consumption

It has been found that alcohol causes alteration of the MSX1 and Transforming growth factor beta number 3 genes (TGFβ3) which can lead to certain congenital malformations. These individuals show certain degree of clefting as well as other orofacial features including smooth philtrum, thin vermillion border of the lip and small palpebral fissures (141).

A well documented research demonstrated that alcohol use in pregnancy is more related to CLP than to overall malformations evolved from cranial neural crest cells (including malformations of ear, face, anterior neck, and upper heart) (218). Women who consume five or more alcoholic drinks per drinking occasion have an increased risk of having a child with orofacial clefts (182).

4.1.4.2.3 Nutritional Factors

Numerous nutrition factors are related with the CLP. Among them are Zinc, cholesterol, folic acid, folate, vitamin B12 and vitamin B6 (85, 144). Women consuming vitamins containing folic acid at the time of conception were demonstrated to have a lower risk of having children with OFC. It is well documentated that folic acid supplementation during the first 4 months of pregnancy provides significant protection against cardiovascular defects and neural tube defects

(34, 39, 221). Vitamins of B complex including folic acid supplementation during pregnancy proved effective in preventing cleft lip and palate in humans (194).

4.1.4.2.4 Medications

Steroid consumption during the first three months of pregnancy has been associated with clefts, increasing the risk 3-5 times more than normal (27, 28, 160).

Anticonvulsants are associated with a clearly increased risk of congenital defects (phenytoin/hydantoin, oxazolidinediones and valproic acid). All these three therapeutic classes are liable to produce CLP (40, 61, 187).

Retinoid Acid (RA) is mandatory for various biological processes and normal embryonic development but is teratogenic at high concentrations. In rodents, one of the major malformations induced by RA is CP**.** Isotretinoin induced facial malformations in humans, include underlying external ears, absent or imperforate auditory canals, deformed and small skull, cleft palate, depressed midface and anomalies of the brain, jaw and heart (43, 116, 146).

4.1.5 Embryological Development

Embryological development of face and lip is one of the most complicated but exciting events. The development of face and lip take place between 4th and 9th week of pregnacy. The period between fourth and eighth week is referred as the embryonic period. Cleft lip is a result of failure of fusion (at 4-6 weeks in utero) between the medial nasal, lateral nasal and maxillary swellings. Cleft palate is a result of failure of fusion (at 8 weeks in utero) of the lateral palatal swellings.

Nowadays, with the newest developments to the field of craniofacial biology numerous genes such us the growth factors TGFs, PDGFs, EGFs, BMPs, signaling molecules from WNT family, H and transcription factors MSX, DLX, LHX are shown to be involved in the development of craniofacial region (61). In order to understand the pathogenesis of orofacial clefting, it is useful to understand the normal embryological processes involved in the formation of the lip and palate.

a) Development of the Face

Face originates from five primordial structures: one single frontonasal prominence and paired maxillary and mandibular prominences. The face develops around the stomedeum (mouth) and is formed from the fusion of the five face primordia which develop during the fourth week and fuse during fifth and eighth week of development the time when each germ layer, ectoderm, mesoderm and endoderm, gives rise to a number of specific organs and tissues.

At the end of the fourth week, facial prominences consisting primarily of neural crest derived mesenchyme are formed from the first pharyngeal arch (148). During the fifth week, the nasal placodes invaginate to form nasal pits creating a ridge of mesenchymal tissue at it is periphery, which proliferates to form nasal prominences, the medial and lateral.

The former is on the inner edge and the latter is on the outer edge of the pits. The lateral rims of the nasal placodes become the lateral nasal swellings, which will become the alae (wings) of the nose.

The medial rims of the nasal placodes, known as the median nasal swellings, fuse together to form the intermaxillary segment, which will form the bulbus of the nose. Going on the process of growth anteriorly to this intermaxillary segment and inferiorly to the nose creates the inferior aspect of the nasal septum, columella of the nose, philtrum of the upper lip, labial tubercle, and primary palate (premaxilla). These events take place during the sixth and seventh week (100).

The anterior teeth and their supporting structures as well as the gingiva will also develop from the intermaxillary segment. Afterwards the intermaxillary segment comes across with the maxillary swellings that had moved anteriorly fusing with it to seal the nasolacrimal groove.

During this period, the mandibular processes have fused anteriorly, forming the mandible, thereby reducing the size of the primitive mouth. Meanwhile, mesoderm of the second arch has invaded the area, resulting the formation of the muscles of facial expression (75). (Figure 1)

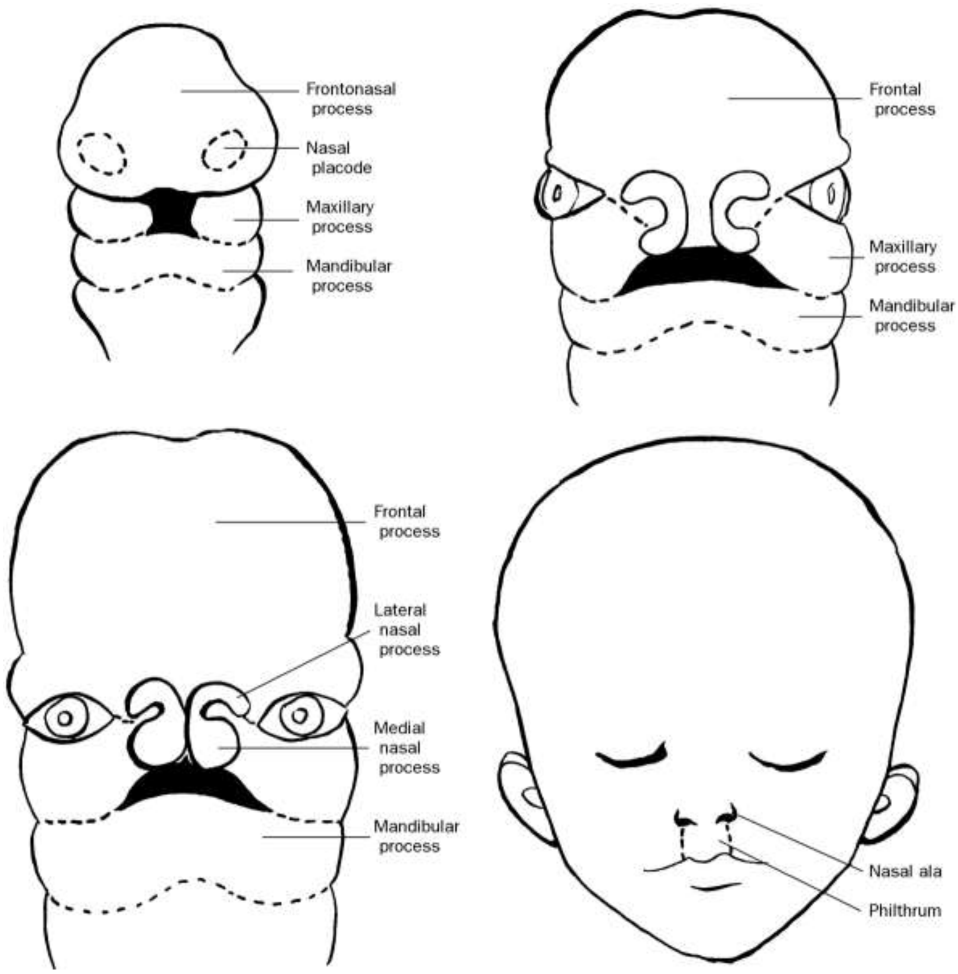


Figure 1 Development of the face (75)
http://www.med.umich.edu/lrc/coursepages/m1/embryology/embryo/images/development_of_face.gif(Accessed on: 1/6/2012)

b) Development of the Primary and Secondary Palates

Palate is formed from two primodia primary and secondary palate. During the sixth week of development primary palate takes shape from the deep part of the intermaxillary segment of the maxilla, which forms the premaxilla arising from the medial nasal process and extend to form the floor of the nasal cavity (137). The secondary palate is formed from the two maxillary swellings which is the primordium of the hard and soft palate that extend posteriorly from the incisive fossa (6). Each develops a shelflike structure that grows inferiorly to project obliquely on the side of the tongue into the sublingual sulcus. At the seventh week of development and as the tongue falls from nasal to oral cavity palatine shelves move to a horizontal position above the tongue and fuse together in the midline, forming the secondary palate (75). Fusion of the secondary palate with the primary palate separates the oronasal cavity into the nasal cavity and the oral cavity. Fusion is completed around the twelfth week. The hard palate forms when ossification occurs in the anterior two-thirds of the palate and the soft palate is formed from the remaining unossified area (Fig. 2).

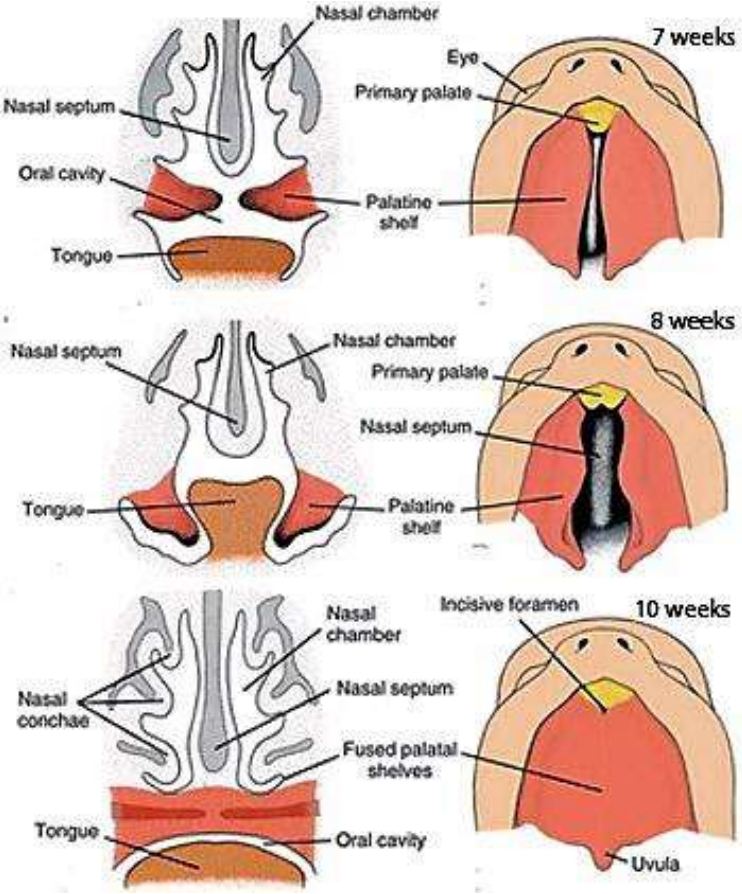


Fig. 2: Development of the Palate (137) http://www.duke.edu/web/anatomy/embryology/craniofacial/headEmbryoImage15.jpg(Accessed on: 1/6/2012)

4.1.6 Types of CLP

Although various types of cleft lip and palate are existing, three main categories can be distinguished: isolated cleft lip and/or alveolus (CL), isolated cleft palate (CP), and combined cleft lip, alveolus, and palate (CLP). The distribution between the clefts show that CLP is the largest group, followed by CP and CL, CLP is more frequent in males, but CP is twice as common in females (46, 47, 69). Any type can be subdivided to complete or incomplete (including Simonart's bands) and bilateral or unilateral. All types of clefts can be differentiated significally in size, development, shape and position. The sideness is distributed according to the ratio left:right:bilateral=6:3:1. (185).

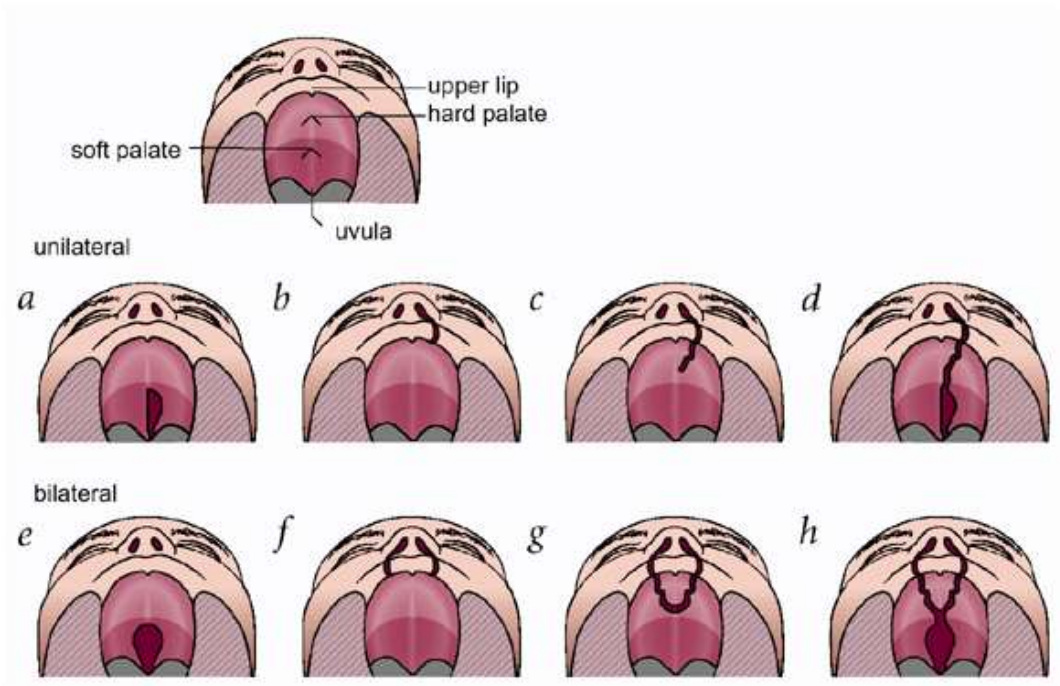
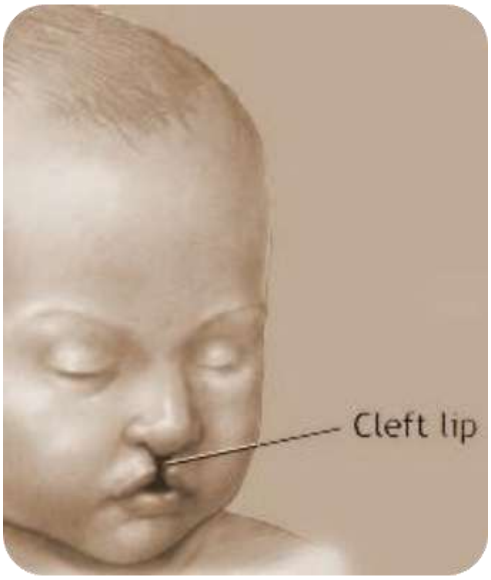


Fig. 3. Various types of orofacial clefting (185). Normal lip and palate in top panel. A,e : Unilateral and bilateral cleft of the soft palate only). B,f, Unilateral and bilateral cleft of the lip. C, g : Unilateral and bilateral CLP (involving the hard palate). D, h : Unilateral and bilateral complete CLP (involving hard and soft palate and uvula). Note that unilateral and bilateral CL/P can be easily differentiated (b, c, f, g), whereas this is not the case for unilateral or bilateral clefts of the soft palate http://www.nature.com/ng/journal/v32/n2/images/ng1002-219-F1.gif

(Accessed on 3/6/2012)



4.1.6.1 Median Cleft Lip

Median cleft lip or “Hare lip” (Fig. 4) is due to the incomplete merging of the two medial nasal prominences, therefore leading in most cases (with deep midline grooving of the nose) to various forms of bifid nose (59).

Fig. 4: Infant with median cleft lip (59). http://www.hsanctuary.com/Services/images/cleftliprepair_2.jpg, (Accessed on 3/6/2012)

4.1.6.2 Lower Lip Cleft

Lower Lip Cleft is an extremely rare craniofacial deformation and is due to the failure of fusion of mandibular processes during embryogenesis (138).

4.1.7 Classification

Cranio-facial malformations and between them, facial clefts, were first described by doctors, anatomists, genetists and dentist through the ages. The general rule was to nominate each malformation with its own name.

Classifications are very important tools to the hands of clinicians for precise and accuarate diagnosis and treatment plan. Moreover, they help to develop a common language of communication between physicians all over the world and from different diciplinies.

Several attempts to classify CLP had been carried out through the last decades, but only few have received widespread clinical acceptance.

The first classification of CLP was intoduced by Davis and Ritchie (46) back in 1922 and was quite simple. Davis and Ritchie classified the congenital clefts into three groups according to the position of the cleft in relation to the alveolar process.

Group I: Pre-alveolar clefts, unilateral, median, or bilateral.
Group II: Post-alveolar clefts involving the soft palate only, the soft and hard palates, or a submucous cleft.
Group III: Alveolar clefts, unilateral, bilateral, or median.

Their classification had many shortcomings such as, insufficient descriptions of cleft lip, cleft of the primary palate with intact secondary palate and presence or absence of alveolar involvement, and the incisive foramen. In 1931 Veau classified the degrees of deformity by a simple numerical scale (fig. 5).

Type-1: Cleft of the soft palate only.
Type-2: Cleft of the hard and soft palate extending no further than the incisive foramen, thus involving the secondary palate alone.
Type- 3: Complete unilateral cleft, extending from the uvula to the incisive foramen in the midline, then deviating to one side and usually extending through the alveolus at the position of the future lateral incisor tooth.
Type-4: Complete bilateral cleft, resembling type 3 with two clefts extending forward from the incisive foramen through the alveolus. When both clefts involve the alveolus, the small anterior element of the palate, commonly referred to as the premaxilla, remains suspended from the nasal septum.

Although he ignored clefts of lip and alveolous totally still his classification has a lot of followers even to our years (52, 213).

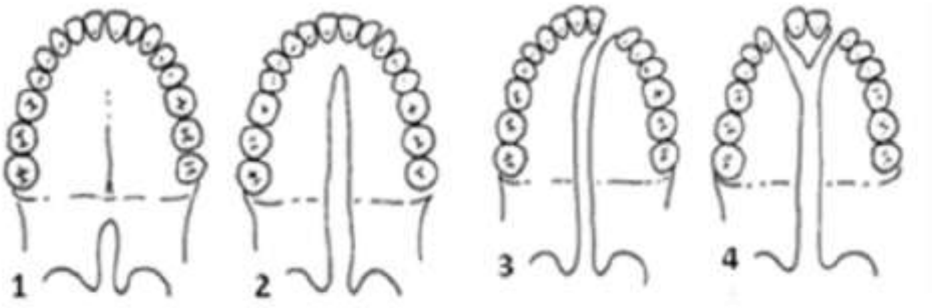


Fig. 5. Veau’s classification of cleft lip and palate (123)

The classifications that were intoduced by Davis and Ritchie and Veau were based clearly on anatomical findings. Recent data to the field of genetics as well as recent advances in understanding better the embryology of CLP lead scientists, organizations and foundations to more complicated and detailed classifications (105).

Kernahan and Stark in 1958 (92) revealed a new classification system using the incisive foramen as a boundary system. Kernahan and Stark recognized the need for a classification based on embryology rather than morphology. Primary palate comprised of premaxilla, anterior septum, and lip. The roof of the mouth - from the incisive foramen or its vestige, the incisive papilla, to the uvula - is termed the secondary palate. The incisive foramen is the dividing line between the primary and secondary palates.

- Clefts of primary palate: Unilateral, Bilateral and median.
- Clefts of Secondary palate: Unilateral, Bilateral and median.
- Clefts of primary and secondary palate: Unilateral, Bilateral and median.

To this classification must be added the cleft of the mesoderm of the palate, or submucous cleft, which may be camouflaged unless the uvula is cleft.

A classification system based on the resemblance of an intra-oral view of a cleft lip and palate to the letter 'Y', was proposed in 1971 by Kernahan (91). He has represented the most severe and extensive form of cleft lip with cleft palate deformity as a ‘Y’. The incisive foramen can be represented symbolically by a small circle with the dividing pointing between the primary and secondary palates. Each right and left limb is divided into three portions representing respectively the lip, alveolus and area between alveolus and incisive foramen.

The stem of the Y (Fig. 6) is similarly divided into three portions representing hard palate (7, 8) and soft palate (9). Each individual can be diagrammatically represented by stippling appropriate areas of clefting. In submucous cleft of palate the appropriate section is cross hatched, Simonart's band can be represented by cross hatching the anterior portion of the limb of the Y. By assigning numbers to the striped Y segments, classification and retrieval of information can be achieved with ease.

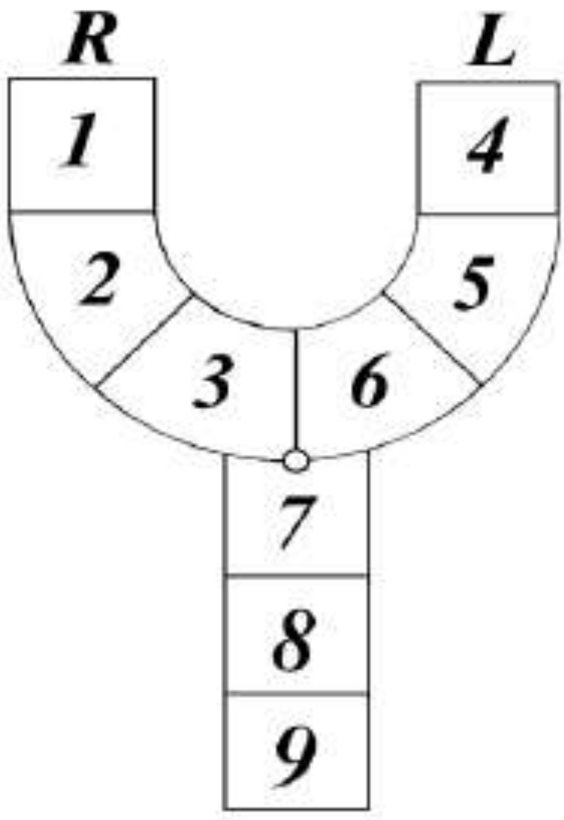


Figure 6 : Kernahan ‘’striped’’ Y classification The Kernahan striped Y classification of cleft lip and palate (91).

1 - Right lip, 2 - right alveolus, 3 - right premaxilla, 4- left lip,

5 -left alveolous, 6 left premaxilla, 7, 8, 9 –hard/soft palate

Elsahy (51) in 1973 modified Kernahan Striped Y classification in the following ways (Fig. 7).

1. New triangles 1 and 5 atop the arms of the Yrepresent the right and left nostrils.
2. Circle 13 between the arms of the Y represents the premaxila
3. Squares 2 and 6 represent the right and left aspects of the lip.
4. Squares 3 and 7 represent the right and left alveolous.
5. Squares 4 and 8 represent the prepalate on the right and left sides.
6. Squares 9 and 10 represent the hard palate proper with both right and left sides.
7. Square 11 represents the Velum, both right and left sides.
8. Circle 12 below the stem of the Y represents the posterior pharyngeal wall.

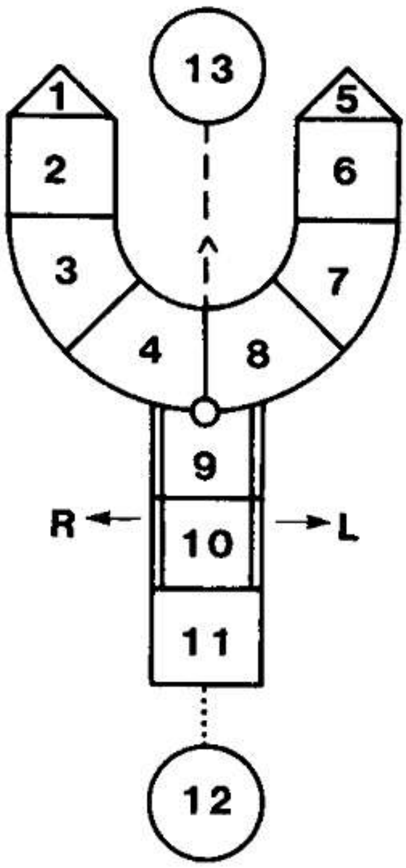


Figure 7: Symbolic representation of Elsahy Y modification (51)

Elsahy gave further instructions for elaboration of his modified striped Y as follows: Protrusion of maxilla can be shown by extending a line from circle 13, by which the length represents its degree. Notching of the vermillion border or alveolar ridge can be indicated by a narrow band of stippling in the lower portion of segments 2/6 or the upper portion of 3/7 respectively.

Maxillary segment collapse can be depicted by shading or stippling segments 3/4 or 7/8 for right and left sides respectively. Displacement of palatal segments in complete cleft palate can be shown either by drawing double vertical lines on the sides of segments 9 and 10 with right and left arrows to indicate the direction of deflection or by drawing an X over the appropriate right and /or left arrow on the diagram. Submucous clefting of the palate can be depicted by cross hatching. The competence of velopharyngeal closure can be denoted by drawing a line between square 11 and circle 12, the length of which represents closure adequacy from no line (no closure) to full length connection (complete closure).

Millard in 1977 firstly and in 1990 secondly, (130, 131) modified further Elsahy's point of view of Y classification by adding inverted triangles a the top of the upright triangular segments 1 and 5 to stand for the right and left aspects of the nasal arch (Fig.8).

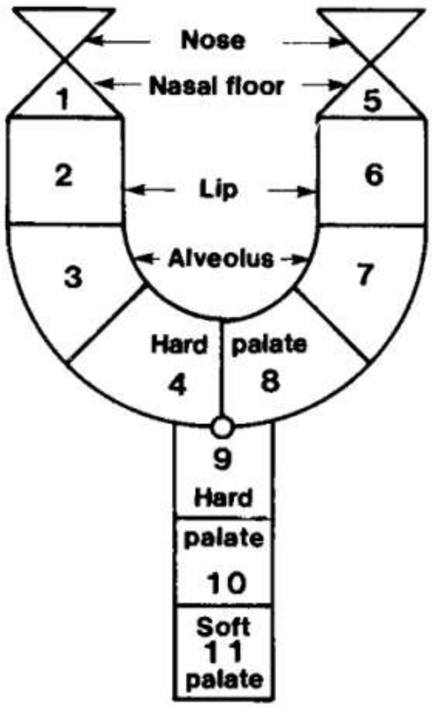


Fig. 8: .Symbolic representation of Millard classification (130, 131)

Friedman et al in 1991, (45, 57) proposed a combination of Elsahy's and Millard's that incorporates various cleft microforms and assigns severity scores to the anatomic and functional deformities. Instead of shading the blocks in the diagram to indicate the severity of the deformity a number is placed in each diagrammatic segment to represent.

One of the most widely spead classifications was developed in Bremen in 1985 by Otto Kreins (96). A completely new recording-system (Fig. 9) for the diagnosis and treatment planing of cleft lip and palate malformations is the LAHSHAL. It is based on the letters of the palindrome LAHSHAL, which represent the two sides of the lip (L), alveolus (A), hard palate (H) and the soft palate (S). It has been modified on the recommendation of the Royal College of Surgeons by omitting one H. It is compatible with ICD (International Classification of Diseases) and allows clefts to be coded for computer use, most importantly on the Craniofacial Anomalies Register. The main disadvantage of the LAHSHAL system is the inflexibility to describe a complex cleft malformation. So, it is not able to distinguish a submucous cleft from microforms of clefts (96).

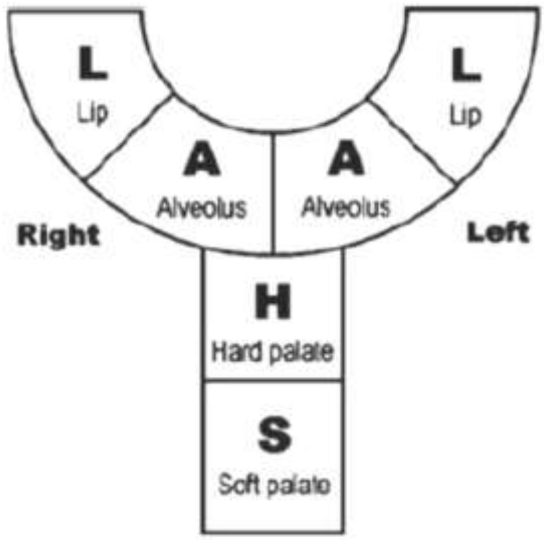


Figure 9: Lahshal system for classification of CLP (96)

Percy Rossell-Perry introduced the Clock diagram in 2009, which is the design of a new diagram for cleft lip and palate, based on the degree of severity of the four basic cleft components: nose, lip, primary palate, and secondary palate (162).

The Clock diagram (Fig.10) is a circle divided into four areas, one for each cleft component. Each area is subdivided into three segments, which represent the three degrees of severity-mild, moderate and severe. He assigns the clock numbers (1 to 12) to each degree of severity of the four components as follows:

a) Right superior quadrant (nasal deformity). Degrees: Mild (1), Moderate (2), Severe (3).
b) Right inferior quadrant (medial segment lip and prolabium deformity). Degrees: Mild (4), Moderate (5), Severe (6).
c) Left inferior quadrant (primary palate). Degrees: Mild (7), Moderate (8), Severe (9).
d) Left superior quadrant (secondary palate). Degrees: Mild (10), Moderate (11), Severe (12).

There are some major merits of this Clock Diagram method:

1. It characterizes the clefts according to their severity.

2. It is possible to incorporate elements that are not considered in other approaches and to describe all possible clefts.

3. Clock diagram describes unilateral and bilateral cleft lips and/or palates, by assessing the severity of each of the four cleft components.

4. This method provides a very valuable tool for the evaluation of progress in patient rehabilitation.

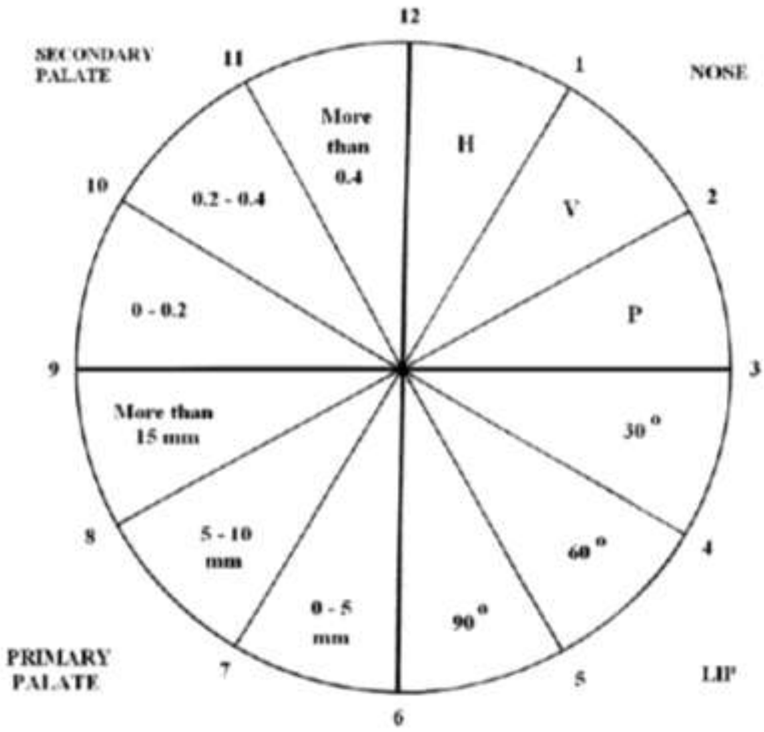


Fig 10. The Clock diagram of Percy Rossell-Perry (162)

Also recently, Marazita has reported (112) in a review article demonstrating evidence that subepithelial orbicularis oris muscle defects are part of an expanded phenotype for CL/P, revealing an increased number of subclinical orbicularis oris muscle defects among noncleft relatives of cleft subjects (10.3 percent) compared to controls (5.8 percent). Grooves in the philtrum as a sign of disruption of orbicularis oris muscle and lateral fistulas of the upper lip are considered as minimal involvements of CL (61).

In cleft subjects, agenesis of the lateral incisor on the noncleft side has been suggested to represent an incomplete form of bilateral clefts of the lip (103).

In 2012 in a thesis presented in Marmara University of Istanbul (62) titled ‘’Yeni Doğan Dudak-Damak Yarıklı Bebeklerde,Yarık Tipinin ve Şiddetinin, Sayısal Modeller Aracılığıyla Oluşturulan Yeni Bir Sınıflama Metodu ile Belirlenmesi’’ by Dr. Buket Coşkuner Gönül, a new classification system was proposed. The classification was made on the digital models according to the measurements of two examiners.

In this classification, the numbers between 1 and 5 are used to create 3 digit number. The hundreds digit represents the type of the cleft (Table 2), tens digit represents the width of the cleft (Table 3) and the single digit represents the amount of dislocation (Table 4).

Table 2: Types of cleft

1	**2**	**3**	**4**	**5**
Soft palate cleft	Hard palate cleft	Incomplete cleft (Bilateral & Unilateral)	Unilateral Complete cleft	Bilateral Complete cleft

Table 3: Width of cleft

1	**2**	**3**	**4**	**5**
1- ≤3mm	3- ≤ 5mm	5-≤7mm	7-≤10mm	>10mm

Table 4: Amount of dislocation (in clefts of soft-hard palate, length of the cleft)

1	2	3	4	5
1- ≤3mm	3- ≤ 5mm	5-≤7mm	7-≤10mm	>10mm

In unilateral clefts to the end of the code R (right) or L (left) letter will be added, that represents the localizaiton of cleft according to midline. Midline clefts were not included in this classification.

The types of clefts accompanied by several syndromes that are rarely seen were exlcuded. In the soft and hard palate clefts the alveolar process is not effected so the number in the single digit represents the length of the cleft.

4.1.8 Pre-natal Diagnosis

Prenatal diagnosis employs a variety of techniques to determine the health and condition of an unborn fetus. Without knowledge gained by prenatal diagnosis, there could be an untoward outcome for the fetus or the mother or both. High-resolution ultrasound is the only available technology allowing prenatal detection and evaluation of an orofacial cleft.

On the other hand it is not uncommon for a cleft lip to be first noted at delivery. Most palatal defects are discovered upon the first examination of the neonate (216).

From the early 1980s, ultrasound diagnosis of orofacial clefts has formed a routine part of the antenatal care process (87). Although the midline structures of the face are fused by 8 week's gestation, successful imaging of the fetal face is not reliably achieved with transabdominal ultrasound until gestational week 15 because of the position of the head and small size of the face relative to the transducer (33).

The fetal face should be examined in three planes, coronal, sagittal and transverse to ensure that maximum information is obtained. The lips are best imaged in the coronal plane, the fetal profile in the sagittal plane and the alveolar ridge in the transverse plane. Multiple views in each plane, rather than a single section, should be used to evaluate the relevant structures, the early diagnosis for orofacial clefts, it is very important for the clinicians to consider further actions such as fetal surgery or even termination of the pregnacy (16). Isolated CP is more complex to diagnose prenatally due to the acoustic shadow from the facial bones (87).

Recently the 3D ultrasonography has been introduced and is particularly useful for examination of the fetal face in which it consistently displays facial abnormalities with accuracy and clarity (129).

Both 2D and 3D images appear to illustrate clefts of the lips, alveolus and primary palate, but not of the secondary palate. The alveolus is clearly detectable on a 2D oblique face view and indeed 2D has the advantage that the size of the defect can be measured accurately (87, 129).

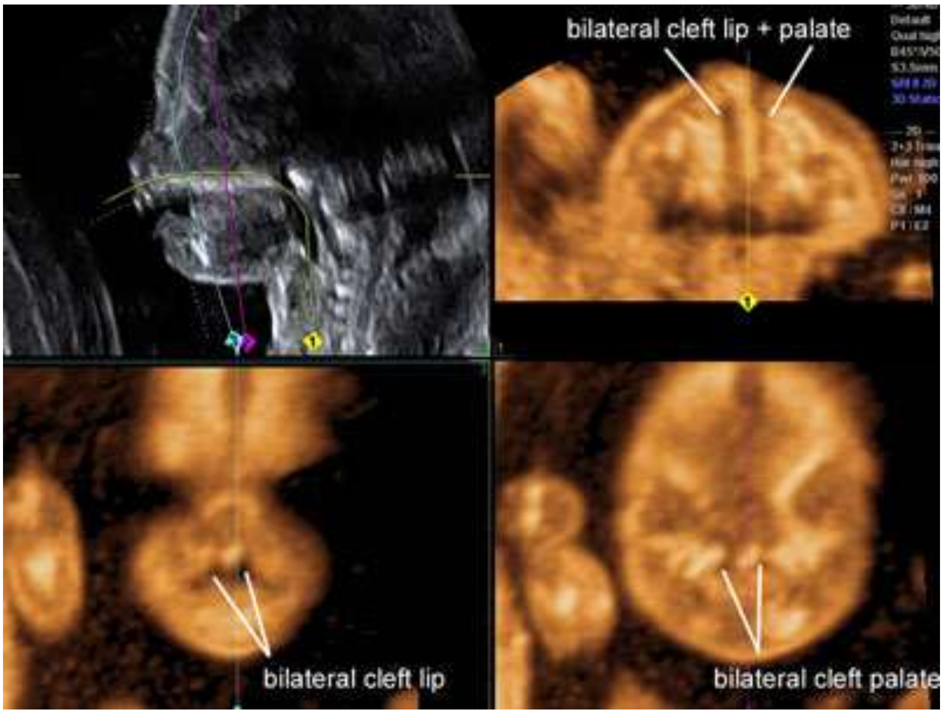


Fig. 11:
Bilateral cleft lip and palate with 3D RF (129)
http://www.glowm.com/resources/glowm/graphics/atlases/Atlas_of_ultrasound/thumbs/09_cleft-lip-and-palate-bilateral-copia.jpg (Accessed 5/6/2012)

Campbell et al (25) in 2003 proposed a new tecnique, the 3D 'reverse face' view. The 3D RF view can provide unique diagnostic information on the integrity of the secondary palate (Fig. 11).

The pre-natal diagnosis is a useful tool not only in the hand of the clinician but also in the hand of the parents of orofacial clefts. Parents who delayed obtaining information about clefting turn their attention to the internet sometimes dowloading or reading inaccurate and unauthorized data causing them more anxieties (88).

Parents occasionly when a child is born with any kind of craniofacial deformity feel guilty. Mothers especially may feel intense guilt as they feel their bodies are the custodians and nurturers of their unborn child (115).

Parents show many different emotional reactions, including shock, hurt, helplessness and disappointment, when they are confronted with the information of a cleft bearing child.

Stresses due to craniofacial deformity at the time of birth may be devastating, leading to parents carrying an impression with them for a long time after (116).

Prenatal diagnosis may allow for planned neonatal care and preparation for feeding immediately after birth. Disadvantages of a prenatal diagnosis of CL and/or P may consist of an extra parental anxiety following the diagnosis, the potential for false positive or negative results and an inability to predict the severity of the cleft (153).

4.1.9 Maxillofacial Characteristics of Unilateral Clefft Lip and Palate

The morphological characteristics of UCLP are affected by three major groups of factors. Firstly, are the congenital developmental deficiencies, secondly the functional deformities affecting the shape, the position and the growth of normal and abnormal parts. Most common growth functional factor comes mainly from the muscle activity before repair and causing facial assymetries to the UCLP patients. Finally, thirdly, iatrogenic factors presented during the treatment period (184).

4.1.9.1 Anatomy of UCLP

Several undoubtful maxillofacial characteristics are related to infants with UCLP. Of course it has to be mentioned that because of the abundant range of variation of types of clefts, the following description is going to be a general overall description of the craniofacial characteristics of UCLP.

Infants with UCLP display the integrated effects of a cleft inhabitance to lip, nose and alveolus (cleft can be located on the right or the left side) and the inhabitance of cleft into the palatal part of the maxilla separating the palatal bone at the level of the nasal septum.

The premaxilla in the non-cleft area has a frontal rotation and a lifted mandibular plane conducted with the cleft in palate where the mandible and maxilla are relatively retrusive. The alveolar arch and palate are divided into a large and a small segment. The smaller segment is usually located more posteriorly and the anterior part is slightly higher curved, compared to the larger segment (164).

The UCLP also is assosiated with deformities that take place in the nose region. Spina nasalis anterior and the cartilaginous nasal septum follow the larger palatal segment and often deviate to the noncleft side. On the contrary, bony nasal septum is recurrently circumlocated to the cleft side (214).

The columella is deflected and shortened and the alar cartilage on the cleft side is disloged from its normal position. The medial crus is lowered into the columella, separated from the opposite alar cartilage, and the lateral crus is flattened, spread and stretched across the cleft at an obtuse angle.

The alar base is rotated outwards in a flare and the alar rim often has a web, which further reduces the apparent length of the columella on the cleft side. The resulting nostril aperture on the cleft side is positioned along a horizontal axis rather than in a vertical direction as in the normal nostril aperture (132).

On the contrary a comprative study has demonstrated that lateral crus of the alar cartilage in the cleft side is neither smaller nor histologically different from the noncleft cartilage (161).

Bardach and Cutting (11) described, the nasal deformity in unilateral clefts to three major factors:

(1) imbalance of the facial musculature
(2) hypoplasia of the skeletal base
(3) asymmetry of the skeletal base

In the UCLP, the skin is both retrograded, and displaced secondary to the initial hypoplasia and a lack of normal muscular function (191). Medially the columellar skin slopes down into the cleft paralleling the dome deformity. The philtrum is shortened and its crest is abnormal.

Laterally the nasal floor and sill tissue are pulled downward into the upper portion of the lip. The lateral labial skin is also retracted causing vertical lip shortening.

Nasal skin is slightly differenciated from lip skin: it is thinner, hairless and finely grained. A typical cleft mucosa also replaces normal vermilion mucosa. It is more dry, lacking the glandular elements and is thus prone to scaling.

Thus, in the UCLP, nasal skin is found in the upper portion of the lip medially and laterally. Labial skin is retracted in the presence of muscle dysfunction. A modified white roll and philtral crest are present (191).

The anatomy of the lip and muscle of the UCLP infants has been also analyzed from numerous three-dimensional anatomical studies. One of these studies revealed that the philtral ridges are formed by thickened dermis and dural appendages (166).

The labial elevators are the most prominent muscles and insert into the dermis lateral to the ridges. A study using 3D reconstruction, showed that fetal unilateral cleft lip specimens exhibit a 3.5-week delay in overall muscle development, asymmetrical fiber distribution, and abnormal fiber insertions (136).

The attachment and orientation of the palatal muscle fibres in the soft palate are varied, and the muscles enter along the posterior edge of the hard palate rather than joining at the midline.

As a result, the muscle control of the Eustachian tube is lost, often leading to chronic otitis media and risk of permanent hearing loss (211).

Collagen tissue is also increased relative to the number of muscle fibers. Histochemical stains and histographic analysis revealed that the muscle fibers have a nonneurogenic atrophy or hypoplasia with fibers closest to the cleft the most atrophic and disorganized (192).

It is critical that the balance of facial growth through the reclamation of ideal muscular anatomy is achieved. Failure to do this procedure will lead to the typical secondary deformities (114).

A

B

C

Photo 1. Intraoral impression (A) intraoral view (B) extraoral view (C) of a left sided UCLP

4.1.9.2 Orthodontic Concerns of UCLP

It is crucial for the physicians that are involved in the multi-disciplinary approach of UCLP patients and specially the orthodontist to be aware of the anatomical characteristics of craniofacial region not only of the untreated but also of the treated patients.

The facial traits and the dental arch relationships of treated UCLP patients are well documentated and described. The upper facial height is smaller compared to a normal control group.The maxilla is short, and there is a greater height development in the lower face (41).

According to Nollet et al's study group of UCLP both the maxilla and the mandible showed a retrusive facial pattern. As a sum up from all the studies is that the face of a patient treated for a cleft differs in a specific way from individuals without clefts (151).

Functional problems are caused by impaired nasal breathing, deviating tongue position, and the cleft lip muscles and their insufficient functioning. Diah et al found that unoperated patients present tissue deficiency mostly in the anterior part but the sagital development values are close to the general population (48).

Numerous studies have revealed the dental arch relationships of treated and untreated UCLP patients. The treated UCLP pateints demonstrated retroclination of the incisors and more Class III relationships (135). The unoperated patients showed a median collapse of the smaller segment causing crossbite and a tendency of the non-cleft segment to rotate anteriorly (6). Even some studies are presenting retroclination of the upper incisors of the untreated UCLP to be due to the variety of different racial, social and enviromental backround of these patients. It is extremely difficult to do a well documented anatomical description of UCLP (201).

4.1.10 Implications of CLP

Children with orofacial clefts are believed to have distinctly elevated risk for a variety of adverse social-emotional outcomes including behavior problems, poor self-concept, and parent-child relationship difficulties.

Also numerous implications reported: ear infections, dental/orthodontic concerns, airway obstruction, and difficulty with speech-language development (19). There are two main categories of implications: child's emotional, enviromental and behavioral impact and somatic consequences.

4.1.10.1 Child's Emotional Enviromental and Behavioral Impact

The first outcome is coming from the point of view of the parents that they have to come to terms with the idea of the loss of the anticipated ‘’perfect’’ child according to their social standards (17).

Moreover, for parents, having a child with an orofacial cleft raises anxieties about the cause of the condition, concern about the reactions of peers and others to their child, and questions regarding the developmental implications of the disorder. On the other hand, parents of children with clefts may be more tolerant of misbehavior in their child and are more likely to spoil their child by being overprotective (50).

Many children with CLP present less attractive facial appearance or speech than their peers. A high incidence of teasing over facial appearance is reported among those with cleft lip and palate (82).

Also, children with clefts are more socially withdrawn and inhibited than controls, particularly in the classroom (175). The factors that straightly affect the psychological development of a child born with cleft lip and palate involve speech and language disorders, facial disfigurement, and hearing loss (176).

As far as the psychosocial problem, the majority of the studies on CLP patients did not detect any. Mostly behavioral attitudes have been reported that deal with apppearance, depression and finally anxiety (207).

4.1.10.2 Somatic Concequences

CLP is related with several anatomical defects and functional problems. The lip, nose and alveolus have a cleft at the left or right side. In wide clefts the tongue in rest is sometimes twisted into the nose. The origin, the attachment as well as the orientation of the muscle fibers are altered (164).

Depending on the position, the size and the shape of the cleft feeding and breast feeding can be a real challenge for parents. The main obstacle to feeding is the failure to generate sufficient negative intraoral pressure to produce suction during feeding. This reduction in suction affects the baby's ability to attach to the nipple or teat, affecting the extraction of the milk, as well as the organization, retention and swallowing of the bolus (42). Also, sequelae to oral nasal coupling are excessive air intake, nasal regurgitation, fatigue, choking and gagging on fluids, prolonged feeds and discomfort (173).

Children with a cleft lip generally do not experience significant difficulties feeding and even more so if the cleft is of the unilateral nature (139).

No single intervention can be prescribed with confidence to improve feeding outcomes for cleft infants however, parents together with the multidisciplinary cleft team, can employ various combinations of techniques to overcome feeding difficulties and optimise situations. The feeding bottle that is used in the most CLP clinics is ''The Special Needs'' feeder.

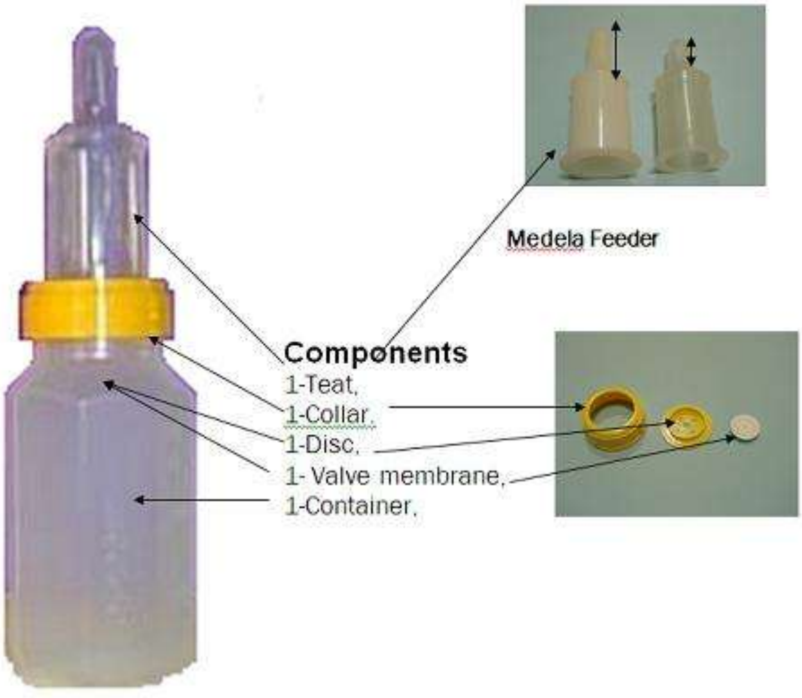


Figure 12: The Special Needs' feeder and its components (77)
http://t1.gstatic.com/images?q=tbn:ANd9GcRzlDzWKUHEdKyPAM5dJ5DhW0FYJDDKS3fv6mb-Za6DwWou-_FR (Accessed on 10/6/2012)

Numerous functional problems are present in orofacial clefts. Main functional implications are the swallowing of the air and aspiration of milk. Another one is that affected children often have a reduced middle ear function and a depression of hearing, which persists even after surgical reconstruction of the palate (77).

There are many dental issues associated with CLP including problems involving hypodontia, hyperdontia, misshapened teeth particularly in the area of the cleft and further orthodontic and occlusal problems such us malformation, ectopic and delayed eruption of teeth that require multidisciplinary approach (24).

Babies with CLP are often reported to have higher caries activity and higher levels of streptococci mutans and lactobacillus species which are associated with a high caries index (224).

Finally, children with CLP are at a higher risk of developing speech difficulties due to the structural issues of velopharyngeal function, fluctuating middle ear disease, hearing loss and the use of dental or occlusal interventions (97).

4.1.11 Feeding Devices

Feeding devices are mostly passive acrylic plates which are placed in the infant's oral cavity to act as an artificial palate to aid in the infant's suckling and swallowing. It has a great effect on the physical as well as the psychological growth of the infant and also helps in achieving the mother-child bond, which is very important to establish a sense of security and to enhance the mental abilities of the child (178).

4.1.12 Presurgical Orthopedics in CLP treatment

The orthodontic treatment of patients with cleft lip and/or palate aims at creating an aesthetically pleasant occlusion with an acceptable function. To achieve these goals cooperation between specialists in different sections of medicine and dentistry such as pediatric dentists, orthodontists and maxillofacial surgeons is necessary (22, 209).

The effect of infant orthopedics (IO) on maxillary arch dimensions in UCLP has been studied for decades. IO aims to facilitate feeding, reduce the cleft width and to normalize and maintain the shape of the upper dental arch, pre and post surgery. Opponents of this therapy claim that lip surgery alone has the same exact effect and that the presurgical orthopedic plate is only an expensive appliance used to comfort the parents by starting treatment at the earliest moment possible (29).

It is the aim of IO to mold the alveolar segments either passively or actively, as well as to facilitate feeding. The first appliances were semi-active or active plates. Semi-active plates were constructed on plaster models after alignment of the alveolar segments by sectioning the plaster models. Active plates were constructed with palatal screws or springs and sometimes pinned to the underlying bone. Both types of IO were often used in combination with extra-oral strapping in order to push and rotate the alveolar segments together.

In 1956 Mc Neil, a pediatric dentist, revealed a new treatment modality for reducing the cleft in UCLP infants in order to speed up the surgery. This technique involved stimulation of bone growth using gentle pressure over a large area of the hard palate.

McNeil's appliance was constructed by sectioning and reorienting the maxillary segments on the dental cast. A plate was then made on the reconstructed cast, which forced the palatal segments in the preferred position. He believed that by this way he could prevent undesirable effects of lip closure on the dentition and the subsequent development of cross bites, and favor speech development (124, 125).

Robertson (180) in 1971 found signifficant variation in the changes produced by presurgical orthopedics as part of the growth. Also he found that there was the possibility of reduction of the palatal width of the cleft without collapsing or reducing the arch width.

Hotz et al (79, 80) advocated use of these tecniques to create and maintain good initial palatal width and occlusion. Hotz concluded that combination of orthopaedic guidance together with suitably timed primary surgery has a beneficial effect on maxillary development and therefore, facial contour.

Hellquist (73) in 1971 advocated presurgical orthopedics combined with a periosteoplasty to accomplish expansion of the markedly collapsed maxillary segments.

Georgiade and Latham (60) in 1975 described an arch aligment appliance for bilateral cases being able to expand the palate and retract the prepalate using a pinned screw system. Rosenstein also in 1975 (183) reported stabilization of segments by means of an autogenus bone graft in addition to IO. The limitation to this research was the insufficient justisfaction for using these procedures.

In 1980 Latham (101) presented a screw assisted intraoral device used during the preoperative period. This intra-oral appliance appeared to exploit the anteroposterior adjustment potential of the maxillary sutures in the unilateral cleft lip and palate infant.

The orthopedic molding appliances were used from shortly after birth through 18 months of age. Such a long term of use resulted in general hygiene problems. It has been show that lactobacilli and Streptococcus mutans required nonshedding surfaces (teeth or acrylic molding plate) to build up recordable levels (65).

4.1.13 Nasoalveolar Molding (NAM) in CLP Treatment

In 1993 Grayson and Cutting (66) introduced Nasoalveolar Molding (NAM). In the first months of birth, the plasticity of cartilage and mouldabilty of the alveolar bone segments are high due to the high levels of hyaluronic acid and maternal oestrogen circulating in the neonate (65). With this technique, the pre-maxillary retraction, derotation and approximization of alveolar segments can be achieved prior to surgery (84).

NAM devices typically consist of intraoral palatal plates which obturate the oronasal defect and extra-oral attachments which mainly consist of combinations of, tapes and a nasal stent.

The aims of NAM devices are to ”mold’’ the alveolus, in other words, to achieve alignment of the pre-maxillary segment, to correct the alveolar ridges and the lip segments and to elongate the columella optimizing conditions for cheiloplasty and nasoplasty (188).

NAM technique involves a molding plate made of acrylic resin secured by adhesive tapes applied from the cheeks. The molding plates are fabricated of clear acrylic resin.

Modifications take place every week. These adjustments are made by selectively removing the hard acrylic and adding the soft denture liner to the molding plate. No more than 1 mm of modification of the molding plate should be made at one visit. The alveolar segments should be directed to its final and optimal position. Care must be taken to prevent the soft denture liner from building up on the height of the alveolar crest as this will prevent complete seating of the molding plate. The absolute goal is to align the alveolar segments and achieve reduction of the alveolar cleft gap (65).

When the alveolar cleft width has been reduced to less than 6mm, the nasal stent may be added to the molding plate so that nasal cartilage molding may begin. Nasal stents are constructed using 0,036 inch round stainless steel wire and taken the shape of a ‘‘Swan Neck’’. They are covered at the ends by resin bulbs which are inserted into the nostrils (photo 2B).

It is a projection of acrylic that is fabricated on the labial flange of the oral molding plate and through gradual additions of small amounts of acrylic resin, the stent is positioned inside the nose and underneath the apex of the nasal cartilage on the cleft side. In bilateral cases, there is a need for two retention arms as well as two nasal stents which are similar in shape to the unilateral stent (64).

The effectiveness of molding therapy is enhanced by adequatly supporting the appliance against the palatal tissues and by taping the lip segments together across the cleft. Moreover, in bilateral CLP patients the premaxilla is retracted simultaneously with the lengthening of the columella and the stretching of the nasal lining, using a tape attached to the prolabium (photo 2A). The plate is held to the palate with soft denture liner (65).

The molding plate is checked for overextension especially in the area of the vestibular folds as well as along the posterior border to check for any sharp edges or rough surfaces that may irritate the soft tissue. The appliance is then secured bilaterally extraorally to the cheeks by surgical tapes that have orthodontic elastic bands at one end.

The surgical tapes are a quarter inch in width and about 3–4 inches in length. The elastic on the surgical tape is looped on the retention arm of the moulding plate and the tape is secured to the cheeks.

The elastics (inner diameter 0.25 inch, wall thickness heavy) should be stretched approximately two times their resting diameter for proper activation force of about 100 grams. The amount of force could vary depending on clinical objective and the mucosal tolerance to ulceration.

Additional tapes may be necessary to secure the horizontal tape to the cheeks. Parents are instructed to keep the plate in the mouth full time and to remove it for daily cleaning. The infant may require time to adjust to feeding with the NAM appliance even from the first day (64).

A

B

Photo 2: Bilateral NAM to an infant: **(A)** Extraoral view **(B)** Intraoral bilateral molding plate appliance with the nasal stent

In contrast to earlier forms of infant orthopedics, unilateral nasoalveolar molding is concluded by 3 to 4 months of age, and bilateral nasoalveolar molding is usually completed by 5 months. In both unilateral and bilateral treatment, the molding plate is not used after surgery.

Therefore, there is a period in which the mouth is free of all nonshedding surfaces after completion of orthopedic treatment and before eruption of the deciduous dentition at 6 months of age (65).

4.1.14 Complications of Presurgical NAM

Irritation to the oral mucosa, gingival tissue or nasal mucosa is the most usual problem during the NAM procedure. Intraoral tissues may ulcerate from excessive pressure applied by the appliance. The oral and the nasal cavities of the infant should be carefully examined on each visit for ulcerations and appropriate adjustments should be made to the molding plate to relieve sore spots.

The intranasal lining of the nasal tip can become inflamed if too much force is applied by the upper lobe of the nasal stent. The area under the prolabium can become ulcerated if the tape is too tight.

Another area of tissue irritation are the cheeks. Extreme care should be taken while removing the cheek tape to avoid any irritation to the skin. Skin barrier tapes like Tegaderm™ (3M, Meriden, USA) underneath the usual tapes are recommended. Slight relocation of the position of the tape during treatment is also recommended to provide rest to the tissues in case they become irritated. It is also recommended that an aloe vera gel or baby oil be applied to the cheeks when changing tapes (65).

Another potential problem of NAM if applied incorrectly is nostril overexpansion, so-called mega nostril, that occurs when the alar rim in the unilateral deformity becomes too large in comparison to the unaffected side (83).

Complications can also take place during impression-taking process. Normally, these complications arise primarily due to the fact that infants are obligatory nasal breathers (170). According to Chate, difficulty in removal of the impression due to the engagement of the undercuts, the fragmentation of the impression during its withdrawal from the mouth, with subsequent respiratory obstruction due to its lodgment in the respiratory passage and cyanotic episodes due to asphyxiation are the common hazards which have been encountered by the dentists who are involved in the care of CLP patients (31).

The construction of an acrylic plate is the basic tool for the clinician to facilitate presurgical IO and for the parents to feed the baby. For the preparation of the acrylic plate for CLP patients, plaster models need to be prepared. The most important part of acrylic plate preparation is the impression.

Taking impression of an infant with a cleft palate is a critical procedure. The impression tray should be wide enough to include the lateral maxillary segments, to posteriorly cover up to the maxillary tuberosities and to provide a good reproduction of the mucobuccal folds.

Heavy body silicone impression material, polyvinyl siloxane impression material, low fusing impression compound and alginate have been employed for making impressions of neonates with orofacial clefts (64). Nowadays alginate impression technique is rarely being used, because, once set, alginate becomes very fragile. Alginate pieces that break off and get entrapped within the cleft undercuts may obstruct the airway.

4.1.15 General Aspects of IO

In the past, orthodontic treatment for CLP was applied at the time of canine eruption, usually by the age of nine to eleven years sometimes even later. Nowadays, many authors propose orthopedic-orthodontic treatment to be initiated earlier in life.

NAM is the most recently introduced technique among many presurgical orthopedic techniques available.

However its effectiveness is still not well documented and is a controversial subject between proponents and opponents (29, 161).

The proponents of IO claim that IO with any kind of appliance (active, semi-active, passive) results in elimination of feeding problems, less danger of aspiration, keeping the tongue out of the cleft, a more normalized tongue tip function, normal restoration of the symmetry of the maxilla, facilitation of lip surgery due to the narrowed cleft, minimization of the severity of skeletal and dental deformities, thus less orthodontics and surgery later on, better speech development, psychological support for parents and for the child due to better child-parent interaction (55, 63, 81, 154).

The proponents of NAM also claim a better and more predictable surgical outcome, less scar tissue formation, stable nasal change, better lip and nasal form, thus less surgical revisions, reduced need for alveolar bone grafting in addition to the benefits of any IO technique, and the treatment enables parents to actively participate in the habilitation of their child (1, 102).

Singh et al measured the three-dimensional (3D) nasal changes following NAM in UCLP patients revealed that bilateral nasal symmetry in patients with unilateral cleft lip and palate was improved before surgical repair. Furthermore, slight overcorrection of the alar dome on the cleft side using pressure exerted by the nasal stent is indicated to maintain the NAM result (202).

Santiago et al compared a group who underwent presurgical infant alveolar molding with another group that did not. Sixty percent of alveolar cleft sites treated with presurgical orthopedics, did not need a secondary alveolar bone graft in the mixed dentition (188).

Maull et al (120) and Grayson et al (66) studied the long-term effects of NAM on 3D nasal shape in unilateral clefts by using nasal cast of the subjects. They scanned these casts in three dimensions and a numerical asymmetry score was determined. The mean asymmetry index for the NAM group was 0.74, and for the control group it was 1.21. This difference was statistically significant ($P < .05$). They concluded that presurgical NAM significantly increases the symmetry of the nose.

Shetty et al (200) compared three study groups: group I (n = 15) was treated with NAM within 1 month of age, group II (n = 15) treated with NAM between 1 and 5 months of age and the control group III (n = 15) comprised non-cleft 18-month old children. Seven linear anthropometric measurements were compared using dento-facial models. Statistical analysis before and after NAM revealed that group I patients demonstrated 81%, 198%, 69% and 145% improvement in intersegment distance, nasal height, nasal dome height and columella height respectively, whilst group II patients demonstrated 51%, 33%, 21% and 38% improvement.

Deng et al (47) observed clinical effects of presurgical NAM in infants with complete cleft lip and palate. After 108 to 152 days of therapy, the average width of alveolar cleft decreased by 5.3 mm in 26 patients with unilateral cleft lip and palate. Nasal profile was improved in 76% of cases.

Liou et al (106) assessed 25 infants for the progressive changes of nasal symmetry, growth, and relapse by direct linear measurements on photographs and concluded that the nasal asymmetry was significantly improved after NAM and was further corrected after primary cheiloplasty. The nasal asymmetry significantly relapsed in the first year postoperatively and then remained stable and well afterwards. The relapse was the result of a significant differential growth between the cleft and noncleft sides in the first year postoperatively.

Brijesh Mishra et al (20) studied patients of cleft lip and palate who received NAM at an early age. Lip repair was done after at least two months of molding. These patients along with the control group (without NAM) were followed up for one year. The results demonstrated that nostril height was larger in patients in the experimental group (P = .18), while nostril width and alar perimeter were not changed significantly. Children with NAM showed significant lengthening of the columella (P = .02).

Pai et al (157) in their study concluded that molding improved symmetry of the nose in width, height, and columella angle, as compared with their presurgical status. There was some relapse of the nostril shape in width (10%), height (20%), and the angle of columella (4.7%) at 1 year of age.

Matsuo and Hirose, studied the role of preoperative molding in changing the cartilage memory of the deformed nasal cartilage, which happens because these cartilages have a higher amount of hyaluronic acid, which gradually diminishes after a few months of birth (118, 119).

Recent evidence suggests that IO devices either active or passive offer no benefit in terms of feeding. Prahl et al in 2005 compared one group that wore passive maxillary plates during the first year of life, with an other group that did not, found no significant difference on feeding or consequent nutritional status (165).

The same research team in 2003 (166) studied the effect of IO on the maxillary arch in patients that have attended to the cleft palate centers of Amsterdam, Nijmegen and Rotterdam in the Netherlands. They found that comparable arch forms with no contact or overlap of the maxillary segments were seen at birth in both groups (one group wore passive maxillary plates during the first year of life the other group did not). All other interventions were the same. With time the frequency of collapse increased, with no significant differences between groups. No significant group differences were found with respect to the survival experience of contact and collapse or for the severity of collapse at the end of the observational period (166).

Bongaarts et al found that IO (half of the patients were treated with IO by means of passive plates until surgical soft palate closure, and half did not get a plate) has no effect on maxillary arch dimensions in the deciduous dentition of children with complete unilateral cleft lip and palate (29).

Adali et al in a study that had as an objective to evaluatemthe effects of IO used active plates in all 14 cases until the time of palate repair at 6 months of age. These consisted of two overlapping acrylic components controlled by a U-shaped spring. The plates were activated using the spring and were worn full time. They were left out 1 week prior to lip repair/vomer flap at 3 month of age to allow mucosal recovery. At the time of lip repair/vomer flap, the plate was then made passive by blocking out the moveable components with acrylic. As a conclusion they found that there was no evidence that IO produced any significant effect on archform, raising questions for its continued use in this context. Lip repair had a greater impact on arch dimensions than did IO (2). However, IO has an impact on lip repair.

4.2 Records of I.O Treatment

Records have always been very important in orthodontics because they are objective diagnostic tools used for holistic treatment planning. Orthodontic records can be divided into three main groups: radiographs, photographs and dental study casts. Records must be taken before, sometimes during and after every orthodontic treatment.

The use of dental study models is an integral part of both dental practice and dental research. Models provide a useful tool for teaching purposes and are essential for orthodontics, orthognathic surgery, extensive restorative work and finally for prosthodontics. The plaster models are routinely taken before and after orthodontic treatment (13).

Study models are a reliable and popular form of diagnostic record also to the field of clefts. Since they are a dimensionally accurate representation of the intraoral situation, a number of measurements and analyses such as cleft width can be obtained from plaster study models. Models can be mounted on articulators to visualize centric relation and centric occlusion as well as tooth size-arch length discrepancies (163). The low cost of the plaster models and their ability to be dublicated are major advantages to their diagnostical value (179).

On the other hand, although traditional plaster study models have been used for many years, they have many limitations. Continued use for measurements and display can wear away plaster, decreasing accuracy and increasing the likelihood of fracture due to brittle nature of dental casts. Storage is another concept presenting both space and time problems. Another problem is the portability. Communication is difficult when only one set of models exist. Duplication is both costly and time consuming. Finally, significant errors can occur through the different ways of measurement and analysis. Dividers, calipers, and Boley gauges have provided the standard of measurement against which newer methods have been evaluated. These problems highlight the need for an alternative method for storing study models (122, 163, 171).

The need for interdisciplinary communication and treatment planning is essential and should be immediate. Several techniques, other than direct clinical measurement, have been used to quantify facial and intraoral proportions.

Digital photography and digital radiography are replacing analogue systems and are providing diagnostic quality images at a reasonable cost. Computer based charts and patient management systems constitute a digital patient record. These computer-based records eliminate the need for physical record room or chart storage facilities. However, the accuracy, reliability, efficacy and effectiveness of the computer-based models have not been systematically evaluated.

Holographic and stereophotogrammetric images, computed tomography scans, have also been investigated however, most early technologies required complex capture equipment and proved costly. Laser technology is also limited in capturing areas between adjacent teeth, which are overlapping. None of these methods has been used routinely for quantification because these either require time and money wasting, sedation or general anesthesia or expose to radiation and necessitate precise positioning. Moreover, image resolution is poor, especially for dental morphology because of the difficulty of obtaining the fine pitch of contour lines (8, 23, 107, 147, 163, 171).

It appears that these techniques cannot replace the use of the original methods. Also, there is still a need for a method to record the study models in digital format, which can be stored on a personal computer. These are the reasons why 3D representation of the plaster models are being investigated.

In 1989, 3D models were created from plaster models for the first time. The surface was scanned and converted into an optical three dimensional model. The major benefit from this evolution is that the generated 3D models can be easily stored and transferred into the virtual environment (99).

Nowadays, the use of digital models become widespread and scanning techniques have been improved. Computer-based record is a keeping routine in many orthodontic clinics worldwide. Since CLP cases require a multidisciplinary approach, digital models can be preferred for being easily accessable through internet to all team members during treatment.

More specificly, these virtual casts can be kept in digital format, eliminating the storage problem with study models in our offices. The digital images can be enlarged for easier localization of anatomic points. Also digital photos are suited for immediate data transmission for instance to a colleague via internet for an orthodontic diagnosis.

Moreover, digital study casts can be demonstrated to patients in order to motivate them in their treatments and the measurements can be made on digital casts in an easy, accurate and automatic way. Finally, the digital casts and their measurements can be accessed at any time and at any distance for diagnostic and clinical and information purposes (159).

4.2.1 Digital Measurements on Plaster Models

There are several methods to measure plaster models in the digital environment. These methods are a) photocopying, b) holography, c) Moire Topography, d) Fotostereometry.

Plaster models need to be digitized and then measurements are performed using non-specific 3D software available on the market (71, 140).

Photocopying method is intended to record the occlusal appearance of a plaster model placed on a scanner. The obtained images are transferred to the computer and used for measurements (228).

Holography, uses 3D modeling technique for replication of the plaster models (71).The obtained 3D image is called Hologram.

There is a specially designed camera that records the occlusal, frontal, right buccal and left buccal image of the plaster model. Holography allows direct measurement of 3D displacements of a few micrometres (13).

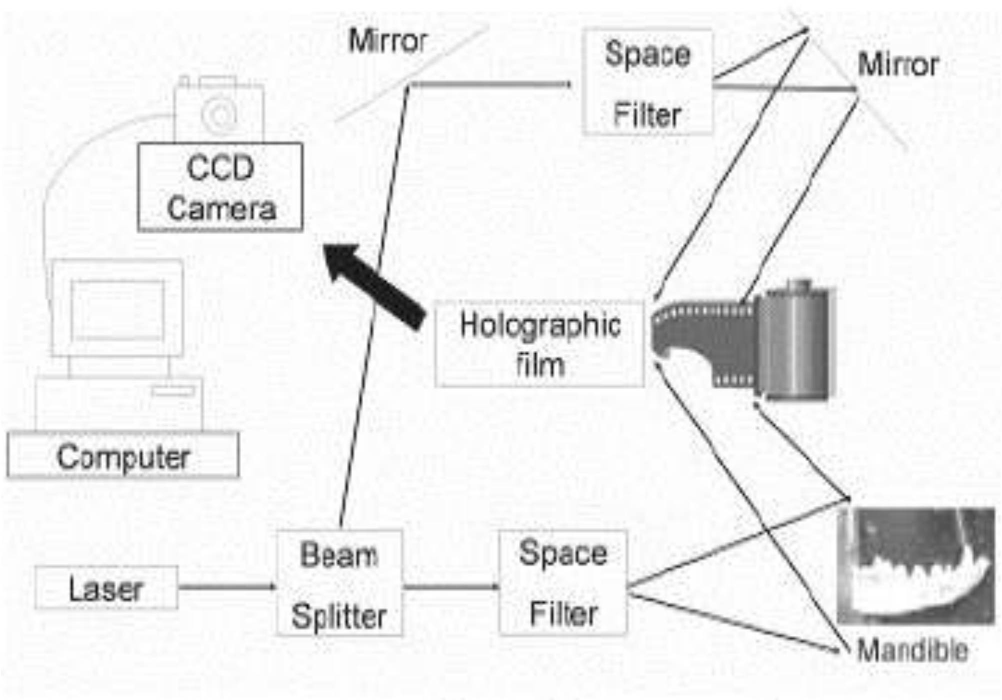


Fig. 13: Schematic represantation of a holografic set up (71)
http://www.scielo.br/img/revistas/bdj/v17n4/v17a03f02.jpg (Accessed on 11/6/2012}

Moire Topography has also been employed by dental researchers to store study models. According to Bell et al (13) with this technique, the outcome is a poor quality with low-resolution image and is not used very often today, because of the failure to store the digital formats and also because of the difficulty of obtaining the fine pitch of contour lines.

Ayoub et al back in 1997 (9) presented the computerized digitizing method named photostereometry competing with the surface screening. Plaster models recording in the digital environment was perfomed by using a pair of stereo video camera connected to the computer using special colored lighting.

This method also can obtain the image of the face. On the other hand during the scanning of the face and the eyes, a permanent damage may happen so it is not recomended for facial 3D representation (10).

4.2.2 3D Surface Imaging

After data acquisition, several steps are needed to be conducted to create 3D surface images. From the large number of methods for acquiring 3D shapes from images, 4 were selected and are described below: a) Stereo Analysis b) Shape from shading c) Photometric Stereo d) Structured lighting (71).

Improvement of computer-vision tools makes it possible to conduct all measurements on 3D and subsequently statistical shape analysis can be applied (140). The introduction of sophisticated three-dimensional devices means that the soft tissues of the face and the intraoral models can be evaluated in a quicker, non-invasive manner to conventional anthropometric techniques.

4.2.2.1 Stereo Analysis

The easiest way to understand Stereo analysis, is the similarity to human vision. The first step (stereo analysis) includes the production of geometric mode of visualization or wireframe which is made up of a series of x, y and z landmarks coordinates. Mathematical algorithms are used to connect the points with each other and express 3D model in triangles or polygons.

Two cameras are used to capture the image of the object. The cameras are placed distant so the picture that they take are slightly different because of the parallax. Two images of the scene will be created,one from each camera.

Any point in the scene is projected onto two corresponding points in the two images. To be able to find the distance of a point in the scene from the cameras, the disparity between the corresponding image points is measured. Knowledge of the distance between the cameras and their focal length, allows to calculate the distance from the cameras to the objects. Depth resolution is also better for objects close to the cameras (71, 140).

4.2.2.2 Shape from Shading (SFS)

Another method the human brain uses to infer 3-D form is shape from shading. In this second step, colour information is added to the wireframe, which consists of a layer of pixels called texture mapping. This depends on three main factors: global illumination, or the intensity of the light source, the reflecting properties of the object and the steepness of the surface of the object in relation to the eye and to the light source (71, 140).

4.2.2.3 Photometric Stereo

Photometric stereo is an extension of SFS methods and seems almost the reverse of stereo analysis. There are two light sources and one camera included. Two images of the object are taken, one image with one light source and the other image with the other light source. The camera is not moved, so there is no correspondence problem, as in stereo analysis. Because the light sources are a distance apart, each surface patch of the object receives light from a different direction for each of the two images. The brightness in each image and the differences in brightness between the images provide much more information than in simple SFS methods. This allows the solution of the problem with less constraints and assumptions. Using three light sources instead of two can eliminate most assumptions about the scene.

4.2.2.4 Structured Lighting

Structured lighting methods project known patterns of light on an object to infer its shape. The simplest method is the projection of a bright spot of light, typically produced by a laser.

This final step is called rendering, in which the computer converts the anatomical data into a life-like 3D object viewed on the computer screen (71, 140, 217).

4.2.3 Laser Scanning Method

Laser scanning is another way to picture 3D objects. This technology depends on projecting a known pattern of laser light onto the object of interest which is based on geometric principles to create a 3D model of the object. (111).

It is a valid and reliable technique that is used to detect minute and microscopic defects in the automotive and aerospace industries. The accuracy and the precision of laser scanning has been tested by many studies.

Kau et al in 2005 in their prospective clinical trial evaluated the reliability of a 3D facial scanning technique for the measurement of facial morphology. By using two commercially available Minolta Vivid 900 (Konica Minolta, Osaka, Japan) laser scanning devices they found that capturing the soft tissue morphology of the face with this technique is clinically reproducible within 3 minutes and 3 days of the initial records (89).

Gwilliam et al in 2006 evaluated the reproducibility of 24 soft tissue landmarks on six 3D facial scans. The scans were taken on a DSP400 facial scanner and were viewed using a customized software program. This study found a higher degree of reproducibility for a single assessor placing landmarks than between assessors. For good reproducibility, landmarks must be well-defined and clearly understood (67).

The use of 3D scanners to determine the surface contour of objects by optical methods has become important in scanning of dental structures to create a 3D model and to assess the dental arch form and jaw morphology parameters.

In 2009, Adaskevicius et al in a study (3) used a new multi-camera system to create a 3D model. The system’s operation was based on the laser triangulation method. The rotating platform is driven by a step motor, with a flat surface over which a dental cast is placed. This platform has the ability to rotate 180°. The dental cast surface intersects with the known position of the laser plane, so using standard vector mathematical techniques it is possible to discover 3D locations of individual surface points. As a result of this study it was suggested that 3D representation of plaster models could be easily specified.

Laser scanning gives a noninvasive, accurate, and reproducible means for medical applications such us orthognathic surgeries (70). However, this technology has some disadvantages such as a long scan time, making it difficult to apply for children and, the laser scanner is unable to capture soft tissue texture which results in difficulties in identification of landmarks. Moreover, the patient's eyes must also be closed for protection and the head must be kept in a fixed position.

4.3 Orthodontic Digital Models

Digital dental casts are now part of the veryday life of many orthodontists. Generated digital models have several advantages over plaster models and can be transformed by using private scanners (stereophotometric scanner, the laser scanner, CT, etc.) (12, 44, 70, 219).

The orthodontic digital casts can be stored easily in a digital enviroment providing quick access anywhere and any time. The interdisciplinary communication can be done over the internet. Plaster models can be easily archived saving time for both doctors and staff. Three dimensional records in the computer can be used for precise diagnosis and detailed treatment planning (219).

Although there are numerous advantages in favor of digitized models, there are also some major disadvantages. Three dimensional model analysis lacks a globally accepted software. Also the transformation from gypsum to digital model due to scanning procedures is expensive (12, 44). The reliability of measurements done on digital models compared to plaster models was performed mostly with two dimensional imaging techniques. Measurements that have been performed on both, digital and plaster models, revealed no significant differences (62, 208, 219).

In 1998, Heidbüchel et al (72) calculated the maxillary arch dimensions in bilateral cleft lip and palate from birth until four years of age in boys on 3D models. This was a retrospective, mixed-longitudinal study. Palatal arch dimensions were digitized on dental casts. A comparison between BCLP and noncleft dimensions was made at fixed time intervals. Result revealed that during the first 4 years of life, maxillary arch dimensions in children with BCLP showed a unique development that is significantly different from that in noncleft children.

In another research, Darvann et al (44) investigated the relationship between corresponding two-dimensional and 3D measurements on maxillary plaster casts taken from photographs and 3D surface scans, respectively. Measurement of 3D palatal segment surface area on a two dimensional photograph showed photographic distortion (2.7%), interobserver error (3.3%), variability in the orientation of the plaster cast (3.2%), and natural shape variation (4.6%). The total error of determining the cleft area/palate surface area ratio was 15%. In well-calibrated setups, a two dimensional measurement of the cleft area/palate surface area ratio may be converted to a 3D measurement by use of a multiplication factor of 0.75.

Oosterkamp et al (156) demonstrated that virtual models obtained by laser scanning neonatal cast models of bilateral cleft lip and palate patients could be used reliably and validly to perform linear measurements between existing reference points on the surface of the models. However, measurements between reference points constructed outside the surface of the model (line drawn for the dislocation amount of premaxilla) could not be validly performed on the 3D virtual model with the software used in this study. This is because the lines applied using Viscam RP version 2. (Marcam Engineering, Bremen, Germany) software during digital measurements overflow from the model.

Braumann et al (18) have recorded the 3D morphological changes in the maxilla of CLP patients mainly using two-dimensional cast analyses and found that with this method it was possible to quantify the changes of the volume of defined alveolar segments and that 3D analysis developed was an ideal tool for the examination of 3D morphological changes in the edentulous maxilla of patients with CLP

Yu et al (231) used on the contrary the ability of 3D imaging to produce quantifiable measures of maxillary denture volume and shape, which make it possible to obtain an accurate and reliable digital denture model of UCLP infants on the basis of laser surface scanning in the absence of the patient.

Prassand et al (168) made quantitative 3D maxillary arch evaluation of two different infant managements for UCLP but without using any of the managements being NAM.

Finally, Chiarella Sforza (197) and his colleagues obtained casts of 96 babies with unilateral CLP. Measurements were made on the maxillary models. The same models were transformed with a specific stereophotogrammetric system (VECTRA-3D, Canfield Scientific, Inc.121, Fairfield, NJ, USA) into 3D images. Measurements were repeated on digitized maxillay models.

Measurements made using the same coordinates and the same reference points, in the stereophotogrammetric analysis were shown to be highly reliable. On the other hand, measurementds done directly in the mouth were easier, more detailed and cheaper than those made on the plaster models.

5. MATERIALS AND METHODS

5.1. Materials

Material of the present study consists of digital and stone models from the archive of Infant Cleft Lip and Palate Clinic of the Orthodontic Department of Marmara University, Istanbul, Turkey. The total number of infants that received presurgical UCLP and had a digitized initial plaster model was 90. Out of these, only 32 had extraoral and intraoral digital models. Finally, from this archive the digital models of 24 non syndromic newborn infants were selected. Eight patients were exluded due to low diagnostic and imaging quality of the plaster models that had been digitilized. All models belonged to patients who had received NAM as IO in the Orthodontic Clinic of Marmara University before they underwent primary lip repair surgery combined with primary nasal correction. Our sample consisted of digital models of 13 boys and 11 girls with Unilateral Complete Cleft Lip and Palate with a mean age of 21 days ranging from 1 to 40 days. The average length of therapy was 91 days. The nasal stent was added to the appliance only after the anterior cleft width (ACW) was reduced to 6 mm or less.

Five boys and two girls demonstrated right sided UCLP and nine girls and eight boys demonstrated left sided UCLP (Table 5). All were newborn Caucasians from the same geographic region (Turkey). The inclusion criteria were patients (1) having complete unilateral cleft lip and palate, (2) without any syndromic defect that would conjunct with cleft lip and palate, and (3) who had not received any maxillary orthopedic and nasoalveolar molding treatment.

Gender	LUCLP	RUCLP	Total
Girls	9	2	11
Boys	8	5	13
Boys & Girls	17	7	24

Table 5: The distribution of research material

A facial and a palatal impression had been taken from all patients at two stages of treatment: 1) before NAM (T_1) 2) before the lip repair and nasal correction surgery (T_2). All infants were treated with NAM within one month of age. After NAM treatment consecutive impressions of the face and maxilla of each patient had been digitally scanned with 3Shape R700 scanner (CAD BLU DENTAL, Chicago, USA) with the scaning program 3 Shape Scanitorthodontics 2008-2 patch (build 5.2.0.2, CAD BLU DENTAL, Chicago, USA), and digitally uploaded to the OrthoModel Server (v1.0), (ORTHOMODEL ®, Istanbul, Turkey).

5.2 Methods

5.2.1 Production of Digital Models

The clinical protocol of the Infant Cleft Lip and Palate Clinic of Orthodontic Department of Marmara University for impression taking of CLP patients necessitates the application of a two stage impression technique (double impression) with hydrocompatible condensation silicone (polysiloxane, Zetaplus, 3M Company, Meriden, USA). The impressions are cast 30 minutes to 72 hours and plaster models are prepared from these impressions.

For converting plaster models to 3D models, the plaster models are sent by cargo to OrthoModel company for scanning with 3Shape R700 3-axis high-resolution laser surface scanner, using two cameras and a laser transmitter approximately for 60-75 seconds. Once converted into digital data models are uploaded to OrthoModel Server (v1.0) (ORTHOMODEL ®, Istanbul, Turkey) and are accessible via internet.

5.2.2 Machines and Software Used in the Study

The brand of the laptop computer that the measurements were performed was the HP Pavilion dv2000 (Hewlett-Packard Development Company, LP, USA) with

80x800 resolution screen, Windows Vista 32-bit operating system, Intel ® Core ™ 2 Duo CPU T7300, 2.00GHz processor, 2.00 GB of RAM. The digital models were measured using the Orthomodel (v.1.01) software combined with a wireless mouse (Logitech Performance MX (Logitech International SA, Apples, Vaud, Switzerland).

5.2.3 Measurements on the Digital Models

All measurements were performed by one researcher.

5.2.3.1 Extraoral Landmarks and Measurements

The extraoral landmarks used to evaluate the 3D changes in the nose, to quantify nostril and columella width, height and length, are the following :

1. ABW: Alar base width. (53) Measurement from the most lateral points on the lateral ala, the widest dimension. (photo 3)

2. CoW: (53) Columella width. Measurement was taken at the base of the columella from its lateral edges (photo 4).

3. CNW and NCNW: (53) Width of the clefted nostril and width of the nonclefted nostril. Measurements were made connecting the midpoint of the columellar base to the widest point of inner rims of lateral ala (photo 5).

4. CoL: Columella length. Measurement were made conecting the midpoint of the columellar base to the midpoint of cleft and non cleft Columella anterior (photo 6).

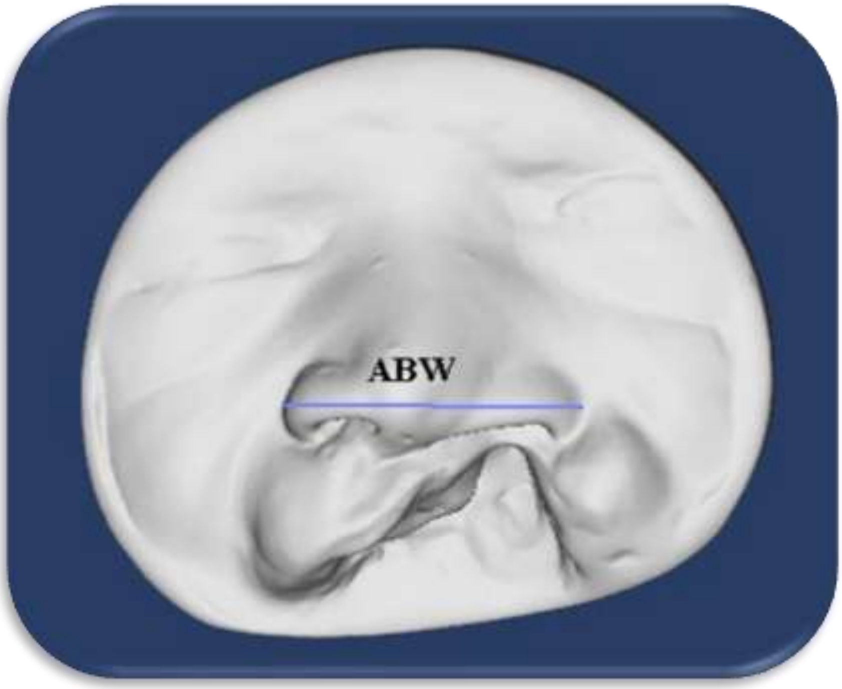


Photo 3: ABW Alar base width

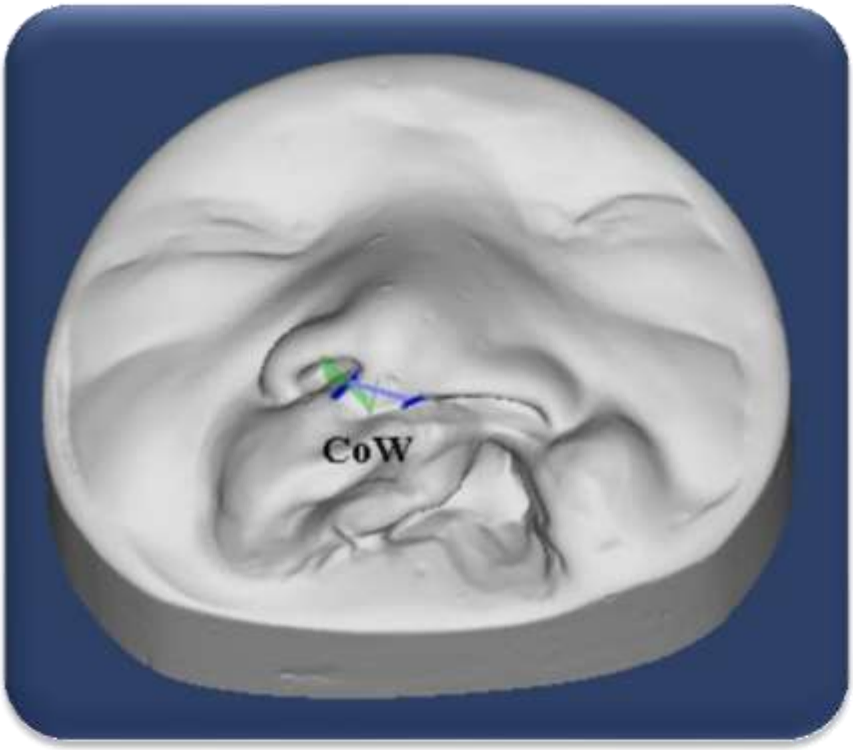


Photo 4: CoW measurement was taken at the base of the columella from its lateral edges

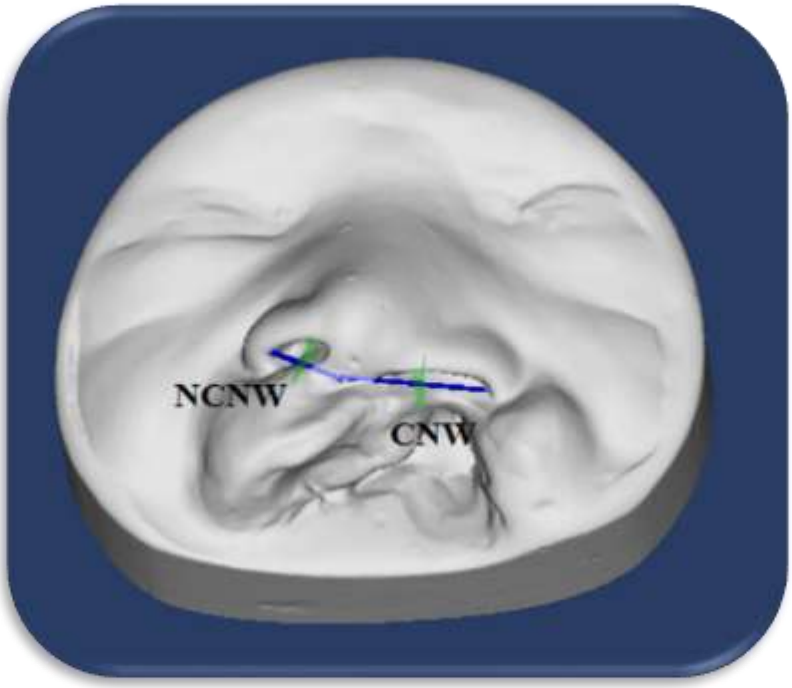


Photo 5: CNW and NCNW measurements were made connecting the midpoint of the columellar base to the widest point of inner rims of lateral ala

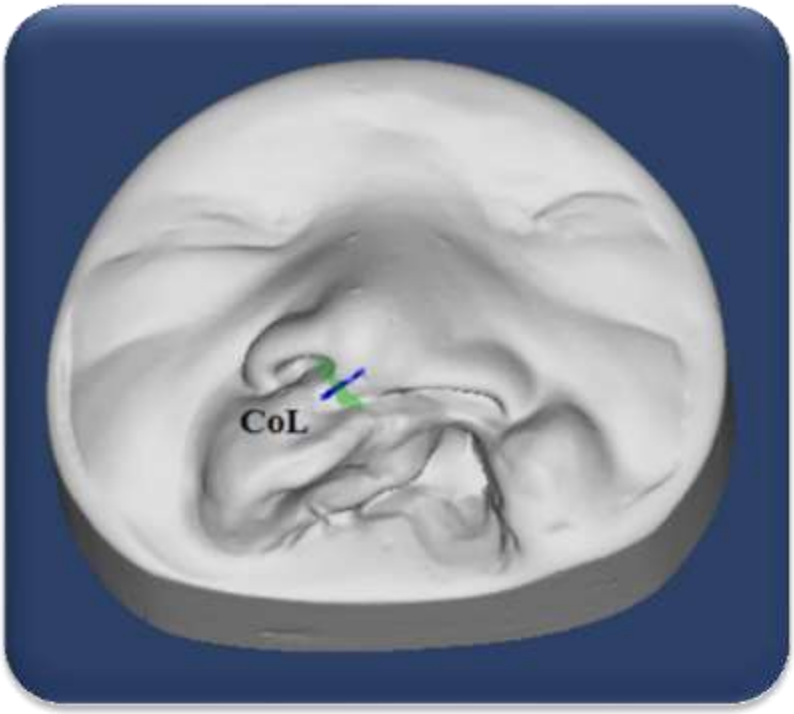


Photo 6: CoL. Columella length. Measurement was made conecting the midpoint of the columellar base to the midpoint of cleft and non cleft Columella anterior

5.2.3.2 Intraoral Landmarks and Measurements

The intraoral landmarks used to evaluate 3D changes in the maxilla, to quantify cleft width and dislocation of alveolar segments, are the following (Fig. 12):

1. ACW: Anterior cleft width (photo 7)(2, 53)
   - G : The most mesial point of big segment on alveolar crest.
   - L : The most mesial point of small segment on alveolar crest.

2. PCW: Posterior cleft width (2, 18, 62).

   Distance between the Q points (gingival groove and palatal sulcus intersection), (photo 8).

3. BSD: Big segment dislocation (the perpendicular distance from I point to ideal arch)(18,62).
   - I: incisal point where big segment dislocation is measured.

4. SSD: Small segment dialocation (the perpendicular distance from L point to ideal arch)(62).
   - C, C’: The point where alveolar crest and lateral sulcus are intersecting (the points used to create the ideal arch) (18,62).

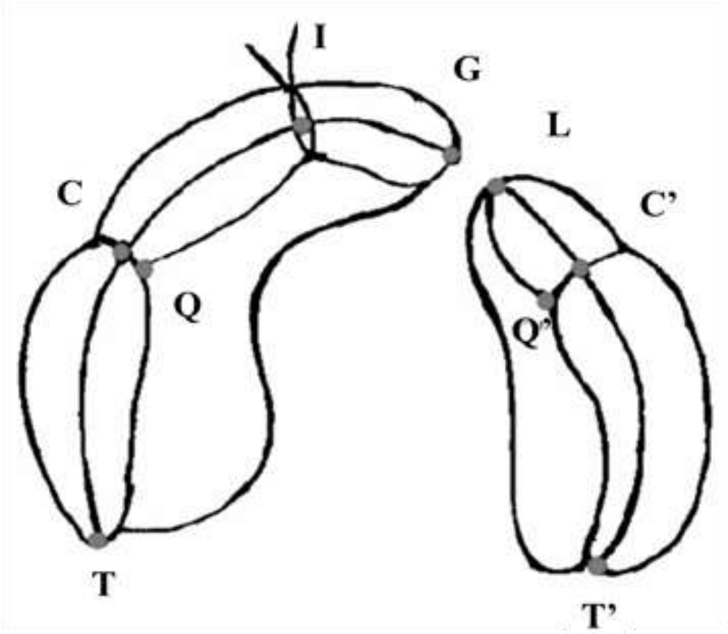


Figure 12: The intraoral measurement points used in our study

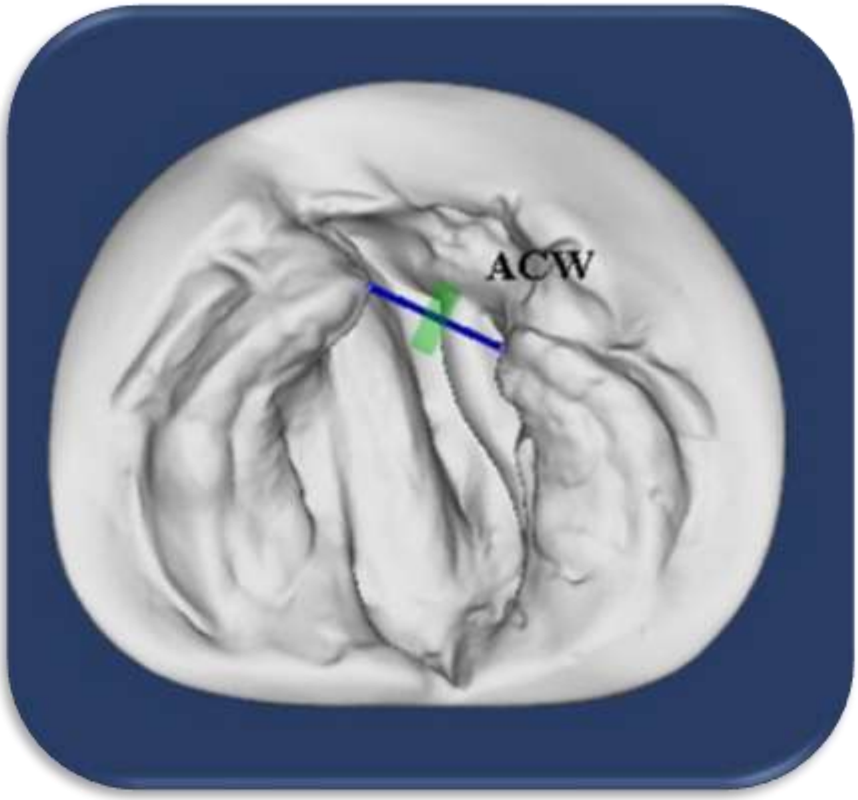


Photo 7: ACW anterior cleft width

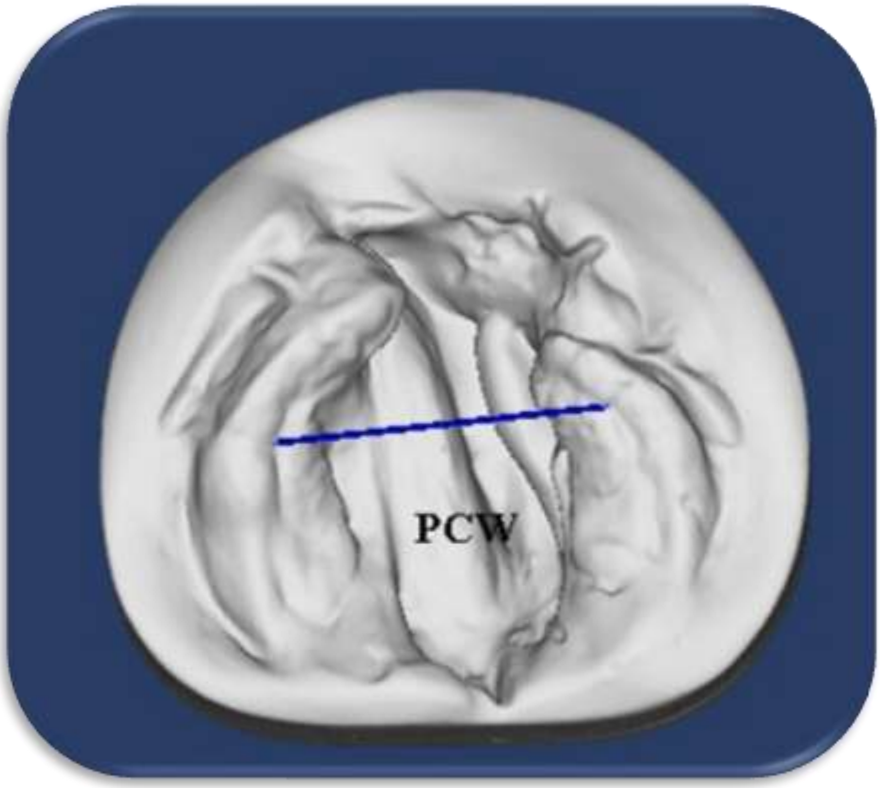


Photo 8: PCW: posterior cleft width

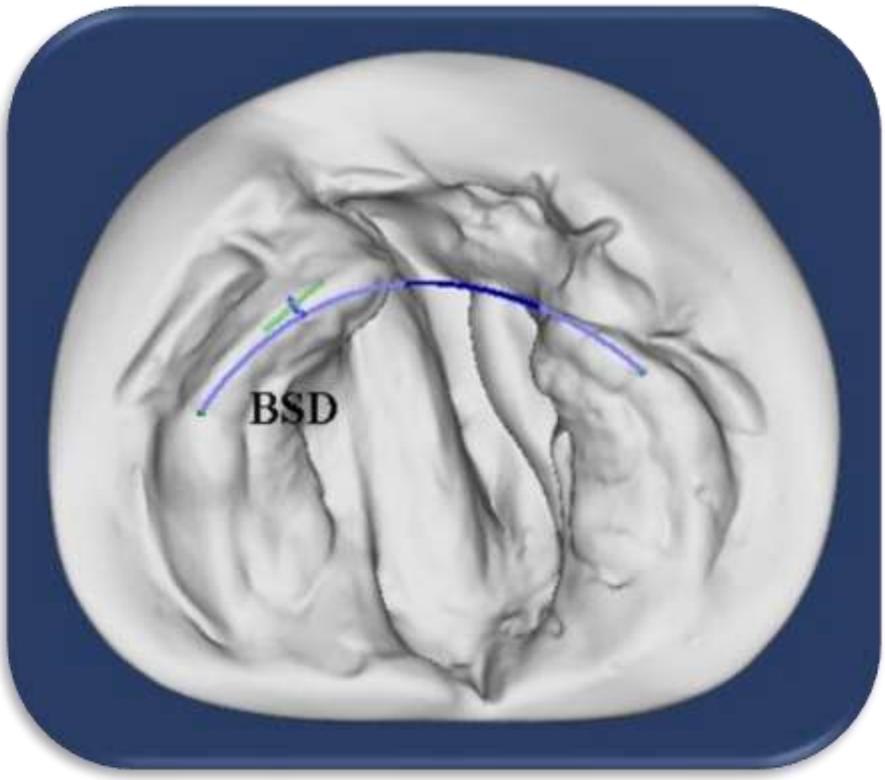


Photo 9: BSD big segment dislocation

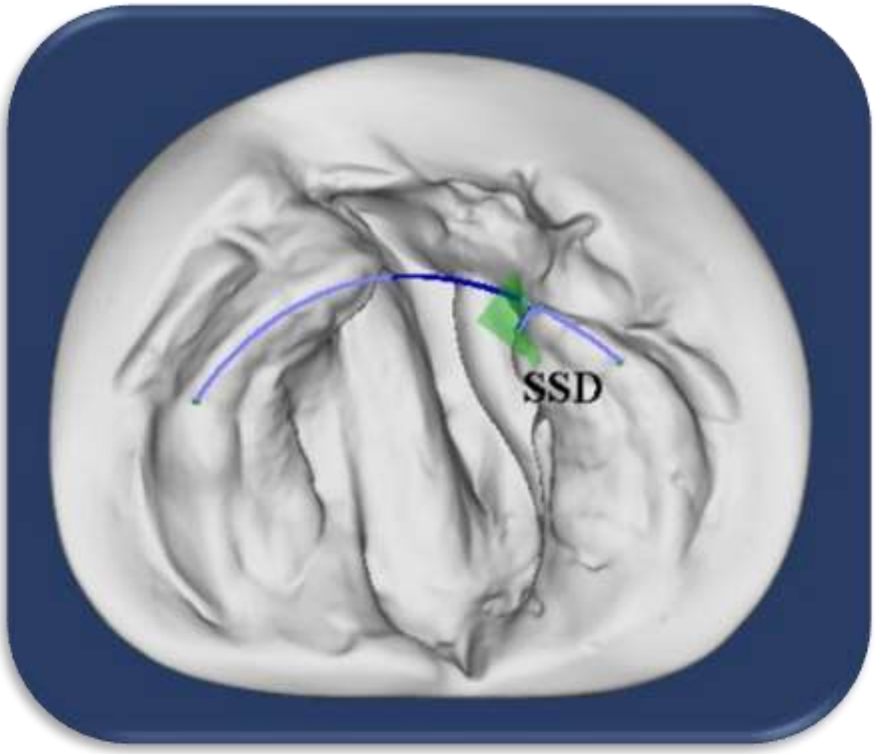


Photo 10: SSD small segment dislocation

5.2.4 Statistical Evaluations

Data assessment was done using SPSS (Statistical Package for Social Sciences) for Windows 15.0. Conformity to the normal distribution was assessed by using the Kolmogorov–Smirnov test. Students t test was used for intergroup comparisons of parameters with normal distribution and Mann Whitney U test was used for the intergroup comparisons of parameters without normal distribution.

Paired Samples t test was used for the intragroup comparisons of parameters with normal distribution. Wilcoxon Signed Rank test was used for the intragroup comparisons of parameters with normal distribution. For the analysis of the reliability of the method, intraclass correlation coefficient (ICC) was calculated. Significance was evaluated at a level of $p<0.05$.

6. RESULTS

6.1 Evaluation of the Reliability of the Method

Results regarding the reliability of the method calculated individually for each parameter are shown in Table 6 and Table 7. The intraclass correlation coefficient (ICC) and the lower and upper limits of 95% confidence interval determined for each measurement are given in Table 6. ICC determined in all measurements was found to be close to the value of 1.00.

The results of analysis of intraclass correlation coefficient showed that intraoral and extraoral measurements could be repeated within the p= 0,001 level.

Table 6: Reliability of the measurements before NAM

T_1	ICC	95% CI	*p*
Extraoral			
ABW	0,997	0,994-0,999	***0,001*****
CoW	0,987	0,970-0,994	***0,001*****
CNW	0,997	0,994-0,999	***0,001*****
NCNW	0,992	0,982-0,997	***0,001*****
CoL	0,946	0,879-0,976	***0,001*****
Intraoral			
ACW	1,000	1,000-1,000	***0,001*****
PCW	1,000	1,000-1,000	***0,001*****
BSD	1,000	1,000-1,000	***0,001*****
SSD	1,000	1,000-1,000	***0,001*****

ICC: Intraclass correlation coefficient *** p<0,01*

Table 7: Reliability of the measurements after NAM

T_2		ICC	95% CI	*p*
Extraoral				
	ABW	0,995	0,989-0,998	***0,001****
	CoW	0,961	0,913-0,983	***0,001****
	CNW	0,997	0,993-0,999	***0,001****
	NCNW	0,993	0,983-0,997	***0,001****
	CoL	0,899	0,780-0,955	***0,001****
Intraoral				
	ACW	1,000	1,000-1,000	***0,001****
	PCW	1,000	1,000-1,000	***0,001****
	BSD	1,000	1,000-1,000	***0,001****
	SSD	0,992	0,981-0,996	***0,001****

ICC: Intraclass correlation coefficient *** p<0,01*

6.2 Evaluation of Extraoral Changes

Results of the data (Table 8) derived from the extraoral measurements demonstrated the following:

ABW levels increased significantly after NAM (p<0.05). CoW levels decreased significantly after NAM (p<0.05).

No statistically significant difference was observed when the mean post NAM, CNW compared to the mean CNW on the initial models (p>0.05). No statistically significant difference was observed when the mean post NAM, NCNW was compared to the mean NCNW on the initial models (p>0.05).

Finally, CoL increased significantly after NAM (p<0.01).

Table 8: Changes in extraoral measurements

Extraoral	Initial Mean±SD (mm)	After NAM Mean±SD (mm)	*p*
ABW	29,97±3,02	31,31±3,15	***0,027****
CoW	4,53±1,34	3,84±0,93	***0,015****
CNW	17,99±3,19	17,34±3,21	***0,209***
NCNW	7,12±1,72	7,28±1,75	***0,603***
CoL	3,48±0,59	4,02±0,52	***0,001*****

Paired Sample t test ** p<0.05* *** p<0.01*

6.3 Evaluation of intraoral changes

Results of the data (Table 9) derived from the intraoral measurements demonstrated ACW, PCW, BSD and SSD decreased significantly after NAM

Table 9: Changes in intraoral measurements

Intraoral	Initial Mean±SD (Median) (mm)	After NAM Mean±SD (Median) (mm)	*p*
ACW	9,77±4,72	5,59±3,35	***0,001*****
PCW	14,34±3,55	11,96±2,98	***0,001*****
BSD	2,10±1,02	1,32±0,65	***0,001*****
SSD	0,62±1,02 (0)	0,29±0,59 (0)	***0,012****

Paired Sample t test *+ Wilcoxon sign test* ** p<0.05* *** p<0.01*

6.3 Evaluation of Measurements According to Gender

6.3.1 Evaluation of Extraoral Measurements According to Gender

Results of the data derived from the extraoral measurements demonstrated that there was no statistically significant difference in inter- (Table 10) or intragroup (Table 14) comparisons in any of the extraoral parameters according to gender (p>0.05). Exception is CoL measurements. CoL increased significantly in boys after NAM.

Table 10: Evaluation of extraoral measurements according to the gender

Extraoral		Female (n=11) Mean±SD (mm)	Male (n=13) Mean±SD (mm)	^{+}p
ABW	**Before NAM**	29,79±1,79	30,13±3,85	***0,779***
	After NAM	30,77±3,09	31,76±3,26	***0,458***
	^{++}p	***0,180***	***0,090***	
CoW	**Before NAM**	4,63±1,03	4,44±1,59	***0,737***
	After NAM	3,83±1,24	3,85±0,63	***0,960***
	^{++}p	***0,087***	***0,108***	
CNW	**Before NAM**	17,97±2,14	18,01±3,96	***0,976***
	After NAM	16,85±3,39	17,75±3,13	***0,510***
	^{++}p	***0,071***	***0,751***	
NCNW	**Before NAM**	7,74±1,60	6,60±1,70	***0,106***
	After NAM	7,51±1,16	7,08±2,15	***0,562***
	^{++}p	***0,576***	***0,278***	
CoL	**Before NAM**	3,65±0,72	3,33±0,43	***0,202***
	After NAM	4,10±0,58	3,96±0,48	***0,542***
	^{++}p	***0,095***	***0,001*****	

+ Student t test *++ Paired Sample t test* *** p<0.01*

6.3.2 Evaluation of Intraoral Measurements According to Gender

Results of the data derived from the intraoral measurements demonstrated that girls showed higher ACW initially, as well as after NAM compared to boys ($p<0.01$).

There was no statistically significant difference in inter- (Table 11), (Table 15) comparisons in any of the other intraoral parameters according to gender ($p>0.05$). There were some intragroup differences ACW, PCW and BSD decreased significantly after NAM in both boys and girls

Table 11: Evaluation of intraoral measurements according to gender

Intraoral		**Female (n=11)** Mean±SD (Median) (mm)	**Male (n=13)** Mean±SD (Median) (mm)	^{+}p
ACW	**Before NAM**	12,57±2,55	7,41±4,90	***0,004*****
	After NAM	8,08±2,56	3,49±2,37	***0,001*****
	^{++}p	***0,001*****	***0,001*****	
PCW	**Before NAM**	15,64±3,02	13,25±3,71	***0,102***
	After NAM	13,13±2,13	10,98±3,30	***0,078***
	^{++}p	***0,023****	***0,017****	
BSD	**Before NAM**	2,15±0,83	2,05±1,20	***0,817***
	After NAM	1,43±0,72	1,23±0,60	***0,467***
	^{++}p	***0,002*****	***0,003*****	
SSD	**Before NAM**	0,85±1,29 (0)	0,42±0,73 (0)	***0,534***
	After NAM	0,44±0,80 (0)	0,17±0,32 (0)	***0,629***
	^{++}p	***0,068***	***0,068***	

+Student t test was used for ACW,PCW and BSD and Mann Whitney U test was used for SSD

++ Paired Sample t test was used for ACW, PCW and BSD and Wilcoxon sign test was used for SSD

** p<0.05 ** p<0.01*

6.4 Evaluation of Measurements According to Cleft Side

6.4.1 Evaluation of Extraoral Measurements According to Cleft Side

Results of the data derived from the extraoral measurements demonstrated that there was no statistically significant difference in inter- (Table 12), (Table 16) comparisons in any of the extraoral parameters according to cleft side (p>0.05). There were some intragroup differences CNW decreased significantly and CoL increased significantly in girls after NAM.

Table 12: Evaluation of extraoral measurements according to cleft side

Extraoral		Left (n=17) Mean±SD (Median) (mm)	Right (n=7) Mean±SD (Median) (mm)	^{+}p
ABW	**Before**	30,37±3,23 (29,98)	29,00±2,39 (28,19)	***0,193***
	After	31,27±3,36 (31,13)	31,28±2,84 (32,02)	***0,975***
	^{++}p	***0,210***	***0,091***	
CoW	**Before**	4,38±1,04 (4,18)	4,89±1,94 (4,29)	***0,634***
	After	3,91±0,85 (3,99)	3,67±1,17 (3,95)	***0,824***
	^{++}p	***0,062***	***0,128***	
CNW	**Before**	18,49±3,03 (18,85)	16,79±3,49 (16,85)	***0,120***
	After	17,88±2,62 (17,65)	16,03±4,30 (17,94)	***0,546***
	^{++}p	***0,031****	***0,398***	
NCNW	**Before**	6,81±1,57 (6,42)	7,88±1,95 (6,94)	***0,216***
	After	6,92±1,25 (7,15)	8,15±2,51 (7,44)	***0,325***
	^{++}p	***0,554***	***0,866***	
CoL	**Before**	3,50±0,51 (3,45)	3,42±0,80 (3,53)	***0,975***
	After	4,03±0,48 (4,02)	4,01±±0,64 (3,95)	***0,824***
	^{++}p	***0,003*****	***0,091***	

Mann Whitney U test *++ Wilcoxon sign test* ** p<0,05* *** p<0,01*

6.4.2 Evaluation of Intraoral Measurements According to Cleft Side

Results of the data derived from the intraoral measurements demonstrated that there was no statistically significant difference in inter- (Table 13), (Table 17) comparisons in any of the intraoral parameters according to cleft side (p>0.05). As for intragroup comparisons ACW, PCW, BSD and SSD decreased significantly in left side clefts, while only ACW and BSD decreased in right side clefts.

Table 13: Evaluation of intraoral measurements according to the cleft side

Intraoral		Left (n=17) Mean±SD (Median) (mm)	Right (n=7) Mean±SD (Median) (mm)	^{+}p
ACW	**Before**	9,77±5,01 (12,05)	9,79±4,30 (10,34)	***0,975***
	After	5,62±3,24 (6,98)	5,52±3,87 (4,32)	***0,874***
	^{++}p	***0,001****	***0,018****	
PCW	**Before**	14,65±3,92 (15,08)	13,60±2,54 (13,20)	***0,427***
	After	11,83±3,18 (11,76)	12,30±2,59 (11,86)	***0,775***
	^{++}p	***0,003****	***0,237***	
BSD	**Before**	2,17±0,98 (2,02)	1,92±1,19 (1,83)	***0,568***
	After	1,40±0,69 (1,27)	1,12±0,55 (1,16)	***0,193***
	^{++}p	***0,001****	***0,046****	
SSD	***Before***	*0,78±1,12 (0)*	*0,24±0,63 (0)*	***0,212***
	After	*0,40±0,67 (0)*	*0,03±0,09 (0)*	***0,162***
	^{++}p	***0,018****	***0,317***	

*+ Mann Whitney U test ++ Wilcoxon sign test * p<0,05 ** p<0,01*

6.5 Evaluation of the Changes in Extraoral Measurements After NAM According to Gender and Right Left Side

Evaluation of the changes in extraoral measurements after NAM according to gender and right left side showed that there was no significant difference between the groups.

Table 14: Evaluation of changes in pre- and post-NAM extraoral measurements according to gender

Extraoral (Difference)	Female (n=11) Mean±SD (Median) (mm)	Male (n=13) Mean±SD (Median) (mm)	^{+}p
ABW	-0,98±2,27 (-0,31)	-1,63±3,19 (-1,63)	***0,543***
CoW	0,79±1,39 (1,22)	0,58±1,22 (0,29)	***0,369***
CNW	1,11±1,83 (0,86)	0,26±2,94 (0,72)	***0,582***
NCNW	0,23±1,32 (0,53)	-0,48±1,53 (-0,23)	***0,213***
CoL	-0,44±0,80 (-0,37)	-0,62±0,55 (-0,49)	***0,582***

Mann Whitney U test

Table 15: Evaluation of changes in pre- and post-NAM extraoral measurements according to right and left sides

Extraoral (Difference)	Left (n=17) Mean±SD (Median) (mm)	Right (n=7) Mean±SD (Median) (mm)	^{+}p
ABW	-0,95±2,80 (-0,63)	-2,27±2,63 (-3,33)	***0,357***
CoW	0,46±1,05 (0,31)	1,22±1,69 (0,78)	***0,465***
CNW	0,61±2,46 (0,73)	0,76±2,75 (1,18)	***0,874***
NCNW	-0,11±1,16 (0,06)	-0,26±2,12 (-0,23)	***0,874***
CoL	-0,52±0,59 (-0,39)	-0,59±0,87 (-0,66)	***0,546***

Mann Whitney U test

6.6 Evaluation of the Changes in Intraoral Measurements After NAM According to Gender and Right Left Side

Evaluation of the changes in intraoral measurements after NAM according to gender and right left side showed that there was no significant difference between the groups.

Table 16: Evaluation of changes in pre- and post-NAM measurements according to gender

Intraoral (Difference)	Female (n=11)	Male (n=13)	^{+}p
	Mean±SD(Median) (mm)	Mean±SD (Median) (mm)	
ACW	4,49±2,12 (5)	3,91±2,95 (4,28)	***0,794***
PCW	2,51±3,11 (1,98)	2,26±2,96 (2,18)	***0,931***
BSD	0,72±0,58 (0,66)	0,82±0,79 (0,69)	***0,931***
SSD	0,41±0,66 (0)	0,25±0,47 (0)	***0,629***

Mann Whitney U test

Table 17: Evaluation of changes in pre- and post-NAM intraoral measurements according to right and left sides

Intraoral (Difference)	Left (n=17)	Right (n=7)	^{+}p
	Mean±SD (Median) (mm)	Mean±SD (Median) (mm)	
ACW	4,14±2,49 (5)	4,27±2,94 (3,55)	***0,975***
PCW	2,82±2,76 (2,32)	1,29±3,37 (1,15)	***0,216***
BSD	0,77±0,65 (0,69)	0,79±0,83 (0,66)	***0,657***
SSD	0,37±0,57 (0)	0,20±0,54 (0)	***0,307***

Mann Whitney U test

1

7. DISCUSSION

7.1 Discussion of the Aim Materials and Methods

Cleft lip and palate is the most common and difficult orofacial deformity to be treated (185, 190, 220). The treatment of CLP requires multidisciplinary approach (78). Photographs, plaster or digital models and numerous classification methods are used routinely in order to ensure inter-disciplinary communication.

The purpose of this thesis was to assess the morphological changes in the face and maxilla of patients with Unilateral Complete Cleft Lip and Palate after presurgical NAM treatment. The assessments were made on digital models instead of the traditional plaster models.

This is the first study that evaluates 3D intraoral and extraoral changes after NAM. Most of the studies in this field, evaluate only the extraoral changes after presurgical orthopaedics. Even fewer studies investigate the effects of NAM.

A total number of 90 newborn non syndromic UCLP infants that had received presurgical NAM were evaluated in the present study. Out of these, only 32 had all the required extraoral and intraoral digital models. Models with poor imaging quality were omitted and the digital models of 24 patients remained in the study. Only unilateral complete cleft cases have been included in order to form a homogenous sample.

There was no control group in this study because it was not ethical not to treat infants with UCLP and to leave them as controls. Our sample consisted of digital models of 13 boys and 11 girls with UCLP with a mean age of 21 days. Five boys and two girls demonstrated right sided UCLP and nine girls and eight boys demonstrated left sided UCLP. All were newborn Caucasians from the same geographic region (Turkey).

The measurements were performed in two specific times of treatment: 1) before (T1) and after (T2) NAM.

Traditionally, the measurements are performed on plaster models with the help of a digital caliper or on photocopies/photographs of the plaster models. Numerous researchers have measured the effect of NAM by that way (1, 32, 53, 150, 200, 222). This thesis aimed to evaluate the effects of NAM using digital models and digital measuring tools.

There is a variety of computer software for creating digital models. Reliability of these softwares have been assessed in various studies (37, 110, 121, 174).

Darvann et al (44) investigated the relationship between corresponding two-dimensional and 3D measurements on maxillary plaster casts taken from photographs and 3D surface scans, respectively. Measurements showed photographic distortion, interobserver error, variability in the orientation of the plaster cast, and natural shape variation.This variation could be observed due to the lack of good calibration of the setups. Moreover, according to author well-calibrated setups, a two dimensional measurement of the cleft area/palate surface area ratio may be converted to a 3D measurement by use of a multiplication factor of 0.75.

For evaluation of the accuracy of our linear measurements on the digitized models compared to measurements made on the stone models. Identical linear measurements were made on both, digital and plaster models. There was no statistically significant difference between them (202). There are numerous studies that found similar results with us (18, 156, 197, 231).

The results of our study shows that the methodology of our study is reliable. Incompatibility with the resuts of the Darvann-study may be due to insufficient calibration of their setups or due to limitations of the computer software that was used.

In the current study, both extraoral and intraoral landmarks and measurements were performed. The extraoral landmarks aimed to evaluate the 3D changes in the nose, and to quantify nostril and columella width, height and length. The intraoral landmarks aimed to evaluate 3D changes in the maxilla and to quantify cleft width and dislocation of alveolar segments.

The extraoral measurements chosen alar base width (ABW), cleft and non cleft nostril width (NC/CNW), columellar width (CoW) and finally collumellar length (CoL) have been used in numerous other studies (1, 20, 53, 150, 200, 204).

Liou et al also used similar measurements with the only difference that their sample consisted of BCLP patients (106). Singh et al evaluating the 3D changes in nasal morphology of UCLP employed 28 soft tissue nasal landmarks and linear measurements as a combination of them (202). We chose the most representative measurements to picture the changes occuring in NAM, and preferred not to use too many soft tissues landmarks and measurements in order to keep the data simple and comprehensible.

On the other hand, there are studies using angular measurements as well, like Chien Jung-Pai et al (32). They measured the inclination of the columella from the cleft side (a line bisecting the columella was drawn from the tip of the nose to the reference line, and the angle was measured from the affected nostril). Keçik et al also used landmarks in the graphic representation of the scanned nasal model (90). The reason we avoided to use angular meausurements is the shortcomings of the program we used.

We chose four different measurements to cover changes occuring in NAM. Anterior and posterior cleft width (ACW, PCW) and dislocation of big and small segment (BSD, SSD).

Braumann et al (18) used the same measurements to measure the change in both anterior and posterior cleft width (ACW), (PCW) as we did. They also used the junction of the crest of the alveolar ridge with the outline of the tuberosity (TK/TK') as reference point.

Ezzat et al (53) as well as, Shetty et al (200) and Adali N. et al (2), Keçik et al (90) performed measurements to calculate the anterior cleft width as we did. The same measurements also were performed by Nazarian Mobin et al (150) in a study to compare the efficacy of presurgical NAM in treating unilateral versus bilateral CLP patients.

Brijesh Mishra et al (20) had only one intraoral measurement in their study which was the anterior cleft width. There are investigations that utilize more complex measurements. Moreover, the comparison of presence of alveolar gap was performed at 1-year follow-up after lip repair Prasad et al (168) in a two-institution retrospective study to determine whether two different prepalatoplasty protocols quantitatively affect maxillary arch morphology in infants with complete UCLP. Their measurements included directly measured (cleft segment and hemialveolar ridge lengths) and derived (alveolar base width, alveolar cleft gap, maxillary frenum-alveolar base perpendicular angle, and rates of change over time of digitized cleft segment and hemialveolar ridge lengths) variables.

As a conclusion, it should be said that in this thesis it was prefered to select those measurements that represented treatment changes in a clear way and could be compared easily with most of the other studies about the effects of NAM. It was also decided to perform additional comparisons of intraoral and extraoral changes between males and females, as well as between right and left sides.

7.2 Discussion of the Results

Treatment of the unilateral cleft lip and palate has been a challenge in regard to nose shape and symmetry. The aim of our study was to evaluate the 3D morphological changes in the face and maxilla of patients with UCLP after NAM. Measurements demonstrated statistically significant changes intraorally and extraorally. Different from other traditional presurgical infant orthopedic procedures, NAM aims to correct also part of the nasal deformity prior to the initial surgery. Using NAM, nasal symmetry as well as nasal projection is enhanced in addition to the alignment of the maxillary segments.

The degree of plasticity in neonatal cartilage is highest after birth and gradually reduces as infants grow. This might be due to high levels of hyaluronic acid in estrogen that was transferred from the mothers to the infants. The cartilage subsequently loses its pliability at around 6 weeks. Therefore, presurgical NAM is most successful during the first 3 to 4 months of life (118). However, the use of NAM is limited to a few centers and the numbers of patients for a study of this nature is limited.

Lengthening of the columella is one of the major goals of nasal molding. Accordingly, columella length (CoL) measurements increased significantly after NAM ($p<0.01$). Mobin et al (150) in their study comparing NAM in Unilateral and Bilateral CLP did not find any significant change in the UCLP group for CoL measurements, whereas in the BCLP group they found a more effective increase ($p=0.002$).

On the other hand, Brijesh Mishra et al (20) evaluating the role of NAM when comparing unilateral and bilateral clefts, found that lengthening of the columella was more pronounced in unilateral cases than in bilateral cases ($P=0.02$). The very small sample size (6) of the BCLP group may account for this controversial result.

Shetty et al (200) in their study which had as objective to compare the effects of NAM in complete UCLP infants presenting for treatment at different ages, found 0.2 mm (38%) increase in columella length in infants treated within one month of age after NAM. This figure is slightly lower than our results (0,54 mm). The study of Shetty et al showed that there was a much higher increase of columella length if NAM was started within first month, which is the case in the present research as well

Singh et al (202) in their study evaluated the 3D nasal changes following NAM in patients with UCLP and found that cleft side columella increased in height by 30%, but the noncleft side increased by only 10%.

Our study as well as numerous other studies (1, 20, 66, 150, 200, 202) demonstrated that the columellar length increases. We assume that this is due to the fact that forces are exerted on the nasal structures, when approximating the alveolar segments. That permits straightening of the columella and correction of alar cartilage displacement. The nasal stent produces pressure on the alar dome, leghthening the columella. Lengthening or uprighting of the columella can be expected because, treatment of presurgical NAM, if initiated as soon as possible after birth, may be acting as an inductive mechanism that stimulates the activity of immature nasal chondroblasts, producing an interstitial expansion that is associated with improvement in nasal morphology (158).

Alar base width (ABW) increased significantly after NAM (1,34 mm). We assume that this small change was due to growth and maturation of the infants. Also an other reason could be the limitations due to the limited sample size.

A nonsignificant increase in alar base width was observed in the study by Ezzat et al (53). The improvement in the nasal symmetry of the affected nostril was accomplished by maintaining or slightly increasing the width of the nasal base.

Also Pai et al found slighty increased ABW and according to them this is because of the missing or lowered nasal floor that can be corrected only by cheiloplasty (157).

On the contrary, Mobin et al (150) found significantly decreased bialar width in UCLP patients (2,67 mm). Moreover, according to Keçik et al (90), the alar width and the nostril area of the unaffected side remained unchanged during molding therapy, however, the nostril area and the alar width of the cleft side changed significantly (6 mm). The increase in the nostril area of the cleft side was significant, despite the decrease in the alar width; with the reshaping effect of the nasal stent, the alar cartilages of the cleft side became nearly symmetrical to the noncleft side They both presume that the reason for this, is because the traction caused by tape on the segments is more effective due to one side immobility in UCLP patients.

Columella width (CoW) decreased significantly after NAM (0,69 mm). Mobin et al (150) on the contrary, found an increase in columellar width (0,35 mm) in BCLP infants. We assume that a decrease in CoW can happen by the pressure of the nasal stent on the alar dome stretching the columella resulting in the decrease of columellar width.

On the other hand, according to Ezzat et al (53) there was a statistically significant increase in columellar width (0,25 mm) which is in contrast to our findings.

Our results showed no statistically significant difference in nostril width levels on the cleft- and non-cleft sides (0,35 mm decrease for CNW and 0,16 mm increase for NCNW). Keçik et al (90), found that the nostril area of the noncleft side did not change significantly; however, the increase in the nostril area of the cleft side was statistically significant (4,19 mm). A decrease in the CNW could be expected because NAM decreases the anterior cleft width and simultaniously approaches the lip segments bearing the lateral and medial nasal cartilages. The reason we could not see the expected decrease might be the relatively small sample size, but also the varying degree of success in achieving treatment goals could be responsible. This is in accordance with the results of Brijesh Mishra et al (20).

Ezzat et al (53) observed a nonsignificant decrease in affected CNW. As previously mentioned, they assume that the improvement in the nasal symmetry of the affected nostril was accomplished by maintaining the width of the nasal base.

Pai et al (157) reported that the ratio of nostril width of the affected side to the nonaffected sides, was 1.7 initially. The width of the nostrils became more symmetrical (ratio, 1.2) after presurgical NAM. According to the authors the improvement in the symmetry of the nostrils was limited because a missing or lowered nasal floor could be corrected only by cheiloplasty, which would make the nostrils even more symmetrical in terms of height, width, and columella angle.

Generally, for the extraoral measurements in our study we can assume that the combined effect of pushing the nasal tip forward and pressing back on the nasolabial fold resulted in gradual tissue expansion and uprighting of the columella. At the same time, the domes of the lower lateral nasal cartilages are brought together in the midline, resulting in better symmetry (65).

Our results concerning the intraoral measurements demonstrated that the anterior cleft width (ACW) decreased significantly after NAM (4,18 mm). Numerous studies in the literature (1, 20, 47, 53, 66, 90, 106, 150, 157, 200) also found that after NAM, there was a statistically significant decrease in intersegment alveolar cleft distance for unilateral CLP.

It is one of the main treatment goals of presurgical NAM to guide maxillary alveolar segments into a normal position, deceasing the gap in between them. A complete osseous bridge might form following surgery when the surgical procedure includes gingivoperiosteoplasty (20, 66, 106, 157, 200). The fact that the mean ACW after NAM is still around 5 mm shows that the goal of closing the alveolar gap was not achieved in many of the patients in our study. The large standard deviation shows also that there is a great individual variability. Since NAM was started within the first month in our patients, this poor result should not be due to the late treatment start, but rather due to a lack of excellence in the technique. This could be an implication of the treating doctors still being in training.

PCW levels decreased significantly after NAM (2,38 mm). We assume that this result occured because the appliance prevents the tongue from posturing in the palatal cleft, thereby allowing this normalization to occur. There is also no acrylic extension protruding into the cleft area in order to allow horizontal bone growth and to decrease the cleft gap. While the molding appliance prevents further segment displacement, it does allow for additional, even though slower than normal, transverse growth of the posterior maxillary arch. Another explanation might be the misdirecting of the alveolar segments, or “locking out,” that refers to the misalignment of the greater segment posteriorly more quickly than the lesser segment (83).

The PCW measurement is complementary to the AW measurement (between the tangents to the widest curvature of the maxillary arches), that Ezzat, Mobin and Shetty et al used (53, 150, 200). Mobin et al found no significant change of the arch width. Shetty et al found the mean alveolar width increase was 1.0 mm (3%) in the early treatment group.

Also Brijesh Mishra et al (20) found that unilateral cleft lip patients had more reduction of the alveolar gap than bilateral patients. They explained that the rotation of the anterior aspect of the alveolar arch does not translate into a major change posteriorly where the alveolar width was measured. Moreover, the comparison of presence of alveolar gap was performed at one year follow-up after lip repair

Big segment dislocation (BSD) levels decreased significantly after NAM (0,78 mm). Moreover, small segment dislocation (SSD) levels also decreased significantly after NAM (0,33 mm). Abida Ijaz in her study found that the correction in the aligment of the major alveolar segment was highly significant (1). This result is also the major goal of the alveolar molding process, the NAM plate improves alveolar shape and positions, thus the approximation of cleft alveolar segments.

A contradictory finding was published by Adali et al (2) evaluating the effect of presurgical orthopedics on maxillary arch form up to 6 months of age. They found that there was no evidence that presurgical orthopedics produced any significant effect on arch form, raising questions for its continued use in this context. Lip repair had a greater impact on arch dimensions than did presurgical orthopedics. But since in this study passive presurgical orthopedics was used instead the NAM, a comparison would not be valid (64, 65, 66).

There is a certain number of complications and limitations that should be taken into account in this thesis. Compliance by the caretaker is crucial in the success of NAM therapy. Poor compliance by the parents can cause loss of valuable treatment time. Weekly follow up was required but few patients were not regular for their appointments, for whatever reasons, affecting the results of molding. Patient were also coming from a long distance, their parents feel it difficult to continue the follow up. Doctors also find it difficult to continue the follow-up, even though patients are called with six months intervals.

Molding plates must be removed daily and cleaned regularly to reduce the risk of infection. In addition, frequent appointments and attention to the positioning of the nasoalveolar molding device must be maintained. Moreover, it has to be mentioned that infants were treated by different postgraduate doctors following the same treatment protocol under the guidance of the same supervisor.

The, evaluation of the measurements according to the cleft side did not reveal statistically significant differences in inter comparisons in any of the intraoral-extraoral parameters.

Evaluation of intraoral and extraoral measurements according to gender demonstrated that girls showed higher ACW levels initially, as well as after NAM compared to boys ($p<0.01$). But this finding should be interpreted cautiously because there is no other evidence in the literature and our sample size is small.

The comparison of the pre and post NAM measurements in groups formed according to gender and cleft side did not produce parallel results with the comparison made in the whole group. This can be attributed to the small sample sizes of the subgroups of boys/girls and right/left side cleft.

Finally, the weakness of this study was the absence of a control group. The comparison of the findings with a control group could have revealed more specific and reliable results; however, the ethical impossibility of taking impressions from a healthy newborn, thus the absence of a control group, caused the authors to evaluate the data only among the patients with cleft lip and palate who have undergone nasoalveolar molding therapy.

8. CONCLUSION

Although the use of presurgical infant orthopedic devices remains controversial, a growing number of studies has shown that presurgical NAM provide safe, effective, and lasting improvements in the esthetics of the nasolabial complex in infants with unilateral cleft deformities (120). It remains necessary to localize and quantify the nasal and maxillary changes using a noninvasive 3D analysis.

In this study, we have compiled 3D data of UCLP patients who underwent presurgical NAM at our institution. These changes were assessed three dimensionally and analyzed by a computer software. The question remains as to what extent the palatal appliances account for these changes. The 3D analysis presented here is an ideal tool for the examination of 3D morphological changes in the edentulous maxilla of patients with UCLP.

The outcomes of this study are:

- A new 3D aproach of evaluating the changes in maxilla and face of UCLP patients was established
- Alar base width increased significantly after NAM
- Columella width decreased significantly after NAM
- Columella length increased significantly after NAM
- Anterior cleft width decreased significantly after NAM
- Posterior cleft width decreased significantly after NAM
- Big and small segment dislocation levels decreased significantly after NAM
- Morphological changes after NAM are not affected by the location of the cleft
- Girls showed larger anterior cleft width initially, as well as after completion of NAM compared to boys

The results will serve as the starting point for a longitudinal study of the treatment outcome, not only of presurgical infant orthopedics but also of surgical procedures. Moreover, understanding these differences may help physicians and dentists to make more realistic estimates and expectations about the effects of NAM in unilateral cleft patients.

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I was born in Thessaloniki, Greece in January 1984. I studied at the Dental School of Aristotle University of Thessaloniki from September 2002, until July 2008. Since September of 2009, I have been enrolled in the MSc program at the Department of Orthodontics, Faculty of Dentistry, Marmara University, Turkey.

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EDUCATION LEVEL

	The Institute Graduated From	**Graduation Year**
Doctorate		
Master		
Licence	Aristotle University of Thessaloniki (A.U.TH.), Thessaloniki, Greece	2008
High school	1st Lyceum, Chalandri, Greece	2002

Work Experience

	MISSION	**INSTITUTE**	**DURATION (year - year)**
1.	DENTAL PRACTICE	PRIVATE PRACTICE	2008-2009
2.	DENTAL PRACTICE	PRIVATE PRACTICE	2008

FOREIGN LANGUAGE	COMPREHENSION *	SPEAKING *	WRITING*
ENGLISH	EXCELLENT	EXCELLENT	EXCELLENT
TURKISH	WELL	INTERMEDIATE	INVALID

*** Evaluate as Excellent , Well , Intermediate , Invalid**

FOREIGN LANGUAGE COMPETENCY								
KPDS	**ÜDS**	**IELTS**	**TOEFL IBT**	**TOEFL PBT**	**TOEFL CBT**	**FCE**	**CAE**	**CPE**
			93/120			**B**	**C**	

it is to be written all the successfull examinations

KPDS: Kamu Personeli Yabancı Dil Sınavı; ÜDS:Interuniversity Board Foreign Language Examination ; IELTS: International English Language Testing System; TOEFL IBT: Test of English as a Foreign Language-Internet-Based Test TOEFL PBT: Test of English as a Foreign Language-Paper-Based Test; TOEFL CBT: Test of English as a Foreign Language-Computer-Based Test; FCE: First Certificate in English; CAE: Certificate in Advanced English; CPE: Certificate of Proficiency in English.

	Quantitative	Equally Weighted	Verbal
Academic staff and graduate education entrance examination (ALES)	60		320
OTHER SCORE			

COMPUTER KNOWLEDGE

PROGRAM	ABILITY TO USE
MICROSOFT OFFICE	EXCELLENT

T.C.
MARMARA ÜNİVERSİTESİ
Sağlık Bilimleri Enstitüsü
Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu

PROJENİN ADI: Three-Dimensional Analysis Of Morphological Changes In The Face And Maxilla Of Patients With Unilateral Complete Cleft Lip And Palate After Presurgical Nasoalveolar Molding Treatment
PROJE YÜRÜTÜCÜSÜ: Prof. Dr. Ahu ACAR
PROJEDEKİ ARAŞTIRICILAR: Ilias ANDREPOULOS
ONAY TARİHİ VE ONAY SAYISI: 21.03.2012 – 3

Sayın Prof. Dr. Ahu ACAR

51 protokol nolu "Three-Dimensional Analysis Of Morphological Changes In The Face And Maxilla Of Patients With Unilateral Complete Cleft Lip And Palate After Presurgical Nasoalveolar Molding Treatment" isimli projeniz Enstitümüzün Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu tarafından incelenmiş ve etik yönden uygunluğuna karar verilmiştir.

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