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Patterns of Cleft Lip and Palate in Sudanese Patients

By
Muawya Sufyan Fakhruddin
M.B.B.S. (Uof K)

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SUPERVISOR: Professor KHALID I. YAG
MB ChB, FRCS, FRCS (Ed)
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Dedication

To my parents, wife and children.
To everyone who supported me in this work.
Acknowledgement

I would like to express my thanks to Professor Khalid Yagi; who was a father and a supervisor; to Mr. Abdel Samie Abdullah for his invaluable help and to my colleagues who helped me to accomplish this work.
ABSTRACT

Cleft lip and palate are common congenital anomalies in Sudan, which have genetic and environmental etiology. They may occur combined or each in isolation. They are widely studied worldwide for types and association.

Objectives: The objectives of the study were to study different anatomical patterns of cleft lip and palate, and to outline their familial and prenatal factors.

Patients and methods: The study was conducted in three main hospitals in Khartoum in the period from March 2004 to March 2005. Sixty five cases were included as they presented. Data was collected using a questionnaire and analyzed by the computer.

Results: Sixty five cases were included, 57 (87.7%) of them had cleft lip and palate, 8(12.3%) had isolated cleft palate, 5(7.7%) had associated anomalies and 6(9.2%) patients had family history of cleft lip or palate. Fifteen (23.1%) of the mothers had febrile illness during the first trimester and 15 (23.1%) used folates supplements. In the group of cleft lip and palate; 27(47.4%) cases were in the left side, 11(19.3%) were in the right side, 18(31.6%) were bilateral, and 7(12.3%) were isolated cleft lip cases. In the isolated cleft palate cases; a total of 8 cases; 6 cases had cleft of the soft palate and 2 cases had complete cleft palate.
**Conclusion:** There are different patterns of cleft lip and cleft palate observed in the study, with different familial and prenatal associations. Further studies are needed to investigate these congenital defects in Sudan. Comprehensive programs are needed for managing the problem in our country.
ملخص الأطروحة

الشفة المشقوقة والحنك المشقوق شواذ وراثي وبيئي، وهم قد يحدث سوء
أو كل على حدة. قد درست على نطاق واسع من حيث النوع والمرض والوراثة والعلاق.
الأهداف: أهداف الدراسة كانت أن تدرس أشكال مختلفة من الشفة المشقوقة والحنك المشقوق وتلبية
علاقتها الوراثية وقبل الولادة.

المريض والطرق أجريت الدراسة في ثلاث مستشفيات رئيسة في الخرطوم بعدها وحدات مخصصة
لهذه الحالات، في الفترة من مارس 2004 إلى مارس 2005. خمس وستون حالة تضمنت حسب
ورودها. البيانات جمعت باستعمال إستبيان وحلت بالحاسوب.

النتائج: ضمن 65 حالة تضمنت، 87.7% كانت حالات شفقة وحنك معًا، 12.3% كانت حالات
شفقة جزء، 7.7% حالة اجتمعت بها شويا وراثية أخرى و9.2% كان لديهم تاريخ عائلي من
الشفة أو الحنك المشقوق. 31.6% الأمهات أصيبت بمرض حمي و27% استعملوا حامض الفوليك
أثناء النصف الأول من الحمل. ضمن 57 حالة شفة واللياة المشقوقة، 42.4% كانتوا ذكورا،
45.6% كان إناثا، 7.4% كانت في الجانب الأيسر، 19.3% كانت في الجانب الأيمن، 31.6%
% كانت في الجانبين معا و12.3% حالات الشفة المشقوقة منفردة. ضمن 8 حالات للحنك
المشقوق، 6 حالات شفتا من اللعابة الناعمة وحالتين شفتا شفا كاملاً.

الخاتمة: هناك أنواع مختلفة من الشفة المشقوقة وليلة المشقوقة بعلاقتها الوراثية وقبل الولادة
المختلفة. تحتاج دراسات أخرى لتحري هذه الشويا الوراثية في السودان.
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CLP = combined cleft lip and palate.
CP = isolated cleft palate.
CHAPTER
ONE
Literature Review

Introduction

Cleft lip is a separation in the continuity of the upper lip. Cleft palate is a defect in the roof of the mouth. Hippocrates (400 BC) and Galen (150 AD) mentioned cleft lip, but not cleft palate in their writings. For centuries, perforations of the palate were considered to be secondary to syphilis, and cleft palate was not recognized as a congenital disorder until 1556, by Fanco. The first record of a palatal operation dates to 500 AD and was prompted by inflammation of the uvula. In 1552, Houlier proposed suturing palatal clefts and 12 years later Ambroise Pare illustrated obturators for palatal perforations. In 1764, Le Monnier, a French dentist, successfully repaired a cleft velum with a few sutures and hot cautery of the edges. von Graefe, 50 years later, produced inflammation of the velar margins before bringing them together in his palatal suture and is credited with performing the first velar repair of a cleft in 1816. JC Warren performed the first velar closure in America in 1824. In 1828, Dieffenbach enhanced the surgical treatment of cleft palate by introducing hard palatal mucosa elevation to allow the closure of hard palatal cleft. von Langenbeck (1859) proposed the creation of a bipedicle mucoperiosteal flap that can be mobilized medially to close the palatal cleft. The improved vascular supply of the mucoperiosteal flap significantly decreased the incidence of dehiscence. With the ability to successfully close the palatal defect, concern about palatal function was raised. It was evident by this time that the short and immobile palate
impaires the speech capability of patients with cleft palate. Veau (1931), Kilner (1937), and Wardill (1937) described the unipedicled mucoperiosteal flap based posteriorly on the greater palatine artery that pushed the flap posteriorly to lengthen the palate. The scarring of the denuded bone areas anteriorly and laterally was suspected as the cause of facial growth retardation posteriorly. In 1994, Schweckendiek advocated the use of a 2-stage cleft palate closure. The soft palate was closed early, with closure of the hard palate delayed until several years later. The rationale for the 2-stage procedure was to provide improved velopharyngeal function during the initial speech development and to accomplish the closure of the hard palate after the cleft narrows with facial growth. Anatomic muscle realignment has also been postulated as essential in improving postoperative velopharyngeal function. These historic developments underlie the existing controversies in cleft palate management.(1)

Classification

Several classification schemes, such as those of the American Association of Cleft Palate Rehabilitation, Karfik, and Van der Meulen et al. have been proposed to describe craniofacial clefts. From a surgeon’s point of view, Tessier classification1 is the most useful since it correlates clinical appearance with surgical anatomy. It integrates topographic clinical observations with the underlying skeletal disturbance.

In Tessier classification, the key landmarks are the orbit, nose, and mouth; through which the craniofacial clefts follow constant meridians. The clefts are numbered 0 to 14 with cleft number 8 forming the equator. Hence, clefts numbered 0 to 7 of the lower hemisphere represent the facial clefts and the
upper hemisphere of clefts numbered 9 to 14 their cranial prolongations, which we are not relevant to this study.

Midline deformities of the upper lip and nose are included in the No. 0 cleft. Midline cleft may be accompanied by either a deficiency of tissue or an excess of tissue. When hypoplasia is the dominant theme, portions of these structures can be missing. Examples are a false median cleft lip and an absent columella. The skeletal deficiencies are reflected by the absence of the premaxilla and nasal septum. The holoprosencephaly malformation represents its combination with a hypoplastic No. 14 cleft. A range of holoprosencephaly type malformations from a cyclops to near normal facies exists. A CT scan of the brain should be obtained. Those with poor differentiation of brain die during infancy, whereas those with normal architecture of the brain have a better prognosis.

At the other end of the spectrum, where there is a relative excess of tissue, a true median cleft lip can be seen as well as a bifid nose. The labial frenulum can be duplicated, and a diastema is present between the central incisors. A midline cleft with an upward titled premaxilla can exist with broadening of the nasal septum and nasal bone.

The No. 1 cleft begins at the Cupid’s bow. The common cleft of the lip is an example of this malformation. The fault continues cephalad through the dome of the nostril.

The skeletal component of the cleft passes between the central and lateral incisors and through the alveolar process. The perform aperture is violated lateral to the anterior nasal spine, but the nasal septum is spared.

The No. 2 cleft is notably rare. The soft tissue defect also begins at the cupid’s bow, as with a common cleft of the lip. The importation of the nasal alar rim is hypoplastic and drawn upward.
On the maxilla, the cleft crosses the alveolus in the region of the lateral incisor. The perform aperture is divided at its base, but the nasal septum is intact and deviated by the surrounding distortion. A notch is frequently present near the junction of the nasal bone and the frontal process of the maxilla, which is widened.

The No. 3 cleft is a well-known entity that was described by Morian over a century ago. Although he called it an oblique facial cleft, it is commonly called an oro-naso-ocular cleft. As with the No. 1 and No. 2 clefts, it begins at the cupid’s bow; hence any common cleft lip must be inspected closely for more significant structural faults.

The cleft undermines the nasal alar base and continues cephalad to end just medial to the inferior punctum of the lower eyelid. The location coincides with the embryonic junction of the maxillary and frontonasal processes, and therefore this cleft makes embryologic sense. The nasolacrimal drainage system is disrupted and is prone to recurrent infections. The lower canaliculus is malformed beyond repair.

The skeletal disruption can be extensive, especially in the bilateral form. The cleft passes between the lateral incisor and the canine to involve the neighboring alveolus and the secondary palate. The lateral portion of the perform aperture is invaded, and the medial wall of the maxillary sinus is lacking. The frontal process of the maxilla is interrupted as the cleft terminates in the lacrimal groove. Thus, a confluent cavity is formed composed of the mouth, nose, maxillary sinus, and orbit.

The No. 4 is an oro-ocular cleft, unlike the first three, begins lateral to the cupid’s bow and skirts around the nose to end in the lower eyelid medial to the punctum. The nose is basically intact but is secondarily distorted by the surrounding hypoplasia; the alar base is deflected upward. Bilateral forms
tilt the shortened nose upward. A functional eye is usually present, but anophthalmia and intermediate grades of microphthalmos can occur.

The osseous component is less extensive than the number 3 cleft. It starts between the lateral incisor and the canine. The perform aperture is spared as the cleft courses cephalad into the medial portion of the inferior orbital rim. A confluence exists between the orbit, maxillary sinus, and oral cavity on each side.

The No. 5 cleft is rare. It begins more laterally than the preceding clefts by originating just medial to the oral commissure. The fault traverses the cheek to enter the lower eyelid in its middle third. The upper lip and lower eyelid are drawn toward each other.

The path of the cleft on the facial skeleton is also distinct. It begins in the region of the premolar teeth and travels lateral to the infraorbital foramen. Recall that the No. 4 cleft passes medial to the foramen; thus, this landmark serves to distinguish the two clefts. The orbit is penetrated in its lateral third causing prolapse of its contents into the maxillary sinus.

The No. 6 cleft represents an incomplete form of the Treacher Collins anomaly. Patients with Nager syndrome possess the same cleft features. A mild coloboma of the lateral third of the eyelid marks the cephalic end of the cleft. The palpebral fissures have an antimongoloid slant. The zone of hypoplasia then descends toward the angle of the mandible leaving the zygomatic eminence with poor soft tissue coverage. The oral commissure is not involved.

On the facial skeleton, the cleft is centered on the zygomaticomaxillary suture and involves the lateral third of the inferior orbital rim. The zygomatic arch remains intact.
Various names have been assigned to the relatively common No. 7 facial cleft, the most popular of which are hemifacial microsomia, craniofacial microsomia\textsuperscript{5}, first and second branchial arch syndrome and otomandibular dysostosis\textsuperscript{8}. Closely related is the Goldenhar’s syndrome with its addition of an epibulbar ocular dermoid and vertebral abnormalities. \textsuperscript{(2)}

\textbf{DEVELOPMENTAL ANATOMY}

Central to facial cephalogenesis is the natural behavior of the cephalic neural crest of the embryo, which involves extremely complicated morphogenetic processes. The human head is the site of enormous evolutionary changes superimposed upon a most conservative set of fundamental structures subserving olfactory, visionary, respiratory, gustatory, masticatory, and auditory functions. The facial regions that house the organs of these functions develop by ontogenetic neural crest migration and proliferation and ectomesenchymal interaction into five prominences (the median frontonasal and the paired maxillary and mandibular prominences) that are patterned upon a primitive phylogenetic metamerism. The early fate map of the initially dorsally located neural crest is determined by the hindbrain’s segmented rhombomeres; these induce mesenchymal somitomeres that parallel the segmentation of the neural anlage. This metamerism is reflected in neural crest migration to specific facial prominences and pharyngeal arches that lay the foundations of facial morphology.

The subsequent swellings, meldings, migrations, and fusions of the prominences, arches, and their contents of skeletal cartilages, mesenchyme, and neurovascular bundles is a cascading set of events, critically timed, to transform the faceless front of the forebrain into human physiognomy.
Morphogenetic movements, mergings, and fusions of the prominences account for the rapidly changing profile of the embryonic face. The underlying brain and the overlying face are inextricably intertwined. The extraordinarily precise proportioning of the minute mesenchymal masses and their delicate epithelial surfaces is mediated by a seething biochemical sac of substrates and enzymes and growth [actors that are translated into a visible phenotypic expression of the underlying unseen but dictating genotype. Thus are the inherited traits of eons of evolution, embedded in the genes, transformed into recognizable formations of familial characterization—the eyes, the nose, the lips of the faces of the father and mother, reflected in the neonate.

The delicate maneuverings of the intertwined embryonic tongue and palatal shelves ensconced within the tiny stomadeum (the shallow pit that foreshadows the mouth) is determined by the intrinsic mechanical forces created by the expansion of proliferating and migrating mitotic masses, hydration of the extracellular matrix, and tissue turgor contained within swelling epithelial sacs. These internal perturbations of mesenchyme are further orchestrated by external mechanical factors that impact upon formation of the floating fetus. The first movements of the primary meckelian jaw joint (well before temporomandibular arthrogenesis) and the lifting of the head, both dependent upon preceding myogenesis and neurogenesis, are essential to the elevation of the vertical for intact palatal formation. The initially vertical floppy flaps are transformed into horizontal rigid shelves by ossification. Failure of any one of these precisely timed events creates the condition to which this journal is dedicated the cleft palate and all its associated anatomic, pathologic, psychological, social, and therapeutic concerns. These events of the first few weeks of intrauterine life are the most
important occurrences predicting one’s entire extrauterine life. What is laid down initially to form one’s face dictates one’s entire future, for one’s face is indeed one’s fortune.\(^3\).

The branchial arches are largely responsible for the formation of the face, neck, nasal cavities, mouth, larynx, and pharynx. The first branchial arch contributes to the maxillary and mandibular prominences and the anterior portion of the auricle. The paired maxillary and mandibular prominences derived from the first arch form the lateral and caudal borders of the stomodeum (primitive mouth), respectively. The frontonasal prominence, a central process formed by the proliferation of the mesenchyme ventral to the forebrain, forms the cranial boundary of the stomodeum. Although the frontonasal prominence is not a branchial arch derivative, it merges with first arch derivatives to form an integral part of facial development. These five facial prominences (two paired and one unpaired) bordering the stomodeum are responsible for the development of adult facial features. The quadrate cartilage within the maxillary prominence forms the incus and the greater wing of the sphenoid bone, while the maxilla, zygoma, and squamous portion of the temporal bone form from membranous ossification within the maxillary prominence. Similarly, Meckel’s cartilage within the mandibular prominence forms the malleolus and provides a template for development of the mandible. As mentioned earlier, however, only the mandibular condyles develop from endochondral ossification of Meckel’s cartilage. The remainder of the cartilage precursor to the mandible serves only as a template for ossification, and is obliterated when the body and ramus of the mandible develop from membranous ossification within the mandibular prominences.
Although the five facial prominences that border the stomodeum are separated externally by grooves, the mesenchyme of all five is continuous. As a consequence mesenchymal migration may occur freely between the facial prominences. Facial development largely occurs between the fourth and eighth weeks, and the face has a clearly human appearance by age 10 weeks. Bilateral thickenings of the surface ectoderm, called nasal placodes, develop at the inferior, lateral aspect of the frontonasal prominence by the end of the fourth week. With further elevation of the margins of the nasal placodes the sides develop into the medial and lateral nasal prominences, respectively, while the depressed central region of the placodes develops into the nasal pit. The nasal pits, initially in contact with the stomodeum, are precursors of the nares. The paired maxillary prominences continue to migrate medially, also affecting medial migration of the medial and lateral nasal prominences. Fusion of the medial nasal, lateral nasal, and maxillary prominences produces continuity between the nose, the upper lip, and the palate.

Fusion of the medial nasal and maxillary prominences results in separation of the nasal pits from the stomodeum and subsequent separation of the oral and nasal cavities. Merging of the medial nasal prominences forms the philtrum and Cupid’s bow region of the upper lip, the nasal tip, the premaxilla and primary palate, and the nasal septum. The lateral nasal prominences form the nasal alae. The nasolacrimal groove develops as a furrow separating the lateral nasal prominence from the maxillary prominence. Rods of epithelial cells sink into the subjacent mesenchyme to line this groove, which extends from the medial aspect of the developing conjunctival sacs to the external nares. The resultant nasolacrimal duct becomes patent only after birth. Lack of fusion of the lateral nasal and
maxillary prominences results in an oblique facial cleft or a persistent furrow that tracks the nasolacrimal groove. This is referred to as a number 3 cleft by the Tessier classification.

As previously stated, adult facial form is largely due to the development of the five facial prominences. Merging of the paired mandibular prominences produces the lower jaw, lower lip, lower cheek, and chin regions of the face. These are the first parts of the face to take on definitive form. The maxillary prominence accounts for the major portion of the upper lip (excluding the philtrum) and the upper cheek regions. The frontonasal prominence forms the forehead and nasal dorsum and the derivatives of the medial and lateral nasal prominences previously discussed.

A unilateral cleft lip results from failure of fusion of the medial nasal prominence and maxillary prominence on one side. A bilateral cleft lip results from failure of fusion of the merged medial nasal prominences with the maxillary prominence on either side. As a result, the merged medial nasal prominences (globular process) are often quite prominent, as they are not restrained by attachment to the maxillary prominences laterally. This is manifest at birth, as in a patient with a complete bilateral cleft lip and anterior overprojection of the premaxilla and prolabium.

Laterally, the maxillary and mandibular prominences join at the lateral commissure of the mouth. Failure of union of these prominences produces macrostomia, due to a cleft of the lateral commissure). This is a number 7 facial cleft by the Tessier classification12. Another rare facial cleft that has been described is a median cleft lip), which is due to incomplete merging of the medial nasal prominences in the midline and is usually associated with deep midline furrowing of the nose, resulting in various degrees of nasal bifidity. This condition is also described as a number 0 cleft by the Tessier
classification. Failure of the mandibular prominences to unite in the midline produces a central defect of the lower lip and chin, which is referred to as a number 30 cleft by the Tessier classification. The palate represents both the frontonasal and maxillary prominences, with the interface between the two becoming the junction between the primary and secondary palates. The median palatine process is derived from the frontonasal prominence and is formed from the merging of the medial nasal prominences. The lateral palatine processes are derived from the maxillary prominences. All three elements are initially widely separated due to the vertical orientation of the lateral palatine processes, which are located on either side of the tongue. During the eighth week the orientation of the lateral palatine processes alters from vertical to horizontal to initiate their fusion. This transition occurs within hours, although the exact mechanism for the transition is not well understood. During this process the mandible becomes more prognathic, thereby allowing more room for partitioning of the oronasal chambers without interference by the tongue. The medial edge epithelium of the palatal shelves degenerates in a process referred to as “programmed cell death,” permitting mesenchymal coalescence of the palatal shelves. However, the epithelium of the oral and nasal surfaces of the palatal shelves remains intact during this process). Fusion then occurs between the lateral palatine processes and the median palatine process. The nasal septum, a downgrowth from the merged medial nasal prominences, also fuses with the developing palate at its nasal surface. The median palatine process subsequently gives rise to the premaxillary portion of the maxilla and forms the primary palate; the lateral palatine processes give rise to the secondary palate. Ossification occurs in the primary palate and the anterior portion of the secondary palate to form the hard palate, while the posterior portion of
the secondary palate does not undergo ossification and remains the soft palate. A palatine raphe can be identified in the adult soft palate, indicating the line of fusion of the lateral palatine processes.

The embryologic basis of cleft palate is failure of the mesenchymal masses derived either from the maxillary prominences (i.e., the lateral palatine processes) or from the medial nasal prominences (i.e., either the median palatine process or the nasal septum) to meet and fuse with each other. The types of clefts seen in clinical practice help one to better understand the embryologic development of the palate. Clefts of the primary palate occur anterior to the incisive foramen and result from failure of the mesenchymal masses in the lateral palatine processes to fuse with those in the median palatine process. Clefts of the secondary palate occur posterior to the incisive foramen, and result from failure of the mesenchymal masses in the lateral palatine processes to fuse with each other and with the nasal septum. Clefting of either the primary or secondary palate can be complete or incomplete, depending on the degree of fusion that occurred during embryonic development.

During the sixth week of development, the nasal pits form from the nasal placodes. The nasal pits deepen as a result of the formation of the medial and lateral nasal prominences, eventually forming nasal sacs. The nasal sacs are initially separated from the oral cavity by the oronasal membrane. Once this membrane ruptures, the oral and nasal cavities communicate via the primitive choanae (foramina). These foramina initially lie behind the primary palate, then shift posteriorly to the junction of the nasal cavity and pharynx after the formation of the secondary palate. The fusion of the lateral palatine processes and the nasal septum are responsible for this final location of the choanae. (4)
Etiology

Numerous theories have been proposed for the etiology of clefting, it is believed that delay in elevation of the palatal shelves from vertical to horizontal is part of the underlying mechanism. Pierre Robin sequence, consisting of micrognathia, glossoptosis, and cleft palate, is one of the best illustrations of the mechanism that is proposed to occur between the tongue and the palatal shelves. With severe micrognathia, the tongue occupies a relatively greater proportion of the developing oropharynx, resulting in glossoptosis relative to the position of the small mandible. The vertically oriented palatal shelves, located on either side of the tongue, may be delayed in their transition to a horizontal position during the eighth week of development due to mechanical interference from the tongue. For this reason, Pierre Robin is described as a sequence and not a syndrome, as it is attributed to the sequence of events that occur during embryonic development. (5)

Genetics factors:

Epidemiological and family studies have suggested that both environmental and genetic factors play a role in cleft lip and palate etiology. However, which genetic and environmental factors are important is still largely an enigma. This has been highlighted in recent reviews concerning both environmental) and genetic risk factors. Cleft lip and palate are among the most common birth defects in the world. Seventy percent of these defects occur as isolated abnormalities. They show up in as many as 1 in 500 births worldwide, but on Margarita Island, the rate is nearly three times as high. Spritz’ team sought a single gene behind the island’s syndrome. The group
suspected that the condition would provide a simple model for the more wide-spread problem of cleft lip and palate. By comparing unaffected people to afflicted islanders and others with a similar syndrome, the team narrowed its gene search to an area on chromosome 11 and eventually to a gene called PVRL1. All islanders with the syndrome had mutations of this gene, which normally encodes a cell surface protein, nectin-1. Spritz’ team reports that in mouse embryos, nectin-1 aids development of the palate, teeth, and skin—the same tissues altered in the affected islanders.

In people, nectin-1 also plays a role in herpesvims infections. “[The virus] uses it like a handhold,” Spritz says. “Herpesvirus basically grabs the sugar on nectin-1 and holds on long enough to punch a hole in the cell and get in.” Spritz says that people with one copy of the mutation might be deficient in nectin-1 without showing the syndrome. They may be at lower-than-normal risk for herpesvirus, an advantage that may explain why the mutation has persisted.

Christensen and Fogh-Andersen (1993) summarized the analyses of Danish CLP and CP twin cases born in the 20th century (130 twin sets). For both CLP and Cp, the probandwise concordance rate is approximately 60% for monozygotic twins, while the corresponding number for dizygotic twins is 10% or less (depending on time period). Based on these data, heritability estimates of approximately 70% or higher are obtained both when the liability threshold model is used (Smith, 1974) and when newer biometrical models are implemented (Neale and Cardon, 1992). These findings indicate that genetic factors play a major role in the etiology of CLP and CP but environmental and/or stochastic factors are also involved.

Some congenital malformations (acardia) only Linkage Studies
Eiberg et al. (1987) studied 58 Danish pedigrees with nonsyndromic CLP using 42 non-DNA polymorphic marker systems, and these authors were the first to find evidence of linkage on Op using the factor 13A gene. Later, Davies et al. (1995) and Carinci et al. (1995) also found suggestions of the involvement of Op in the CLP etiology. Although negative studies have also been published, a primary CLP gene on op is considered to be likely (Murray, 1995). Currently, DNA samples from affected sibling pairs and other relatives born throughout the 20th century in Denmark are collected in order to perform linkage analyses.\(^6\)

The parental craniofacial morphology in orofacial clefting (OFC) has been shown to differ from that of the non-cleft population when evaluated using conventional cephalometric analyses comprising a variety of linear, angular, and area measurements. In spite of this, the shape of the parental craniofacial complex is of greater importance in the search for the morphogenes involved in orofacial clefts.\(^7\)

**Prenatal factors:**

Among those who took 4-5 mg/day of supplementary folic acid plus a diet containing 214 [micro]g/day of folate, the risk of cleft lip/palate was 80% lower than among those who did not use supplements and consumed less than 150 mg/day of dietary folate.\(^6\) Supplement users who had a slightly higher dietary level of folate-236 [micro]g/day--had a 66% drop in the risk for deformed lip or palate, compared with non-supplement users who consumed less than 150 [micro] g/day of dietary folate.

In a population-based case-control study conducted by the California Birth Defects Monitoring Program, 731 mothers of infants with orofacial clefts born between 1987 and 1989 and 734 mothers of normalformed control infants born during the same period were interviewed. Women were
asked about their use of various types of vitamin supplements and cold cereal (many brands of which are fortified with folic acid) during the periconceptional period.

Women who had used multivitamins containing folic acid during the period from one month before conception through two months after had a reduced risk of bearing a child with an orofacial cleft. The degree of risk reduction ranged from 25 to 50% depending on the type of cleft. Among women who did not take supplements, daily consumption of cereal containing folic acid was also associated with a reduced risk of orofacial clefts. These findings indicate that women who take folic acid-containing multivitamins periconceptionally have a decreased risk of bearing a child with an orofacial cleft. However, it is impossible to be certain from these observational data whether this effect is due to folic acid, to some other component of the multivitamin supplements, or to healthy behaviors associated with multivitamin use\(^{(8)}\).

One case-control study about myo-inositol, glucose and zinc status as risk factors for non-syndromic cleft lip with or without cleft palate in offspring. This study demonstrates for the first time that zinc and myo-inositol are important in the aetiology of cleft lip and palate.\(^{(9)}\)

When maternal smoking was considered together with certain genetic background, the combined effect was more significant. Furthermore, van Rooij et al\(^{40}\) found that maternal glutathione s-transferase θ-1 (GSTT1) genotype, combined with smoking, could significantly increase the risk of cleft lip and palate (odds ratio=4.9). And Beaty et al\(^{41}\) reported that maternal smoking and infant MSX1 genotypes contributed to an elevated risk for CLP by 7.16 times. Heavy maternal drinking, apart from causing
foetal alcohol syndrome, increases the risk of CLP. Munger et al42 showed that maternal drinking posted an increased risk from 1.5 to 4.7 times for CLP in a dose-dependent manner. The results were supported by Shaw and Lammer43 that mothers who consumed more than five drinks per occasion had a 3.4 times the risk of CLP developing in the offspring. Low-level alcohol consumption, however, did not seem to increase the risk of orofacial clefts.44 The link between alcohol consumption and genotypes on the risk of Cleft lip and palate has yet to be shown(10).

Antepartum exposures to benzodiazepines have been associated with teratogenic effects (for instance, facial cleft, skeletal anomalies) in some animal studies not others. Early case-control studies in humans found that maternal benzodiazepine exposure increased the risk of fetal deformed lip and deformed palate.78 Subsequent reports implicated benzodiazepines as the cause of major malformations” and abenzodiazepine syndrome similar to fetal alcohol syndrome led to considerable controversy surrounding the use of benzodiazepines Data taken from cohort studies showed no significant association between benzodiazepines taken during the first trimester and either major malformations or malformations of the oral cleft alone. However, data from case-control studies showed a small but significant increased risk for these events. This finding may reflect the substantially higher sensitivity of case-control studies to examine the risk of specific malformations or it may be chance. (11)

PATHOPHYSIOLOGY

Discussions of the pathogenetic role of the tongue in secondary palatal clefting have focused on whether the tongue produces these manifestations or if the tongue responds to an abnormal developmental environment.
Ferguson (1978) has suggested that the disposition of the tongue is a primary factor for palatal shelf elevation and subsequent formation of cleft palate. Diewert (1982) suggested that anterior growth of Meckel’s cartilage through a genioglossus muscle connection results in an anterior displacement of the tongue which, in turn, allowed palatal shelf closure. Humphrey (1969) proposed that fetal mouth opening reflexes that also retract and depress the tongue resulted in oral cavity pressure changes producing palatal shelf closure. Ferguson (1978) concluded that in the laboratory rat, forces intrinsic to the palatal shelves produced closure, but that this event was facilitated by a repositioning of the normal sized tongue and a guiding and buttressing by sections of the anterior and posterior nasal septum. Moss (1971) suggested as part of the Functional Matrix Theory that the growth size and histology of the tongue is a midfacial control mechanism, which determines the growth of the surrounding orofacial elements. Accordingly, an enlarged tongue as a capsular matrix induces components of the oral cavity and mandible to exceed normal size. This role of the tongue would not be demonstrated in normal orofacial growth patterns. Diewert (1980) has noted that tongue development is secondary to palatal clefting using the extra space provided by the cleft to enlarge. Diewert (1986) reviewed the experimental (teratologic) literature relative to human secondary palate formation and found that in most of the studies, a direct relationship between the tongue and cleft palate formation was suggested; Diewert noted that for humans there is no direct evidence for the anomalous features at the time of palatal development.

It was observed that fetal specimens with cleft palate (CLP), from a postmenstrual age of 8 to 21 weeks, exhibited absolute (Siegel et al., 1987) and relative (Kimes et al., 1988) larger sizes of the nasal septum. Such
hyperplasticity observed in the nasal septum, if present in the tongue prior to palatal shelf elevation at about 10 weeks postmenstrual age, would represent a viable hypothesis for a pathogenetic relationship to CLP. In the present investigation, the hypothesis that the size and growth rate of the length and volume of the 8 to 21 week fetal tongue are greater in CLP compared to normal specimens was tested. An attempt was made to determine if these characteristics are present in the earliest 8 to 12 week age category. These findings indicate that CLP tongue size is, at the least, a dysmorphogenetic correlate of secondary palatal clefting, but a comparative look at other studies regarding growth increase of the nasal septum may offer the tongue as a possible instigator of CLP’ phenomena. Mooney (1986) and Siegel et al. (1987) showed that nasal septum volume exhibited 1.34 times more increase in normal and not CLP specimens, a condition similar to the maximum increase of the CRL. These observations are almost exactly the reverse of the results of maximum tongue volume increase from the present investigation. It may be that the CLP tongue does not follow the growth trends of the other midline structures and has realized a prepalatal shelf elevation growth episode. The present investigation has demonstrated that the volumetrically enlarged tongue is present in the earliest 8 to 12 week age category.\(^{(12)}\)

**Epidemiology**

The international incidence of cleft lip and palate is one in 600 (1:600) live births, and 1:1000 live births for isolated cleft palate. The incidence
increases in Oriental groups (1:500) and decreases in the black population (1:2000). The highest incidence reported for cleft lip and palate occurs in the Native American tribes of Montana, USA (1:276).

Although cleft lip and palate is an extremely variable congenital abnormality, several distinct subgroups exist, namely cleft lip with/without cleft palate (CLP), cleft palate alone (CP) and submucous cleft palate.

- cleft lip alone — 15 per cent;
- cleft lip and palate — 45 per cent;
- isolated cleft palate — 40 per cent.

Cleft lip/palate predominates in males. While cleft palate alone appears more common in females. In unilateral cleft lip, the deformity affects the left side in 60 per cent of cases (13).

The number of children born with facial clefts in Denmark varied from 20 in 1977 to 51 in 1992. Related to the number of live births, this gave a range of 1.2 to 2/1000 live births and a mean incidence of 1.7/1000 live births.

Of the total 616 infants, 163 cases (26%) had cleft lip, 239 cases (39%) had isolated cleft palate, and 214 cases (35%) had both cleft lip and palate. Of these 214 infants with complete clefts, 143 were unilateral and 71 were bilateral cleft lip and palate. The expected frequency of malformations in a population of infants without cleft malformations cannot be reliably estimated because some types of malformations (eg, recognized syndromes, facial and endocrine system anomalies) are not reliably registered by the Malformation Registry. One hundred twenty-seven (21%) of the 616 infants had associated malformations which required follow-up and/or treatment. The ratio between boys and girls was similar in both groups (with or without associated malformations, 58% boys and 42% girls (74 boys, 53 girls). Thirteen (8%) of the 163 cases born with isolated cleft lip had associated
malformations, 53 (22%) of the 239 children born with isolated cleft palate had associated malformations, and 60 (28%) of the 214 cases with complete clefts had associated malformations. In children with complete clefts, complete unilateral cleft lip and palate was associated with other malformations in 24% whereas complete bilateral cleft lip and palate was associated with other malformations in 35% \(^{(14)}\)

Children with higher birth order are more likely to have CL/P and CP with odds ratios increasing with birth order to a peak of 3.0 in children birth order "4 or more." Results are not different when isolated and syndromic cases are combined\(^{(15)}\)

In sudanese patients a previous limited study showed that; of all facial clefts there was no significant different between males and females. Of 100 cleft patients there were ten types of cleft lip and cleft palate, the highest percentage (26.0%) was presented by unilateral left cleft lip without cleft palate followed by isolated cleft palate (12.0%), bilateral cleft lip with cleft secondary palate (11.0%), unilateral right cleft without cleft palate (10.0%), unilateral left cleft with cleft primary palate(10%), unilateral right cleft with cleft secondary palate (10%), unilateral left cleft with cleft secondary palate (9%), bilateral cleft without cleft palate(7%), bilateral cleft with cleft primary palate (3%) and unilateral right cleft with cleft primary palate (2%). The percentages of right- sided cleft, left sided cleft and bilateral cleft were (22%), (45%) and (21%) respectively \(^{(16)}\)

The WHO registry meeting reported an incidence of 3.54 per 10000 births in South Africa. \(^{(17)}\)

Population-based data on the incidence of cleft lip and palate were obtained from birth registry information in northern Pakistan. A total of 117 cases
from 61,156 live births reported were identified. The incidence for cleft lip and/or cleft palate was 1.91 per 1000 births (one per 523 births). Cleft lip alone (42 percent) was noted more frequently than isolated cleft palate (24 percent) and combined cleft lip and palate deformities (34 percent). Boys were more commonly affected by cleft lip and cleft lip with cleft palate, whereas girls predominated in the isolated cleft palate cases. Consanguineous marriages were observed in 32 percent of parents versus 18 percent in matched controls. Only 32 percent of cleft mothers received formal prenatal counseling, monthly examinations, and regular laboratory testing during the entirety of the pregnancy. Nutritional and vitamin supplements were given to only 28 percent of mothers of cleft children versus 59 percent in matched controls\(^{18}\).

In spite of uncertainties that are well recognized, it is known that submucosal clefts are relatively rare. Weatherly-White et al. (1972) identified only nine submucous clefts in a survey of 10,836 school-aged children (0.08%). However, they included only children who had all three characteristics of the condition. These characteristics can be detected by visual and tactile examination and do not identify related and equally disabling conditions such as the occult submucous clefts and various motor disabilities. \(^{19}\)

Previously, examination of various populations has been reported by a number of investigators. Meskin, Gorlin, and Lsaacson (1964) reported finding 1.44 percent of 9,701 adult Caucasians they examined had bifid uvulas. Examination of 944 Navajo Indian school children revealed 11 percent had some degree of cleft uvula (Jaffe and Blanc, 1970). Shprintzen et al. (1985) performed intraoral examinations of 2,500 patients, ages 2 to
19, seen in a pediatric practice and reported finding 3.3 percent had some
degree of bifid uvula. Race of the patients was not specified.\textsuperscript{(20)}

**Associated anomalies**

Analyzing data on 5331 people up to age 55 from the Danish cleft
lip and palate register, Christensen and colleagues (p 1405) found that those
with cleft lip and palate or with cleft palate alone were more likely to have
died than the rest of the population or than people with cleft lip alone. The
risk of suicide and all causes of death was higher in people with cleft lip and
palate; mortality due to cancer was marginally higher.

When studying the genetic epidemiology of nonsyndromic CLP, there is
no doubt that monogenic diseases such as Van der Woudes syndrome or
chromosomal diseases such as trisomy-18 should be deleted from the
analyses. There is also general agreement to delete CLP cases with other
major anomalies that co-occur more frequently than expected by chance
(e.g., neural tube defect). However, it is considerably harder to make
uniform ascertainment and classification of minor and more subtle
associated anomalies.

A consistent finding is that the frequency of associated anomalies is
higher among CP cases (usually in the range of 13% to 50%) than CLP cases
(typically in the range of 2% to 13%) (Gorlin et al., 1990). The wide range
in the reported frequency of associated anomalies is partially due to
differences in the definition of associated anomalies, how long after birth
and how carefully the individuals are examined, and the selection of
patients. Associated anomalies are particularly problematic in studies
covering long time periods since the ability to diagnose
syndromes/associated anomalies and the survival of multimalformed
children have changed considerably over time.
The recognition of the velo-cardio-facial syndrome (VCFS) illustrates the problem. Patients with velo-cardio-facial syndrome often display only CP and a minor heart defect and/or learning disability, and many such cases are most certainly undiagnosed (Goldberg et al., 1993; Brondum-Nielsen and Christensen, 1996). Velo-cardio-facial syndrome is associated with a deletion at 22q11, and an inclusion of velo-cardio-facial syndrome cases in a study of nonsyndromic CP will probably reduce the power of the study; the rationale behind having a very narrow definition of nonsyndromic CLP (no other minor or major anomalies) is to reduce etiological heterogeneity.

There are also drawbacks of having a very narrow definition of nonsyndromic clefts if the definition of minor anomalies includes conditions that occur at a rather high frequency in the general population (e.g., learning disabilities), the CLP cases without any such conditions might represent an otherwise very healthy group. Furthermore, using the very narrow definition of nonsyndromic CLP increases the sample size problem discussed below. It also seems likely that a number of environmental and genetic factors could affect both syndromic and nonsyndromic CLP cases, i.e., that syndromic and nonsyndromic case have some common etiological factors. Therefore, as long as the delineation of strictly nonsyndromic CLP cases depends strongly on the length and intensity of the follow-up, the most reasonable approach will be to obtain as much information on associated anomalies as possible and afterwards to perform the analyses with and without the CLP cases with minor associated anomalies (21).

Microform cleft lip is an anomaly consisting of a paramedian scar in the upper lip with the appearance of a healed cleft lip. Microform cleft lip is very unusual, and the only series report in the literature gives a rate of 0.06/10,000 live births. Microform cleft lip is often associated with an
ipsilateral notch in the vermilion border of the upper lip that was not present in our patient and a collapsed nostril that was present in our patient. Both of these features are further evidence of a clefting process.

Castilla and Martinez-Frias (1995) reported 25 cases of microform cleft lip. Eighteen were isolated, five were associated with hydrocephalus, one was associated with vertebral, anal, cardiac anomalies, tracheo-esophageal fistula, renal, and limb anomalies, and one infant had an atypical oblique facial cleft with a single umbilical artery. The majority were found on the left side. In the same series, the majority were males. This is also the case with deft lip, of which microform cleft lip seems to be a variant.

It is speculated that microform cleft lip may result from the defective fusion of the frontal nasal and maxillary processes before week 7 of embryonic life or from a spontaneously repaired open deft lip later on in gestation. A familial predisposition has been proposed.

The association between cleft lip, cleft palate, or both with respiratory distress is better referred to a pediatric cardiologist if possible (22).

Clinical picture

The parents usually seek medical advice for one or more of the following:

1- The unsightly appearance of a cleft lip.

2- Difficulties in breast feeding.

3- Ear or respiratory infections.

4- Speech and hearing problems.

Management

Shortly after birth, the infant with a cleft is seen by a paediatrician, a surgeon, a nurse coordinator, and an orthodontist. The baby’s parents are instructed about feeding, and presurgical orthodontics is begun with the goal
of performing surgical lip repair and gingivoperiosteoplasty at 3 months of age. Palatoplasty may be performed at 11–12 months of age. Palatoplasty at this age results in improved speech development and has a low likelihood of interfering with facial growth. \(^{(23)}\)

Presurgical orthodontic treatment is initiated in the first or second week following birth, with the maximum response occurring during the first six weeks.

The initial lip procedure is deferred until the patient is 10 to 12 weeks of age. Alveolar closure is also performed when the segments are ideally aligned and <2 mm apart. Closure is accomplished with local mucoperiosteal flaps rotated from the alveolar segments (not the vomer). Bone grafts are not employed with early closure of the alveolus. If collapse is present or the gap is too wide, alveolar closure is deferred.

Closure of the residual hard palatal cleft is accomplished when the patient is approximately 18 months of age. When alveolar closure is not completed at the initial lip procedure, a definitive two-layer closure of the alveolus with cancellous bone grafting is performed between 7 and 8 years of age. The timing of this closure is mitigated by presurgical orthodontic treatment to align the segments and the guideline of obtaining surgical closure and bone grafting before eruption of the permanent canine teeth. Correption of the nasal deformity in unilateral clefts is coupled with the rotation advancement repair. Septal repositioning and nasal osteotomies are deferred until late adolescence unless the deformity is severe, in which case they are performed concomitantly with alveolar cleft closure at 7 to 8 years of age. \(^{(24)}\)

Complications of cleft palate repair include bleeding, respiratory obstruction, infection, dehiscence and fistula formation\(^{11,12,18}\). Significant
bleeding is rare, but it may require return to the operating room for exploration and hemostasis. Respiratory obstruction is also rare in the absence of excessive bleeding, but it may be life threatening. The airway should be monitored carefully in the recovery room and only after adequate assessment should the baby be transferred to the floor. Oxygen saturation monitors may be employed on the floor or the patient may be monitored in an ICU setting if the airway is tenuous. Infants with Pierre Robin Sequence or other congenital anomalies affecting the airway either directly or indirectly are at highest risk for airway problems.

Palatal fistulas may present as asymptomatic holes or may cause such symptoms as speech problems and difficulties with dental hygiene.

Disturbances of facial growth may result from palatal surgery. Decreased maxillary width and the resulting cross bite are common abnormalities in clefts and are managed by orthodontic maxillary expansion with a fixed appliance. (25)
Objectives

The objectives of this study are:
1. To study different patterns of cleft lip and cleft palate and their distribution among the affected patients.
2. To study the possible familial factors among the affected population.
3. To study the possible prenatal factors implicated in cleft formation.
CHAPTER TWO
Patients and Methods

Study Design:

This is a descriptive study conducted in Khartoum State hospitals during the period from March 2004 to March 2005, to study the patterns of cleft lip and cleft palate.

Study area:

Mainly in Soba University Hospital, The Dental Teaching Hospital and Omdurman Teaching Hospital; all are in Khartoum State, Sudan. These are the hospitals with reconstructive surgical units where most of cleft lip and cleft palate cases from different parts of Sudan are referred.

Study population:

Patients with cleft lip and palate or cleft palate who were seen in the surgical units in these hospitals.

Sampling:

Patients were included consecutively as they attend to the referred surgical clinics. The number of patients included in the study was 65 patients presented and treated at these hospitals.

Data collection:

A questionnaire was designed including the variables under study (appendix 1). The questionnaire generally is composed of four parts. The first part includes general data about the patient such as age, sex and
residence. The second part deals with the clinical type of cleft and associated anomalies. The third part investigates the family history related to the cleft. The forth fourth part investigates the prenatal and related history. Data was collected by direct interviewing the parents or the patient if possible, clinical examination, and filling the questionnaire prepared.

**Data analysis:**

Data was analyzed using computer analysis by the SPSS ® program. A descriptive analysis was chosen. Tests of significance were used where appropriate, (mainly X 2 test) then results were gathered according to the objectives of the study.

Results were presented in tables and graphical figures designed using Microsoft Excel® program
CHAPTER
THREE
Results

The sample contained 65 patients, 29(44.6%) females and (55.4%)36 males. Table (1). Twenty seven (41.5%) patients were below 2 years of age and38(68.5%) were more than 2 years old .Figure(1)and(2). Places of residence of the patients were; 31(47%) in Khartoum area, 24(36.9%) in central Sudan, 4(6.2%) in western Sudan, 4(6.2) in northern Sudan and 1(1.5%) in southern Sudan Figure( 3). The patients were from 37 different tribes Figure (4).

In the study sample, there were 7(10.8%) cases of isolated cleft lip, 8(12.3%) cases of isolated cleft palate and 50(76.9%) case of both cleft lip and palate Table(2) . The cleft lip and palate (CLP) patients were57 (87.7%) patients; 31 males and26 females, while the cleft palate alone (CP) were 8(12.3%); 5males and 3 females. Table (3).

In the cleft lip and palate (CLP) group the isolated lip cleft were7 (12.3%), while cleft of the lip and primary palate were 13(22.8%) ,and clefts of the lip with cleft of the primary and secondary palate were37(46.9%) of cleft lip and palate patients Table(4) . Twenty seven (27(47.4) patients had left sided clefts(14 males and 13 females),11(19.3%)had right sided cleft(7 males and 4females),18(31.6%)had bilateral cleft (9 males 9 females), and 1(1.8%) patient had median cleft(male) Table(4 ), Figures (5) and (6) . The cleft was left complete in 25(43.9%) patients, left incomplete in 2(3.5%) patients, right complete in 10(17.5%) patients, right incomplete in 1(1.8%) patient, bilateral complete in 15(26.5%) patients, bilateral incomplete in 3(5.3%) patients and median in 1(1.8%) patient of all the57 patients. Figure(7).
In the cleft palate (CP) group 2(25%) patient had a complete cleft of the secondary palate (1 male, 1 female), 6(75%) patients had cleft of the soft palate (2 females and 4 male) and none of the patients had a submucous cleft (Figure 8).

Of all the 65 patients, no patient had other orofacial clefts, but 5(7.7%) patients had other congenital anomalies; 3(4.6%) of them were cleft lip and palate (CLP) patients, 1(1.5%) had cardiac anomaly, 1(1.5%) had craniofacial anomalies and 1(1.5%) had limbs anomaly. The remaining 2(3.1%) patients had cleft palate (CP); one of them had limbs anomaly and the other had both craniofacial and limbs anomalies Tables (5) and (6).

Only 6(9.2%) patients had family history of cleft lip or palate Table (7). They were all patients with cleft lip and palate (CLP) Figure (9). Of all parents of the 65 patients, 26(40.0%) were cousins, 15(23.1%) were far relatives and 24(36.9%) were not relatives. Figure (10). The parents of 23 patients with cleft lip and palate (CLP) were cousins, 15 were far relatives and 19 were not relatives. The parents of cleft palate (CP) patients were cousins in 3 cases and not relatives in the other 5 cases Table (8).

Regarding the patient’s birth order among the other siblings, 39(60%) of all cases had even birth order number (34 CLP and 5 CP), and 26 (40%) had odd number (23 CLP and 3 CP). Figure (11).

The maternal age when the patient was delivered was below 25 years in 6 (9.2%) cases, all were CLP cases, it ranged from 26 to 30 years in 32(49.2%) cases (28 CLP, 4 CP), from 31 to 35 in 20(30.8%) cases (18 CLP, 2 CP), and 36 and above in 7(10.8%) cases (5 CLP, 2 CP). Table (9).

The pregnancy was normal in 61(93.8%) cases (53 CLP, 8 CP), it was complicated by polyhydramnios in 2(1.3%) cases (both were CLP) and
pregnancy induced hypertension occurred in 2 (3.1%) cases (both were CLP) Table (10) . Figure(12).

There was a history of febrile illness during the first trimester in 15(23.1%) patients Figure(13).

Drugs taken during the first trimester were, antimalarials alone in 7(10.8%) patients, antimalarials and folates in 3 (4.6%) patients, antimalarials and antibiotics in 2(3.1%) patients, antibiotics alone in 5(7.7%) patients, antibiotics with folates in 2(3.1%) patients , folates alone in 10(15.3%) patients and other drugs in 2(3.15%) patients. No history of using anticonvulsants during pregnancy Table (11).

The patients birth weight was normal in 53(81.5%) patients(47 CLP, 6 cp), small in 10 (15.4%) patients (9 CLP , 1 CP) and large in 2(3.1%) patients ( 1 CLP, 1 CP ).Figure(14).
**Table (1).**  
Sex distribution of the sample.  

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
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</tr>
<tr>
<td>Males</td>
<td>36</td>
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<tr>
<td>Total</td>
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Table (2).
Primary types of clefts.

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lip only</td>
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<tr>
<td>Lip and palate</td>
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<td>76.9%</td>
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<td>Palate only</td>
<td>8</td>
<td>12.3%</td>
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<tr>
<td>Total</td>
<td>65</td>
<td>100%</td>
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</table>
Table (3).

Sex distribution according to type of cleft.


<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>CLP</td>
<td>31 (47.7%)</td>
<td>26 (40%)</td>
<td>57 (87.7%)</td>
</tr>
<tr>
<td>CP</td>
<td>5 (7.7%)</td>
<td>3 (4.6%)</td>
<td>8 (12.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>36 (55.5%)</td>
<td>29 (44.65)</td>
<td>65 (100%)</td>
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Table(4).
Types of cleft lip and palate (CLP) according to anatomical site.

<table>
<thead>
<tr>
<th></th>
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<th>Bilateral</th>
<th>Median</th>
<th>Total</th>
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<tbody>
<tr>
<td>Lip only</td>
<td>4(7%)</td>
<td>3(5.3%)</td>
<td>0(0%)</td>
<td>0(0%)</td>
<td>7(12.3%)</td>
</tr>
<tr>
<td>Lip &amp; 1ry palate</td>
<td>4(7%)</td>
<td>4(7%)</td>
<td>5(8.8%)</td>
<td>0(0%)</td>
<td>13(22.8%)</td>
</tr>
<tr>
<td>Lip, 1ry &amp; 2ry palate</td>
<td>19(33.3)</td>
<td>4(7%)</td>
<td>13(22.8%)</td>
<td>1(1.8%)</td>
<td>37(46.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>27(47.4)</td>
<td>11(19.3%)</td>
<td>18(31.6%)</td>
<td>1(1.8%)</td>
<td>57(100%)</td>
</tr>
</tbody>
</table>
Table(5).

Associated congenital anomalies among cleft lip and palate (CLP) cases.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
<th>Percent</th>
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<tbody>
<tr>
<td>Cardiac</td>
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</tr>
<tr>
<td>Craniofacial</td>
<td>2</td>
<td>3.1</td>
</tr>
<tr>
<td>Craniofacial + limbs</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>Limbs</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>None</td>
<td>60</td>
<td>92.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>65</strong></td>
<td><strong>100</strong></td>
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</tbody>
</table>
Table(6).
Occurrence of other congenital anomalies in association with types of clefts.

<table>
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<th>cardiac</th>
<th>craniofacial</th>
<th>limbs</th>
<th>none</th>
<th>craniofacial+limbs</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLP</td>
<td>Count</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>54</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>% of Total</td>
<td>1.50%</td>
<td>1.50%</td>
<td>1.50%</td>
<td>83.10%</td>
<td>87.70%</td>
</tr>
<tr>
<td>CP</td>
<td>Count</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>% of Total</td>
<td>0%</td>
<td>0%</td>
<td>1.50%</td>
<td>9.20%</td>
<td>12.30%</td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>60</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>% of Total</td>
<td>1.50%</td>
<td>1.50%</td>
<td>3.10%</td>
<td>92.30%</td>
<td>100.00%</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi-Square</td>
<td>10.334(a)</td>
<td>4</td>
<td>0.035</td>
</tr>
</tbody>
</table>
Table (7).

Presence of family history of cleft lip or palate in the whole sample.

<table>
<thead>
<tr>
<th>Family history</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td>59</td>
<td>90.8</td>
</tr>
<tr>
<td>yes</td>
<td>6</td>
<td>9.2</td>
</tr>
<tr>
<td>Total</td>
<td>65</td>
<td>100.0</td>
</tr>
</tbody>
</table>
**Table (8).**

Parents degree of relation in the whole sample, (comparing CLP and CP groups).

<table>
<thead>
<tr>
<th>CLEFT TYPE</th>
<th>CLP</th>
<th>Count</th>
<th>not relatives</th>
<th>19</th>
<th>far relativesa</th>
<th>15</th>
<th>cousins</th>
<th>23</th>
<th>Total</th>
<th>57</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count</td>
<td></td>
<td>29.20%</td>
<td></td>
<td></td>
<td>23.10%</td>
<td></td>
<td>35.40%</td>
<td></td>
<td>87.70%</td>
<td></td>
</tr>
<tr>
<td>% of Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLEFT TYPE</th>
<th>CP</th>
<th>Count</th>
<th></th>
<th>5</th>
<th>0</th>
<th>3</th>
<th>Total</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count</td>
<td></td>
<td>7.70%</td>
<td></td>
<td></td>
<td>0%</td>
<td></td>
<td>4.60%</td>
<td></td>
</tr>
<tr>
<td>% of Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total</th>
<th>Count</th>
<th>24</th>
<th>15</th>
<th>26</th>
<th>65</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Total</td>
<td></td>
<td>36.90%</td>
<td>23.10%</td>
<td>40.00%</td>
<td>100.00%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Value</strong></th>
<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi-Square</td>
<td>3.736(a)</td>
<td>2</td>
</tr>
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</table>

(a)
Table (9).

Distribution of maternal age according to type of cleft.


<table>
<thead>
<tr>
<th>Age group</th>
<th>&lt;25</th>
<th>26-30</th>
<th>31-35</th>
<th>&gt;36</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLP</td>
<td>6(9.2%)</td>
<td>28(43.1%)</td>
<td>18(27.7%)</td>
<td>5(7.7%)</td>
<td>57(87.7%)</td>
</tr>
<tr>
<td>CP</td>
<td>0 (0%)</td>
<td>4 (6.2%)</td>
<td>2 (3.1%)</td>
<td>2(3.1%)</td>
<td>8 (12.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>6(9.2%)</td>
<td>32(49.2%)</td>
<td>20(30.8%)</td>
<td>7(10.8%)</td>
<td>65 (100%)</td>
</tr>
</tbody>
</table>
Table (10).

Pregnancy associated conditions according to type of cleft.

<table>
<thead>
<tr>
<th>CLEFT TYPE</th>
<th>CLP</th>
<th>Hydramnios</th>
<th>PIH</th>
<th>normal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count</td>
<td>2</td>
<td>2</td>
<td>53</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>% of Total</td>
<td>3.10</td>
<td>3.10</td>
<td>81.50</td>
<td>87.70</td>
<td></td>
</tr>
<tr>
<td>CP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Count</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>% of Total</td>
<td>0</td>
<td>0</td>
<td>12.30</td>
<td>12.30</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Count</td>
<td>2</td>
<td>2</td>
<td>61</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>% of Total</td>
<td>3.10</td>
<td>3.10</td>
<td>93.80</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

<table>
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<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi-Square</td>
<td>.598(a)</td>
<td>2</td>
</tr>
</tbody>
</table>
Table (11).

Drugs used by mothers of the patients in the first trimester, according to type of cleft.


<table>
<thead>
<tr>
<th>Drug</th>
<th>CLP</th>
<th>CP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>5 (7.7%)</td>
<td>0</td>
<td>5 (7.7%)</td>
</tr>
<tr>
<td>Antibiotics &amp; antimalaria</td>
<td>2 (3.1%)</td>
<td>0</td>
<td>2 (3.1%)</td>
</tr>
<tr>
<td>Antibiotic &amp; folate</td>
<td>2 (3.1%)</td>
<td>0</td>
<td>2 (3.1%)</td>
</tr>
<tr>
<td>Antimalarials</td>
<td>6 (9.2%)</td>
<td>1 (1.5%)</td>
<td>7 (10.8%)</td>
</tr>
<tr>
<td>Antimalarials &amp; folate</td>
<td>3 (4.6%)</td>
<td>0</td>
<td>3 (4.6%)</td>
</tr>
<tr>
<td>Folate</td>
<td>7 (10.8%)</td>
<td>3 (4.6%)</td>
<td>10 (15.3%)</td>
</tr>
<tr>
<td>Others</td>
<td>2 (1.5%)</td>
<td>0</td>
<td>2 (3.1%)</td>
</tr>
<tr>
<td>None</td>
<td>30 (46.2%)</td>
<td>4 (6.2%)</td>
<td>34 (52.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>57 (87.7%)</td>
<td>8 (12.3%)</td>
<td>65 (100.0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi-Square</td>
<td>5.826(a)</td>
<td>9</td>
<td>0.757</td>
</tr>
</tbody>
</table>
Figure(1).
Age distribution of the cases less than 2 years of age.
Figure(2).
Age distribution of the cases more than 2 years of age.

Figure (3).
Residence distribution of the whole sample.
Figure(4).
Tribal distribution of the sample.
Figure(5).

L=lip                      l=left
A=alveolus                 r=right
H=hard palate              b=bilateral
S=soft palate              m=median
Figure (6).
The site of cleft (clap) female patients.


L=lip
A=alveolus
H=hard palate
S=soft palate
l=left
r=right
b=bilateral
m=median
Figure(7).

l=left
r=right
b=bilateral
m=median
c=complete
i=incomplete
Figure(8).
Type of cleft in cleft palate (CP) patients according to sex.
Figure(9).
**Figure (10).**
Parents degree of relation in the whole sample.

N=65
Figure(11).
Patients distribution according to birth order.

![Patients distribution according to birth order](image)

<table>
<thead>
<tr>
<th>Order</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13.8%</td>
</tr>
<tr>
<td>2</td>
<td>24.6%</td>
</tr>
<tr>
<td>3</td>
<td>15.4%</td>
</tr>
<tr>
<td>4</td>
<td>16.9%</td>
</tr>
<tr>
<td>5</td>
<td>12.3%</td>
</tr>
<tr>
<td>6</td>
<td>6.2%</td>
</tr>
<tr>
<td>7</td>
<td>4.6%</td>
</tr>
<tr>
<td>8</td>
<td>4.6%</td>
</tr>
<tr>
<td>9</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

**Statistics**

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<th>ORDER</th>
<th>Valid</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>3.1</td>
<td>0.2</td>
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<tr>
<td>Mode</td>
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<td></td>
</tr>
<tr>
<td>Std. Deviation</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Variance</td>
<td>4.6</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percent</th>
<th>25</th>
<th>33.3333</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>66.6666</td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

PIH=pregnancy induced hypertension
n=65
Figure(14).
Birth weight distribution according to type of cleft.

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi-Square</td>
<td>5.826(a)</td>
<td>9</td>
<td>0.757</td>
</tr>
</tbody>
</table>
Discussion

The study sample contained different age groups. Those below two years of age (Figure 1), are patients undergoing different stages of management. Those above two years of age (Figure 2) are either under growing secondary surgeries, or they were neglected patients presenting late. This reflects the ignorance of the community about the ideal age for reconstruction. In many parts of the country, the birth defects are considered as something the God has created that should not be altered.

The distribution of the residence profile Figure (3), reflects availability and affordability to access management centers which are mainly located in the capital. The tribal varieties Figure (4), indicate the impact of migration from different areas of the country the capital.

Regarding the patient’s birth order among the other siblings Figure (11), 39(60%) of all cases had even birth order number (34 clap and 5 cp), and 26 (40%) had odd number (23 clap and 3 cp). This reflects that there is no strict Mandelian distribution. The mean order was (3.69) and the 50th percentile was 3 .That makes the early birth order more implicated than late birth order.

The overall sex distributions of the sample shown by Table (1) shows that 36(55.4%) patients were males and 29(44.6%) were females.
In the study sample there were 7(10.8%) cases of isolated cleft lip, 8(12.3%) cases of isolated cleft palate and 50(76.9%) case of both cleft lip and palate Table(2). The percentage of isolated cleft plate is less while the percentage of cleft lip with cleft palate is more than what is reported in the international literature \cite{14} \cite{15}, but low cleft lip percentage is matching with local literature\cite{17}. Dividing the sample into two distinct categories; cleft lip and palate and cleft palate. 57 patients has cleft lip and palate and eight patients had cleft palate. Table(3)

In the cleft lip and palate (CLP) group, there were 31(54.4%) males and 26(45.6%) females Table(3). The sex distribution of this group closely resembles what is mentioned in the literature. \cite{14} \cite{15}. The cleft involved only the lip in 7(12.3%) cases, the lip and the primary palate in 13(22.8%) cases and the lip and both primary and secondary palate in 37(46.9%) patients Table(4). Regarding the site; Table(4), 27(47.4%) patients had the cleft in the left side, 11(19.3%) patients had the cleft in the right side, 18(31.6%) had bilateral clefts and 1 (1.8%) patient had a median cleft. Each cleft lip might be complete or incomplete as shown in Figure(7). There were some sex variations in the previous results as for males Figure(5); the left cleft lip, primary and secondary palate were 11 cases (35.5% of male cases), followed by bilateral cleft lip and both palates 9 cases (29%), then cleft right lip and primary palate 3 cases (9.7%). In females Figure(6); cleft left lip with both palates were 8 cases (30.8% of females), followed by bilateral cleft lip both palates 5 cases (19.2%), then bilateral cleft lip and primary palate 4 cases (15.4%).
The cleft palate group (CP) consisted of 8 patients 5 males and 3 females. 6 cases had cleft of the soft palate (75% of 8 patients) and 2 (25%) patient had a complete cleft of the secondary palate. Figure (8). (20) (15)

No patient in the study sample had other orofacial clefts, but 5 (7.7%) patients had other congenital anomalies Tables (5); 3 (4.6%) of them were cleft lip and palate (CLP) patients, 1 (1.5%) had cardiac anomaly, 1 (1.5%) had craniofacial anomalies and 1 (1.5%) had limbs anomaly. The remaining 2 (3.1%) patients had cleft palate (CP); one of them had limbs anomaly and the other had both craniofacial and limbs anomalies. Tables (5) and (6). These figures seem lower for the clap group, but the cleft palate group associated malformations resemble the literature (15)

To study the family history of cleft lip and cleft palate may yield some indicators to implicated factors; 6 (9.2%) patients gave positive family history, Table (7); these 6 were all cleft lip and palate patients (10.5% of 57). Figure (9).

Of all parents of the 65 patients, 26 (40.0%) were cousins, 15 (23.1%) were far relatives and 24 (36.9%) were not relatives. Figure (10). The parents of 23 patients with cleft lip palate (CLP) were cousins, 15 were far relatives and 19 were not relatives. The parents of cleft palate (CP) patients were cousins in 3 cases and not relatives in the other 5 cases Table (8). These figures closely what is found in Pakistan. (18)

The maternal age when the baby was delivered, was below 25 years in 6 (9.2%) cases (all were CLP, it ranged from 26 to 30 years in 32 (49.2%) cases.
(28 CLP, 4 CP), from 31 to 35 in 20(30.8%) cases (18CLP, 2 CP), and 36 and above in 7(10.8%) cases (5 CLP, 2 CP). Table (9).

The pregnancy was normal in 61(93.8%) cases, 53 CLP patients and all cleft palate patients Table (10). It was complicated by polyhydramnios in 2(1.3%) cases and pregnancy induced hypertension occurred in 2 (3.1%) cases, all were clap patients Figure (12).

There was a history of febrile illness during the first trimester in 15(23.1%) patients Figure (13). Most of them were diagnose as malaria.

Drugs taken during the first trimester were, antimalarials alone in7(10.8%) patients, antimalarials and folates in 3 (4.6%) patients, antimalarials and antibiotics in 2(3.1%) patients, antibiotics alone in 5(7.7%) patients, antibiotics with folates in 2(3.1%) patients , folates alone in 10(15.3%)patients and other drugs in 2(3.15%) patients. No history of using anticonvulsants during pregnancy Table (11). Alcohol and smoking were not assessed for social reasons. Only 23.1% of the mothers used folate supplement in the first trimester, close to what was found in Pakistan. (18)

The patients birth weight was normal in 53(81.5%) patients (47 clap, 6 cp), small in 10 (15.4%) patients (9clap, 1cp) and large in 2(3.1%) patients (1 clap, 1cp) Figure(14).The birth weight was assessed according to the mother’s judgment comparing the affected baby to his siblings.
Conclusion

- The most common type of clefts is combined cleft lip and palate, followed by isolated cleft palate then isolated cleft lip.
- The most common type in males is left unilateral complete cleft lip and palate, followed by bilateral complete cleft lip and palate.
- The most common type in females is left unilateral complete cleft lip and palate, followed by bilateral cleft lip and primary palate.
- The majority of parents of the affected cases are close relatives; in around one tenth of the cases there is a family history of orofacial clefts.
- History of febrile illnesses during the first trimester of pregnancy was relatively high among the mothers of the affected cases.
- Few mothers of the affected cases used folates supplements during the first trimester of pregnancy.
Recommendations

1. More research is needed to study birth defects in general and orofacial defects specifically in Sudanese patients.
2. Multidisciplinary research is recommended in studying congenital birth defects in Sudan.
3. Methods of antenatal and postnatal care should be focused on prevention, early detection and evaluation of birth defects, to plan a multidisciplinary approach for further management.
4. More training programs in management of orofacial clefts for the health workers in different parts of the country are needed.
5. Health education program to the public Sudanese community about these problems is essential.
6. Establishment of national specialized centres for management of orofacial clefts and providing them with trained staff and support.
7. Establishment of national registry for birth defects with regularly updated data available for research.
References


APPENDIX
Appendix [i]

CLEFT LIP AND PALATE

QUESTIONNAIRE

1. Serial No. ................................. Card No.................................
2. Name:........................................ 3. Sex:.................................
3. Date of birth:......./....../......... 5. Age:.................................
4. Residence:......................... 7. Tribe:.................................
8. Order among siblings: No ............

<table>
<thead>
<tr>
<th></th>
<th>Lt.</th>
<th>Rt.</th>
<th>Bilateral</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lip</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alveolus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hard palate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft palate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

9. Type of cleft:  C for complete   I for incomplete
Other clefts: ................................................................................................

10. Other congenital anomalies: [a]none       [b]cardiac
[c]craniofacial       [d]limbs       [e]other
Type:.................................................................

11. Family history of cleft lip/palate: [a]yes   [b]no
 . Relation:to father..............................................to mother............................

12. Family history of other congenital anomalies : [a]yes   [b] no
Type:................................................................. Relation.................................

13. Parents relation : [a] not relatives      [b]far relatives
14. Pregnancy was: [a]normal [b]abnormal
Abnormality: [a]gestational diabetes [b]polyhydramnios [c]multiple pregnancy
[d]antepartum haemorrhage [e]pregnancy induced hypertension
[f]other: ........................................................................................................

15. Maternal age..............................................................................................

16. Pregnancy associated illness Trimester
Anaemias: ................................................................. ............... 
Febrile illnesses: ............................................................... ............... 
Chronic illness: ........................................................................ ............... 
Others: ....................................................................................... ............... 

17. Medication taken during the first trimester and the preceding 3 months:
Antibiotics: ......................................................................................... 
......................................................................................................
Antimalarial: ................................................................. 
Anticonvulsants: ................................................................. 
Benzodiazepines: ................................................................. 
Folic acid: ................................................................. 
Others: ................................................................. 

18. History of radiation prior to, or during the first trimester: [a]yes [b]no
Type: ................................................................. Time: ............... 

Appendix [iii]

Tesseir classification