Maturation of Cervical Vertebrae in Patients with Complete Unilateral Cleft Lip and Palate

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
Graduate Department of Dentistry
University of Toronto

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Abstract

This retrospective cohort study of 336 lateral cephalometric radiographs from 62 children (34 males and 28 females) with non-syndromic complete unilateral cleft lip and palate from the Hospital for Sick Children and 50 non-cleft children (25 females and 25 males) from the Burlington Growth Centre. Cervical vertebral maturation stages at age 10, 12 and 14 were determined. The cervical vertebral maturation (CVM) was established using the 6-stage method described by Baccetti and coworkers. The reproducibility of classifying CVM stages was high, with an inter-rater reliability (ICC) with the standard (Baccetti et al, 2005) of 80% and intra-rater reliability of 85%. The Cervical vertebral maturation stage for both males and females with UCLP was significantly later than children without a cleft at age 10, 12 and 14. The results suggest that patients with UCLP show delayed skeletal maturation in comparison to non-cleft patients.
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List of Acronyms

ADI – Atlanto-dens interval

BCLP - Bilateral cleft lip and palate

C2 – Second cervical vertebrae

C3 – Third cervical vertebrae

C4 – Fourth cervical vertebrae

C5 – Fifth cervical vertebrae

C6 – Sixth cervical vertebrae

C7 – Seventh cervical vertebrae

CL – Cleft lip

CL/P – Cleft lip with or without cleft palate

CLP – Cleft lip palate

CP – Cleft palate

CS1 – Cervical stage 1

CS2 – Cervical stage 2

CS3 – Cervical stage 3

CS4 – Cervical stage 4

CS5 – Cervical stage 5

CS6 – Cervical stage CVA - Cervical vertebrae anomalies
CVM - Cervical vertebral maturation

CVMS- Cervical vertebral maturation stage

Cvs1 – Cervical vertebral stage 1

Cvs2 – Cervical vertebral stage 2

Cvs3 – Cervical vertebral stage 3

Cvs4 – Cervical vertebral stage 4

Cvs5 – Cervical vertebral stage 5

Cvs6 – Cervical vertebral stage 6

OFC – Orofacial clefts

SMI – Skeletal maturation indicators

SMS – Skeletal maturity scores

TW – Tanner and Whitehouse

TW2 – Tanner and Whitehouse 2 method

TW3 – Tanner and Whitehouse 3 method

UCLP - Unilateral cleft lip and palate
I. INTRODUCTION

1. Statement of the Problem

Numerous investigations have shown a close relationship between craniofacial growth, skeletal maturation, and general body growth. Skeletal maturity can be assessed by means of a series of biologic indicators such as an increase in body height (Hunter, 1966), skeletal maturation of the hand and wrist (Greulich, 1959; Bjork and Helm, 1967; Fishman, 1979), dental development and eruption (Demirjian and Levesque, 1980; Nystrom et al., 1986), chronological age (Hägg and Taranger, 1980) and cervical vertebral maturation (Hassel et al., 1995; Baccetti et al., 2002; San Roman et al., 2002). Every individual matures on his or her own schedule, and the majority of these studies provide sample means for average or “normal growers”, excluding patients with orofacial clefts.

Due to the wide individual variation in the timing of the pubertal growth spurt, chronological age is an unreliable guide for assessment of child developmental status (Grave, 2003). Skeletal maturation is generally determined by evaluating either the stage of ossification of the bones of the hand and wrist. In 1972, Lamparski stated that the cervical vertebrae were as statistically and clinically reliable in assessing skeletal age as the hand-wrist technique. In recent years, evaluation of cervical vertebrae has been increasingly used to determine skeletal maturation in normal subjects. In contrast, skeletal age estimation using the cervical vertebral method of children with clefts has not been determined.
2. Significance of the problem

General rates of skeletal growth have been established for both sexes, and these demonstrate accelerations and decelerations in growth velocities at various developing maturational stages of growth. Because of individual variation in timing, duration and velocity of growth, assessment of skeletal age is essential in formulating a viable orthodontic treatment plan. The technique for assessing skeletal maturity consists of visual inspection of the developing bones, their initial appearance and their subsequent ossification related changes in shape and size. Various areas of the skeleton that have been used are the hand and wrist, and the cervical vertebrae. The classical and most widely used method for skeletal age determination is the hand-wrist bone analysis performed using a radiograph. The hand has received the most attention in the literature, both because it is easy to radiograph and because a wide range of bones is available for study.

Recently, the evaluation of changes in the sizes and shapes of the cervical vertebrae in growing subjects has gained increased interest in the last several decades as a biological indicator of an individual’s skeletal maturity. One of the main reasons for the rising popularity of this method is that the analysis of Cervical Vertebral Maturation (CVM) is performed on the lateral cephalogram of the patient, a type of image used routinely in orthodontic diagnosis.

In the past, many studies have assessed skeletal maturity in subjects without orofacial clefts using the hand-wrist method. Unfortunately, these studies have reported conflicting results due to the inclusion of different types of clefts and ethnic variations. For this reason, this study intends to investigate the CVM method in a cleft population compared with age, sex and ethnicity-matched controls. This might be helpful in determining the skeletal maturity in and provide the orthodontist with an additional tool to assess growth potential in patients with cleft lip and palate.
II. LITERATURE REVIEW

1. Maturation Indices

Maturity is a term used to describe physiological progression; an individual has either undergone or is yet to take place (Tanner et al 1975). It is a developmental process that proceeds from being completely immature to completely mature.

a. Chronological Age:

Rose (1960) stated that chronological age is an ineffectual guide to the growth and development of facial areas in the parapubertal period, defined as extending from 9 to 18 years. Hunter (1966) studied thirty-four females and twenty-five males from the Child Research Council, Denver, Colorado. The author reported a wide variation of the chronological age from the onset and duration of the adolescent growth period in both males and females, with a four year range in males and a five year range in females. Fishman (1979), studied longitudinal series of 60 males and 68 females with chronological ages that ranged from 7 and 15 years. The author concluded that there is a significant discrepancy between skeletal and chronological age, strengthening Rose and Hunter’s statements.

b. Dental Age Assessment:

Bjork and Helm (1967) examined the relationship between pubertal growth in body height and specific indicators of maturation: ossification of the ulnar sesamoid at the metacarpophalangeal joint of the thumb (S), two stages of dental development (DS 4, full eruption of all canines and premolars, and DS M₂, all second molars fully erupted), and menarche in girls. They reported that dental development was a poor criterion for puberty.
Dermijian et al (1973) used a sample of 2,928 French-Canadian children from Montreal’s Growth Centre to develop a maturity scoring system for estimation of overall dental age. Panoramic radiographs were used to analyze developmental changes of the seven permanent teeth in the third quadrant, and described eight stages from the beginning of calcification of the cusp tips to the closure of the root apex. The dental age was determined by adding the scores of all seven teeth (the dental maturity score), and this was converted to dental age using percentile charts. They conclude that dental age based on root formation is a more reliable indicator for dental maturity than the dental emergence method.

In a later study, Demirjian (1985) used longitudinal data of 50 girls from 6 to 15 years to assess five biological maturation indicators: menarche, peak height velocity, 75% skeletal maturity, adductor sesamoid appearance and 90% dental maturity. Dental maturity showed no significant relationship with skeletal maturity. Liebgott (1978) utilized serial longitudinal data of 32 males from 4 years of age to 18 from the Burlington Growth Centre, Toronto. Increases in the skeletal (Tanner – Whitehouse method, 1982), chronological and dental (Nolla’s 22 method, 1960) ages at the time of peak mandibular length (measured from condyline to gnathion) were recorded. Liebgott’s work supported the findings of Dermirjian’s, and concluded that dental age is not a good indicator of increase of mandibular length.

Hägg and Taranger (1982) found sex differences in the relationship between dental development and the pubertal growth spurt. In relation to the dental emergence stages, they found a weak association between pubertal growth spurt and dental emergence ($r = 0.01$ to $0.03$); unreliable for clinical work. The authors concluded that dental emergence stages were not useful for predicting pubertal growth spurt in height.
c. Body Height:
Many authors have shown a significant correlation between facial growth and statural growth. Some authors state that statural growth acceleration generally precedes facial growth acceleration by 6 to 12 months (Hassel et al., 1995; Grave, 1976; Hunter, 1966). Fishman (1982) studied growth patterns and growth rates for statural height and face in female and male longitudinal groups. He concluded that females tend to achieve a higher percentage of their total statural growth than males during early adolescence. However, after the time of maximum growth velocity, both sexes showed similar percentages of growth completed.

d. Skeletal Age Assessment:
Skeletal maturation refers to the degree of development of ossification in bone and involves the interpretation to defined ossification events of certain bones. Skeletal maturation is regarded as being more closely linked to sexual maturity than other biological indicators (Hassel and Farman, 1995).

2. Hand-wrist radiograph evaluation:
Traditionally, orthodontists have relied on hand-wrist films to study the development of various bones in the wrist and hand in order to predict the growth potential of a specific patient (Hassel and Farman, 1995). Many authors have considered the hand-wrist method as the best predictor of maturation (Greulich and Pyle, 1959; Tanner et al, 1975; Tanner et al., 1994; Taranger et al., 1987; Fishman, 1982), and several methods of assessing hand-wrist films have been commonly used. In the Greulich –and Pyle atlas method (1959), the child’s hand-wrist radiograph is matched with a hand-wrist reference radiographs that represents the norm for a given age, and a skeletal age then is assigned.

The Tanner and Whitehouse (TW) skeletal maturation method (1975) and TW2 assess specific ossification centers of the hand and wrist through two systems, RUS (radio, ulna and selected
metacarpals and phalanges) and Carpal, which analyzes the carpal bones except for the pisiform. Individual bones are then matched to a series of written criteria describing eight or nine standard stages, labeled A to H or I. The sum of these scores results in a skeletal maturity score (SMS) that can be transformed into skeletal age. In a later study, the authors renewed the standard reference values and charts for the RUS (radius-ulna-and selected metacarpals and phalanges), incorporating recent data from North America and Europe. This new system is called the TW3 method (Tanner and Whitehouse, 1982, Tanner et al. 1983).

In 1982, Fishman developed a radiographic skeletal maturation assessment (SMA) using four stages of bone formation found at six anatomical locations on the thumb, third finger, fifth finger and radius. Eleven discrete adolescent skeletal maturational indicators (SMIs) covering the entire period of adolescent development were found on these six sites. The sequencing of maturation progresses through epiphyseal widening on selected phalanges, the ossification of the adductor sesamoid of the thumb, the ‘capping’ of selected epiphyses over their diaphyses, and the fusion of selected epiphyses and diaphysis. The result of this analysis, assigned SMI 1 through 11, indicated the amount of skeletal maturation that had occurred (Figures 1 to 3). Widening of the epiphysis relative to its diaphysis is considered applicable as an SMI. Capping occurs when the margins of the epiphysis begin to flatten and point toward the diaphysis; it is the transition between initial widening and fusion of the epiphysis and diaphysis. Fusion between the epiphysis and diaphysis begins centrally and progresses laterally. Ossification of the adductor sesamoid of the thumb appears as a small round center of ossification medial to the junction of epiphysis and diaphysis of the proximal phalanx (Fishman, 1982).


Figure 3. Eleven of skeletal maturity indicators SIM. Reprinted from Fishman LS. Radiographic Evaluation of Skeletal Maturation. Angle Orthod 1982, 52 (2): 88 - 112
3. Cervical Vertebral Maturation (CVM) Methods:

Skeletal maturation has been assessed using the shapes of the cervical vertebrae, and these have been used to estimate skeletal age. Several workers have indicated this to be a superior alternative to the hand and wrist method (Lamparski, 1972; O’Really et al, 1988; Hassel and Farman, 1995; Franchi et al, 2000; Bacceti et al, 2002 and 2005). This method evaluates the first 4 or 5 vertebrae, excluding the atlas, and distinguishes 5 or 6 maturational stages based on the change in the height-width ratio of the vertebral bodies and the depth of the inferior concavity (Hassel and Farman, 1995; Franchi et al, 2000; Bacceti et al, 2002).

a. Lamparski (1972):

Lamparski (1972) described a method to assess skeletal age using maturational changes of the cervical vertebrae. 72 females and 69 males, ages 10 to 15, were selected from amongst 500 patients from the Orthodontic Department of the University of Pittsburg School of Dental Medicine. To create standards, a group of lateral cephalometric images of patients whose chronologic and skeletal age were ±6 months from the age under study. These images were arranged in sequence from the least to the most mature based on vertebral development characterized by the presence of an inferior concavity from C2 to C6 and the shape of the third through sixth vertebral bodies.

A series of 6 standards resulted for each sex, one for each age 10 through 15:

- Stage 1 (Age 10): All inferior borders of the bodies are flat. The superior borders are strongly tapered from posterior to anterior.
- Stage 2 (Age 11): A concavity has developed in the inferior border of the second cervical vertebra. The anterior vertebral heights of the bodies have increased.
- Stage 3 (Age 12): A concavity has developed in the inferior border of the third vertebra.
• Stage 4 (Age 13): All cervical bodies from C3 to C6 are rectangular in shape, a concavity has developed on the fourth vertebra. Concavities on C5 and C6 are just beginning to form.

• Stage 5 (Age 14): The bodies are nearly square in shape, and the spaces between the bodies are visibly smaller. Concavity of the lower border of all 6 cervical bodies is well defined at this stage.

• Stage 6 (Age 15): All cervical bodies have increased in vertical height and all concavities have deepened.


Hassel and Farman stated that skeletal maturation is a continuous process and modified Lamparski’s method (1972). Based on their vertebral development, 10 males and 10 females were categorized into one of eleven skeletal maturation indicator (SMI) groups, numbered 1 through 11. The cervical vertebrae tracings were paired with their respective hand-wrist radiographs that had also been grouped in SMI categories. They defined six categories of CVM:

- **Category 1** was called *Initiation*, at this stage inferior borders of C2, C3 and C4 are flat. The vertebrae are wedge shaped, and the superior vertebral borders are tapered from posterior to anterior.
- **Category 2** - *Acceleration*: concavities are developing in the inferior borders of C2 and C3. The inferior border of C4 is flat. The bodies of C3 and C4 are nearly rectangular in shape.
- **Category 3** - *Transition*: distinct concavities are seen in the inferior borders of C2 and C3. A concavity begins to develop in the inferior border of C4. The bodies of C3 and C4 are rectangular in shape.
- **Category 4** - *Deceleration* is characterized by distinct in the inferior borders of C2, C3, and C4. The vertebral bodies of C3 and C4 are becoming more square in shape.
- **Category 5** - *Maturation*: more accentuated concavities are seen in the inferior borders of C2, C3, and C4. The bodies of C3 and C4 are nearly square in shape.
- **Category 6** - *Completion*: Growth is considered to be complete at this stage. Deep concavities are seen in the inferior borders of C2, C3, and C4. The bodies of C3 and C4 are square.

Associations were made with Fishman’s skeletal maturation indices- SMI(1982); Category 1 corresponded to SMI1 and 2; Category 2 corresponded to SMI 3 and 4; Category 3 corresponded to
SMI 5 and 6; Category 4 corresponded to SMI 7 and 8; Category 5 corresponded to SMI 9; and Category 6 corresponded to SMI 11.


Franchi et al (2000) adopted Lamparski’s original method (1972) for the appraisal of skeletal age in 34 subjects (25 females and 9 males) selected from the files of the University of Michigan Elementary and Secondary School Growth Study (UMGS). They confirmed the validity of the CVM stages as a biologic indicator for the appraisal of mandibular and skeletal maturity on the basis of a single cephalometric observation and without additional x-ray exposure.

Baccetti and co-workers (2002) reported a five-maturational-stage method CVMS I through CVMS V instead of Cvs1 through Cvs 6 (Franchi et al, 2000) in an effort to provide more consistency. The morphologies of the bodies of C2, C3 and C4 were analyzed in 30 orthodontically untreated subjects (18 males and 12 females). The analysis consisted of both visual and cephalometric appraisals of morphologic characteristics of the three cervical vertebrae. They conclude that the five-maturation stage method is useful when skeletal maturity is assessed on a single cephalogram and when only the second through fourth cervical vertebrae are visible.

- CVMS I: The lower borders of all the three vertebrae are flat, with possible exception of a concavity at the lower border of C2. Bodies of C3 and C4 are trapezoid in shape with the superior border tapered from posterior to anterior. The peak of mandibular growth will occur not earlier than one year after this stage.
- CVMS II: Concavities at the lower borders of both C2 and C3 are present. C3 and C4 may be trapezoidal or rectangular in shape. The peak of mandibular growth will occur within one year after this stage.
- CVMS III: Concavities at the lower borders of C2, C3 and C4 are present. C3 and C4 are rectangular horizontal in shape. The peak in mandibular growth has occurred within one or two years before this stage.
- CVSM IV: Concavities at the lower borders of C2, C3 and C4 still are present, and at least one of the bodies of C3 and C4 is squared in shape. The peak of mandibular growth has occurred no later than one year before this stage.

- CVMS V: The concavities at the lower borders of C2, C3 and C4 are still evident. At least one of the bodies of C3 and C4 is rectangular vertical in shape. The peak in mandibular growth has occurred no later than two years before this stage.

In 2002, the authors described a quantitative analysis to evaluate the morphology of the three cervical vertebrae (C2, C3, and C4). Modified reference points described by Hellsing (1991) were adopted partially for the location of landmarks to measure the concavity of the lower border of C2, C3 and C4 (Figure 7). The points for description of the morphologic characteristics of the vertebral bodies were described as follows:
- C2p, C2m, C2a: the most posterior, the deepest and the most anterior points on the lower border of C2
- C3up, C3ua: the most superior points of the posterior and anterior borders of the body of C3
- C3lp, C3m, C3la: the most posterior, the deepest and the most anterior points on the lower border of the body of C3.
- C4up, C4ua: the most superior points of the posterior and anterior borders of the body of C4
- C4lp, C4m, C4la: the most posterior, the deepest and the most anterior point on the lower border of the body of C4.
- C2Conc: a measure of the concavity depth at the lower border of C2, distance connecting C2p and C2a to the deepest point on the lower border of the vertebra, C2m)
- C3conc: a measure of concavity depth at the lower border of C3, distance from the line connecting C3lp and C3la to the deepest point on the lower border of the vertebra, C3m.
- C4Conc: a measure of the concavity depth at the lower border of C4, distance from the line connecting C4lp and C4la to the deepest point on the lower border of the vertebra, C4m.
- C3BAR: ratio between the length of the base (distance C3Lp to C3la) and the anterior height (distance C3ua to C3la) of the body.
- C3PAR: ratio between the posterior (distance C3up to C3lp) and anterior (distance C3ua to C3la) heights of the body of C3.
- C4BAR: ratio between the length of the base (distance C4Lp to C4la) and the anterior height (distance C4ua to C4la) of the body of C4.
- **C4PAR**: ratio between the posterior (distance C4up to C4lp) and anterior (distance C4ua to C4la) heights of the body of C4.

Figure 7. Cephalometric landmarks for the quantitative analysis of the morphologic characteristics in the bodies of C2, C3, and C4. Baccetti T., Franchi L., McNamara JA. An Improved Version of the Cervical Vertebral Maturation (CVM) Method for the Assessment of Mandibular Growth. Angel Orthod 2002; 72:316-323
d. Bacceti, Franchi and McNamara (2005):

In 2005 the authors introduced a further refinement with a six-stage method to assess cervical vertebral maturation (CVM). This more practical method permitted a more direct appraisal of the relationship between CVM and skeletal maturity of the mandible.

- **Cervical stage 1 (CS1):** The lower borders of all the three vertebrae (C2 – C4) are flat. The bodies of both C3 and C4 are trapezoid in shape. The peak in mandibular growth will occur on average 2 years after this stage.

- **Cervical stage 2 (CS2):** A concavity is present at the lower border of C2. The bodies of both C3 and C4 are still trapezoid in shape. The peak in mandibular growth will occur on average 1 year after this stage.

- **Cervical stage 3 (CS3):** Concavities at the lower border of both C2 and C3 are present. The bodies of C3 and C4 may be either trapezoid or rectangular horizontal in shape. The peak in mandibular growth will occur during the year after this stage.

- **Cervical stage 4 (CS4):** Concavities at the lower borders of C2, C3, and C4 now are present. The bodies of both C3 and C4 are rectangular horizontal in shape. The peak in mandibular growth has occurred within 1 or 2 years before this stage.

- **Cervical stage 5 (CS5):** The concavities at the lower borders C2, C3, and C4 still are present. At least one of the bodies of C3 and C4 is squared in shape. The peak of mandibular growth has ended at least 1 year before this stage.

- **Cervical stage 6 (CS6):** The concavities at the lower borders of C2, C3, and C4 still are evident. At least one of the bodies of C3 and C4 is rectangular vertical in shape. If not rectangular vertical, the body of the other cervical vertebra is squared. The peak in mandibular growth has ended at least 2 years before this stage.
In summary, CVM appears to be an appropriate method for the appraisal of mandibular skeletal maturity using a single cephalometric observation and without additional x-ray exposure (Franchi et al., 2000; Baccetti et al., 2002 and 2005).

4. Cervical Vertebrae

a. Cervical vertebral embryology and development:

During the third week of gestation, the primitive streak, well-defined germ layers, and the notochord develop. The notochord and somites are the structures responsible for the development of the future vertebral column. Epiblastic cells migrate from the deep surface of the primitive streak to form the embryonic endoderm. Subsequently, cells continue to migrate from the primitive streak, creating the embryonic mesoderm (Kaplan et al., 2005). Several embryonic growth factors are thought to induce the migration of these cells from the primitive streak (Tabin, 1991; Kaplan et al., 2005). The cells that migrate the most anteriorly form the prechordal plate and the cells that migrate more posteriorly form the notochordal process. The notochordal process develops into the notochord and is an early representation of the future vertebral and bony skeleton. On both sides of the notochord, the mesoderm differentiates into three main areas, the paraxial, intermediate and lateral mesoderm (Kaplan et al., 2005). Forty-two to forty-four pairs of somites will form the paraxial mesoderm by the end of the fifth week. Development of the somites occurs in a cranio-caudal fashion and each somite develops into two parts, a sclerotome and a dermomyotome. The cells of the sclerotome are responsible for the formation of the spine, and the dermomyotomes form muscle cells and the overlying dermis of the skin (Kaplan et al., 2005).

During the fourth week of gestation, cells of the sclerotome begin to migrate toward and around the notochord and neural tube. Fusion of parts of the adjacent sclerotomes creates the centrum, which will further develop into the vertebral body. The centrum allows bone to continually develop around it. The cells that migrated adjacent to the neural tube develop into neural arches which serve to protect to spinal cord, vessels and nerve roots, before leaving the foramina. The centrum and the two
halves of the vertebral arches develop separately and fuse to one another (Kaplan, 2005). During the sixth week of gestation, after cells have migrated and vertebral structures begin to fuse; signals from the notochord are responsible for differentiation, chondroification and ossification of the vertebrae. (Kaplan et al., 2005). Three ossification sites form the first cervical vertebra, the anterior arch or centrum, and the two neural arches. The two neural arches fuse later in life to form the posterior arch. The anterior arch is ossified in only 20% of the population at birth. It becomes visible as an ossification centre by age 1 and the anterior arch fuses with the neural arches by age 7 (Lustrin et al., 2003; Ogden, 1984).

The axis has four ossification centers at birth. There is one center for each neural arch, one for the odontoid process, and one for the body. The odontoid process forms in utero from two separate ossification centers that fuse in the midline by the seventh month of gestation. A secondary center of ossification appears at the apex of the odontoid process between ages 3 and 6, and fuses by age 12. The C2 body also fuses with the odontoid process between ages 3 and 6. This fusion line, also known as the subdental synchondrosis, can be seen until age 11 and be mistaken for a fracture. Between ages 2 and 3, the neural arch fuses posteriorly, and between ages 3 and 6, the arch fuses with the body of the odontoid process (Lustrin et al., 2003; Ogden, 1984; Herman and Pizzutillo, 1999).

The third through seventh cervical vertebrae exhibit the same pattern of development. There are three ossification sites present, the body and two neural arches. The neural arches fuse posteriorly between ages 3 and 6. Secondary ossification centers may appear at the superior and inferior surfaces of the cervical vertebral bodies, and these remain unfused until early adulthood (Lustrin et al., 2003).
b. Cervical vertebral anatomy:

The first cervical vertebra (C1), is named the atlas because it supports the globe of the head. The first cervical vertebra has no body or spinous process. It is a ring-shaped bone consisting of an anterior and posterior arch, and two lateral masses. The anterior surface of the anterior arch is convex and has at its centre, the anterior tubercle. Posteriorly, the anterior arch is concave for articulation of the odontoid process of the axis. The posterior-most point of the arch is the posterior tubercle, which is a rudimentary spinous process. Each of the lateral masses carries two articular surfaces, a superior and inferior. The superior facets articulate with the condyles of the occipital bone, and allow flexion and extension movements of the head. The inferior articular facets articulate with the axis permitting rotational movements of the head. The transverse processes are large, and serve for the attachment of muscles that assist in rotating the head (Gray, 1980)

The second cervical vertebra (C2), is named the epistropheous or axis, and forms a pivot upon which C1 rotates. The most distinctive characteristic is the prominent odontoid process or dens that rises superiorly from the superior surface of the body. The body is deeper anteriorly than posteriorly, and elongated inferiorly anteriorly so as to overlap the upper and anterior surface of the third vertebra. The odontoid process exhibits a slight constriction or neck where it joins the body. The transverse processes are very small, and each ends in a single tubercle. The spinous process is large, very prominent, and can be bifid and tuberculated (Gray, 1980) (Figure 4)

General characteristics (C3 to C6): The bodies of these four vertebrae are small, and broader from side to side than from anterior to posterior. The superior surface is concave transversely, and a lip projects from either side. The inferior surface is concave from anterior to posterior, convex from side to side, and has shallow concavities laterally, which articulate with the corresponding projects of the subjacent vertebra. The laminae are narrow, and thinner above than
below, and the vertebral foramen is large, and triangular in shape. The spinous process is short and bifid. The transverse processes are pierced by the foramen transversarium, which in the upper six vertebrae transmits to the vertebral artery and vein, and plexus of sympathetic nerves. (Gray, 1980).
c. Lateral radiographic appearance of cervical vertebrae:

The anterior tubercle of the atlas (C1) extends anteriorly approximately 3 mm further than the anterior surfaces of the other vertebrae. The posterior arch of the atlas is located 8 to 10 mm below of the base of the skull (Sandham, 1986; Ugar and Semb 2001).

The axis (C2) is the largest cervical unit and can be easily identified by the presence of the odontoid process, which extends superiorly from the body of C2 through the neural arch of the atlas. Radiographically, this process should have a steeply inclined anterior surface and a vertical posterior edge and no intervertebral fibrocartilage (disc) develops between the atlas and the axis (Sandham, 1986; Gray et al, 1964).

The atlanto-dens interval (ADI) is an approximately 4 mm space between the vertical posterior edge of the dens and the inner surface of the anterior arch of the atlas (Locke et al, 1966). The cervical vertebral units of C3 to C6 are all similar with well outlined bodies. C7 has a non-bifid spinous process (Sandham, 1986)
Figure 11. Radiographic appearance of cervical vertebrae (cropped cephalometric radiograph from the Burlington Growth Centre. Toronto, ON. Canada
5. Cleft Lip and Palate:
   a. Embryogenesis
      ii. Morphogenesis of the Face, Lip and Palate

Morphogenesis of the craniofacial regions is dependent upon numerous cell types and tissues. One of the most important cell types in understanding craniofacial morphogenesis is the neural crest cell. While the majority of recent neural crest studies have necessarily dealt with chick and mouse embryos, there is ample evidence to show that basic information and associated technologies gained can be directly applied to neural crest cells in mammalian and human embryos (Burdi, 2006).

Migrating craniofacial crest cells are thought to travel through cell-free intercellular spaces and pathways that have high levels of extracellular matrix molecules (Bronner-Fraser, 1990). Migration is facilitated by the presence of molecular substrates such as fibronectin, laminin, and type IV collagen. A family of attachment proteins called integrins mediates attachment to and migration of crest cells. In contrast, other extracellular matrix molecules in the pathway such as chondroitin and sulfate-rich proteoglycans can impede or block the normal migration of neural crest cells. (Burdi, 2006).

There are two families of neural crest cells, cranial and trunk cells. Trunk neural crest cells extend from the lower cervical to the most caudal embryonic somites in humans, and do not have the capacity to differentiate into skeletal tissues. Cranial neural crest cells appear to be more complex and are a major component of the embryo’s cephalic end. They may differentiate into a wide variety of cell and tissue types, including connective, skeletal, and muscle tissues of the face, and dentin (Burdi, 2006). Cranial neural crestal cells follow specific migratory pathways into specific regions of the embryonic gut tube. Such migrations are extensive and follow very definitive migratory paths.
away from the neural tube and into the facial and pharyngeal regions. In the region of the hindbrain, neural crest cells arise from eight segmented regions on either side of the hindbrain (rhombencephalon) called rhombomeres (numbered R1 to R8) and subsequently migrate into specific pharyngeal arches (Castens, 2002; Couly, 1990).

Crest cells from the R1 and R2 centers migrate into the first pharyngeal arch and play important roles in the formation of Meckel’s cartilage. Crest cells from R4 and R7 migrate into the third arch, and those from R8 migrate into the fourth and sixth pharyngeal arches. Crest cells initially expressed the HOX genes from their originating rhombomeric centre, but specific expression is dependent upon interaction of the crest cells with the arch-specific mesoderm in the pharyngeal arches. HOX genes are not expressed anterior to rhombomere 3, and a different set of coded patterning homeobox genes is required to bring about the developmental of cephalic structures. This set of homeobox genes includes Msx gene family, the Dlx family and the Barx family (Nanci and Ten Cate, 2008).

Defective differentiation, proliferation, and migration of cranial neural crest have been linked with a variety of development defects. Morphogenesis of the facial regions depends on the timely differentiation, directed migration and selective proliferation of these crest cells which arise as a product of neural tube formation. Crest cells from developing midbrain regions migrate into upper facial regions, whereas crest cells from midbrain migrate selectively into the lower facial regions, once the crest cells migrate into specific facial regions, they differentiate into mesenchymal cells that subsequently give rise to connective tissue and muscle cells of those specific facial regions (Noden, 1991).
iii. Formation of the face:

The brachial arches form in the pharyngeal wall as a result of proliferating lateral plate mesoderm and subsequent reinforcement by migrating neural crest cells. Six cylindrical thickenings thus form (the fifth and sixth are transcendent structures in humans) that expand from the lateral wall of the pharynx, pass beneath the floor of the pharynx, and approach their anatomic counterparts expanding from the opposite side. The arches are seen as bulges on the lateral aspects of the embryo and are separated externally by small clefts called brachial grooves. On the inner aspect of the pharyngeal wall are corresponding small depressions called pharyngeal pouches that separate each of the brachial arches internally (Figure 12) (Nanci and Ten Cate, 2008).
Figure 12. A. Development of pharyngeal arches and clefts between them in a 35-day embryo. B. Midline section showing of the arches on the pharyngeal wall and the pharyngeal pouches separating them. Adapted from Nanci and Ten Cate, 2008.

Figure 13. Scanning electron micrograph of a human embryo at around 6 weeks (Courtesy K.K Sulik). Reprinted from Nanci and Ten Cate, 2008.
The first, second, and third brachial arches play an important role in the development of the face, mouth, and tongue. Early development of the face is dominated by the proliferation and migration of ectomesenchyme involved in the formation of the primitive nasal cavities. At 28 days, localized thickenings called olfactory placodes develop within the ectoderm of the frontal prominence. Proliferation of mesenchyme around the placodes produces a horseshoe-shaped ridge that converts the olfactory placode into the nasal pit. The lateral arm of the horse-shoe is called the nasal process, and the medial arm, the medial nasal process. The medial nasal processes of both sides, together with the frontonasal process, give rise to the middle portion of the nose, middle portion of the upper lip, anterior portion of the maxilla, and the primary palate (Nanci and Ten Cate, 2008).

The median growth of the maxillary process pushes the medial nasal process toward the midline, where it merges with its anatomical counterpart from the opposite side. In this way the upper lip is formed from the maxillary processes of each side and the medial nasal process, with fusion occurring between the forward extent of the maxillary processes and the lateral face of the medial nasal process. The merging of the two medial nasal processes results in the formation of the maxilla, which contains the incisor teeth and the primary palate as well as part of the lip. The lower lip is formed by merging of the two streams of ectomesenchyme of the mandibular processes (Figure 13). The face develops between the twenty-fourth and thirty-eighth days of gestation. By this time some of the epithelium covering the facial processes already can be distinguished as odontogenic or tooth forming (Nanci and Ten Cate, 2008).

iv. Formation of the secondary palate:

The formation of the secondary palate commences between 7 and 8 weeks, and is completed around the third month of gestation. Three outgrowths appear in the oral cavity; the nasal septum grows
downward from the frontonasal process along the midline and the two palatine shelves or processes, one from each side, extend from the maxillary process toward the midline and downward on each side of the tongue. After the seventh week of development, the tongue is withdrawn from between the shelves. The shelves now elevate and fuse with each other above the tongue, and with the primary palate. The septum and the two shelves converge and fuse along the midline, thus separating the primitive oral cavity into nasal and oral cavities. For fusion of the palatine shelves to occur, eliminating the epithelial coverings of the shelves is necessary. As the two palatine shelves meet, adhesion of the epithelia occurs so that the epithelium of one shelf becomes indistinguishable from that of the other, and a single midline epithelial seam forms (Figure 14). To achieve this fusion, DNA synthesis ceases within the epithelium some 24 to 36 hours before epithelial contact. The midline seam must now be removed to permit ectomesenchymal continuity between the fused processes. As growth of the seam fails to keep pace with palatal growth, it thins to a single layer of cells and then breaks up into discrete islands of epithelial cells that will transform into mesenchymal cells (Nanci and Ten Cate, 2008).
Figure 14. Formation of the secondary palate. A, at 7 weeks the palatine shelves are forming from the maxillary processes and are directed downward on each side of the developing tongue. B, At 8 weeks the tongue has been depressed and the palatine shelves are elevated but not fused. C, Fusion of the shelves and the nasal septum is completed (From Nanci and Ten Cate, 2008).
v. Clefts of the primary palate and secondary palate:

Clefts of the lip and anterior maxilla result from defective development of the embryonic primary palate. Often when such clefts occur, the distortion of facial development prevents the palatine shelves from making contact when they swing into their horizontal positions. Facial clefts usually result from a deficiency of mesenchyme in the facial region, caused by a failure of the neural crest to migrate or facial mesenchyme to proliferate. When clefts of the palate occur with no corresponding facial cleft, such clefts may result from (1) failure of the shelves and septum to contact each other because of a lack of growth or because of a disturbance in the mechanism of shelf elevation; (2) failure of the shelves and septum to fuse after contact has been made because the epithelium covering the shelves does not break down or is not resorbed; (3) rupture after fusion of the shelves has occurred; and (4) defective merging and consolidation of the mesenchyme of the shelves (Nanci and Ten Cate, 2008).
b. Classification of Cleft Lip and Palate

The early classification systems of cleft lip and palate (CL/P) placed their emphases on the anatomical alveolar ridge as a significant landmark in the division of oral clefts. Kemahan and Stark (1958) described a classification that used the incisive foramen to separate anterior from posterior cleft deformities (Kemahan and Stark, 1958). The most widely used system is the one that employs the incisive foramen as the demarcating boundary between the primary and the secondary palate. Therefore, clefts are classified as involving the lip and/or alveolar process, hard and soft palate, or hard palate alone (Figure 15).

Figure 15. Variations in clefts of the lip and palate (Ross and Johnston, 1972)
c. Epidemiology:

Overall, epidemiologic comparisons between studies of CL/P are difficult because they vary depending on the source of the data (Ross and Johnston, 1972). The incidence of CL/P reported to occur among ethnicities is a gross estimate based on different sources of information, sample size, time of diagnosis, type of classification used, inclusion or exclusion of stillbirths and abortions in the base population (Meskin et al., 1968)

Orofacial clefts (OFC) represent a heterogeneous group of defects with a considerably range of dysmorphological severity (Mastroiacovo et al. - IPDTOC working group). Cleft lip with or without cleft palate is the most common maxillofacial malformation. The prevalence of cleft lip varies between ethnic groups averaging approximately 1 in 700 live births (Nguyen and Sullivan, 1993; Baxter, 2011) to 1 in 1000 live births (Habib, 1978). Several studies have demonstrated that the incidence is highest amongst Asians with the frequency reported to be between 1.6 and 2.71 in 1000 per live births, followed by Caucasians with a frequency somewhere between 0.69 and 2.35 per 1,000 live births, and lowest in people of African descent with frequencies that varied between 0.32 and 0.46/1,000 live births (Habib, 1978; Mitchell, 1997; Derijcke et al, 1996; Gundlach, 2006).

Cleft lip with cleft palate shows the highest incidence, followed by cleft lip alone and then by isolated cleft palate (Vanderas, 1987). Another common finding is the predominance of cleft palate in females, while CL/P is more common in males. Unilateral cleft lip and palate (UCL/P) occurs twice as frequently on the left side than the right, and is nine times more common than bilateral CL/P (Habib, 1978).

d. Cleft lip and palate versus control studies:

The presence of cleft lip and/or palate has been associated with other physical developmental anomalies. Cephalometric studies have shown that there are differences in facial relationships in
populations with and without clefts. These differences have been attributed to the management of the lip, palate or both, functional changes resulting from the mechanical presence of the cleft, genetic pattern, or a combination of these factors (Bishara et al., 1976).

Shprintzen (1985) examined 1,000 patients with clefts of the lip and palate, or both. The results of this study indicated that associated anomalies occur in 63% of patients with clefts. The lowest frequency of associated anomalies was seen with cleft lip (45%) and the highest with cleft palate (72%). Small stature and microcephaly occur most frequently in the cleft palate group and least frequently in the cleft-lip-only group. Clefts were most commonly associated with craniofacial anomalies that include severe maxillary or mandibular hypoplasia, severe orbital hypertelorism, orbital clefts, commissural clefts, nasal defects and facial asymmetry.

A number of studies have reported measurements of the craniofacial complex in order to determine what combination of craniofacial skeletal features might best describe the cleft lip and palate individual and to determine what proportions of the face might be particularly vulnerable to growth disturbances of the cleft lip and palate. Horowitz et al. (1976) conducted a study that compared lateral cephalometric radiographs of 39 children with repaired clefts of the lip and palate and 39 unaffected children matched for age and sex. They were able to identify six factors that together accounted for 92% of the observed variance in skeletal morphology. These factors included the nasopharyngeal-maxillary complex, cranial base, body and ramus of the mandible, the palate and the lower face. The authors also identified certain proportions of the face that appeared to be vulnerable to growth disturbances in cleft lip and palate individuals, such as the angles formed between the upper posterior facial region and the palatal plane, these angles were significantly larger in the cleft group and reflected rotation of the palatal plane in a clockwise direction.
i. Growth and body height:

There has been a debate in the literature as to whether children with clefts are smaller than other children. Duncan et al (1983) reported that children with clefts tend to be smaller than those without clefts. Sequential height determinations were made in 31 patients with isolated cleft palate and in 34 patients with cleft lip with or without cleft palate (CL/P) during an 11 year period. In patients with isolated cleft palate, body height percentiles tended to decrease with age. Beyond 8 years of age, none of the subjects exceeded the 50th percentile, and measurements in 26% of the patients with isolated cleft palate were consistently below the fifth percentile. After 4 years of age, the height percentiles in patients with CL/P were bimodular and clearly separable into a short group (65% below the 50th percentile) and a tall group (35% at or above the 70th percentile). Thus, short stature appears to be a component of nonsyndromic, multifactorial orofacial clefting (Duncan et al, 1983; Ross, 1972). Shprintzen et al. (1985) studied 1,000 patients with clefts of the lip, palate or both. Complete anthropometric and cephalometric data were obtained and compared to established norms. Small stature was a frequent finding, occurring most frequently in the cleft-palate only group and least frequently in the cleft-lip-only group and stated that there is a 28% chance that a child with a cleft will be short of stature. Bowers et al. (1987) compared the general body growth of children with different types of cleft with non-cleft patients. They reported no average differences from United States norms for children with clefts of the lip alone, bilateral cleft lip and palate and children without clefts. In contrast, children with unilateral cleft lip and palate and isolated cleft palate were significantly shorter than the unaffected control sample. They also report sex differences in which males with unilateral cleft lip and palate were significantly shorter and thinner (lower body mass index, BMI) than unaffected ones. In addition, males with isolated cleft palate had average heights even lower than those of unilateral cleft lip and palate males. Females with isolated cleft palate were shorter than unaffected females especially after mid-childhood, and on average were shorter than
females with unilateral cleft lip and palate. However, females with clefts showed no significant differences in the mean BMI scores from unaffected females. Bowers (1988) suggested that age, as well as sex and cleft type, are associated with growth status variation in individuals with oral clefts.

ii. **Growth and development of the facial skeleton:**

Recent literature contains numerous studies on the structure, relative positions, and growth of the maxillae in normal individuals and individuals with cleft lip and palate. Nakamura et al. (1972) compared longitudinal samples of 45 boys and 40 girls grouped according to the extent of their deformities with normal children. Cephalometric measurements included; mandibular ramus height (condylion to gonion), body length (gonion to pogonion), maximum mandibular length (condylion to pogonion), bigonial width, bicondylar width, left to right zygomatico-maxillary suture and left to right pterygomaxillary fissure. The authors found that children with isolated cleft palate showed significantly smaller mandibular length measurements. Boys with cleft palate also showed a significantly smaller right to left pterygomaxillary fissure distance. Children with cleft lip and palate showed significantly greater bizygomatico-maxillary suture widths and smaller mandibular length measurements than did normal children. Fish (1973) studied 30 children with cleft palate and 30 children without clefts between birth and three years of age and found that while posterior width of the maxillary arch was greater at birth in children with clefts than unaffected children, by three years of age the mean posterior and intercanine widths of the arch in the cleft group were significantly less than normal. Krogman et al. (1975) reported an association between palatal clefting and decreased maxillary length in normal and children with cleft palate between birth and six years. With regard to mandibular growth, the cleft group exhibited retrognathism but no micrognathism, and no significant differences in mandibular symphyseal height were found. Mapes et al. (1974) reported that in
unilateral complete clefting of the lip and palate, arch length is not significantly different from unaffected individuals. Hayashi et al. (1976) studied 255 Japanese children with cleft palate and unaffected individuals, and found that in the cleft group, the maxillae were more posterior-superiorly positioned, the mandibular rami were shorter, the gonial angles were more obtuse, and the chins were typically retropositioned. In 1976, Bishara published a cephalometric study evaluating facial growth in 32 unaffected children, 12 repaired and 8 unrepaired individuals with isolated clefts of the palate. Comparison of the total cleft group with the unaffected group indicated that the maxilla and the mandible were both positioned more posteriorly in the cleft group. Maxillary depth was also smaller in the cleft group. No significant differences were found between the two cleft groups. The author also reported a tendency for the mandibular plane to be steeper and the lower incisors to be more lingually positioned in the cleft group than the control- unaffected group.

Changes in facial proportions have been a topic of interest. Nakamura et al. (1972) found that facial growth rates appeared to be the same in children with cleft deformities as in normal children. Krogman et al (1975) found that individuals with cleft palate exhibit increased upper and lower face heights, while Hayashi et al (1976) found that upper facial height is reduced while lower face height is increased. Horowitz et al. (1976) reported that both upper and lower facial heights were affected in cleft lip and palate; the upper anterior facial height was reduced while the lower anterior facial height was increased. Maue-Dickson (1979) suggested that part of the disagreement in studies that evaluate facial proportions in individuals with clefts may result from differences in methodology, particularly in the selection of measurement points or from ethnic differences.

Sagittal deficiency of the midface resulting in a concave profile is the most prominent feature in adult patients with complete unilateral cleft lip and palate (Goyenc et al. 2008). Smahel et al (1991) studied the craniofacial morphology in a sample of 58 adult males with unilateral (right-sided) cleft
lip and palate. They report facial skeletal deviations such shortening of maxillary depth, reduction of the upper face height, widening of some maxillary dimensions (interorbital and of nasal cavity), shortening of the mandibular body and ramus, obtuse gonial angle, acute chin angle, and steeper slope of the mandibular body. There was also a displacement of the whole maxillae backwards, and a reduction of the height and of the thickness of the upper lip.

iii. The cranial base:
Ross (1965) reported that the cranial base in patients with unilateral cleft lip and palate is smaller, with highly significant differences in increased the clivus-orbital plane and the clivus-cribiform plane angles.

Krogman et al (1975) reported that anterior cranial base length and clival length in children with cleft palate are greater than normal. The cleft group also showed a greater flexion of the sella angle that did the normal group, and both linear and angular measurements were noted to be more severe in the cleft lip and palate group than the cleft palate group. The authors suggested that there is a close relationship between the various structural components of the craniofacial midline and specifically, that palatal clefting may have repercussions in adjacent bony structures in both the cranial base (occipital, sphenoid, and ethmoid bones) and facial areas (involving the midfacial complex). Hayashi et al (1976) noted that the cranial base angle was more obtuse in the cleft subjects than in unaffected controls. Sandham and Cheng (1988) compared lateral cephalometric radiographs of 30 patients with combined cleft lip and palate deformities and 61 non-cleft patients, and reported that the cleft group showed a significantly smaller clivus length; the cranial angulation did not differ significantly between the total cleft sample and the control group. The authors suggest the possibility
that the anomaly of cleft lip and palate and changes in the spheno-occipital syncondrosis, which controls clivus length, may be related.

Smahel et al (1991) suggested that subjects with unilateral cleft lip and palate have a slightly smaller neurocrania without marked changes in the cranial base. Nielsen et al. (2005) evaluated the sella turcica morphology and maxillary bone size in 20 unilateral cleft lip and palate and 20 unilateral cleft lip newborn patients. Analysis of the sella turcica morphology was performed on lateral radiographs and analysis of the maxillary bone size was performed on axial radiographs. They found a profound asymmetry in the maxillary areas in unilateral cleft lip and palate, but not in unilateral cleft lip. In both cleft types, approximately half of the individuals had deviations in sella turcica morphology with the most severe deviations occurring in newborns with unilateral cleft lip and palate.

iv. Tooth development:
Several growth factors are of major importance during craniofacial development, and these factors may be overexpressed or underexpressed when a cleft occurs. Furthermore, these can modify odontogenesis by causing abnormalities of the dental lamina (Mitsea and Pyropoulus, 2001). Dental eruption patterns have been widely studied in patients with cleft lip and palate (Pham et al, 1997; Harris et al, 1990; Solis et al, 1998). Most investigators have reported an increased delay in tooth development and a higher occurrence of dental anomalies in cleft palate subjects (Ranta et al., 1986; Shprintzen et al., 1985). Moreover, delay in tooth development, asymmetric tooth development, anomalies in size and shape, and hypodontia have been shown to occur more often in children with clefts (Werner and Harris, 1989; Eerens et al., 2001). Ranta (1986) reported that tooth development is delayed from 0.3 to 1.1 years in cleft patients. Some studies have also shown different effects for females and males with clefts, with males exhibiting more significant tooth delays (Pham et al.,
Borodkin et al. (2008) in a sample of 49 children with cleft lip and palate from 6 to 13 years of age and 49 matched controls determined a correlation between delayed permanent tooth development and cleft lip and palate of 0.52 years with males accounting for all the delay. This delay was independent of the cleft severity, with an equal delay in both unilateral and bilateral cleft lip and palate. The authors suggested a trend toward less dental delay in children with cleft of the primary palate only compared to children with clefts of the primary and secondary palate. It has been suggested that the upper lateral incisor is the most susceptible tooth to injury in the area of the cleft in both deciduous and permanent dentitions, and that this tooth is affected in most instances, even in the cases of microforms of cleft lip (Ranta et al., 1986). In contrast, Harris and Hullings (1990) found that teeth formed early during postnatal development (permanent first molars) were most affected, while those formed later (premolars, second molars) were least affected. Solis and coworkers (1998) found that teeth on the cleft side were delayed, with the degree of delayed corresponding to proximity of the cleft. The lateral incisors were most delayed, followed by the canines and premolars. Borodkin (2008) found that first and second premolars, followed by the second molars were most often delayed in cleft subjects.

Several studies report asymmetric tooth development in patients with clefts (Eerens et al., 2001; Pham, 1986; Harris and Hullings, 1990). Ranta (1986) reported that the prevalence of hypodontia increases strongly with the severity of the cleft and an asymmetric formation of the contralateral teeth is a milder form of hypodontia. Moreover, if hypodontia is present, the tooth development is more severe and this delay may increase with age. Smaller permanent teeth, enamel defects and abnormalities in shape and size of both deciduous and permanent teeth are more common in children with clefts than in normal subjects. More teeth are congenitally missing in the upper arch than from the lower arch in the deciduous dentition, while in the permanent dentition both jaws are equally affected (Ranta, 1989).
e. Skeletal maturity:

The upper face follows Scammon’s neural growth curve (Scammon, 1930; Tanner, 1975) whereas the jaws are influenced by sex steroid hormone level increases at puberty (Enlow et al., 1998). Bowers et al (1987) demonstrated somatic growth deficits in children with clefts in where children with cleft palate and with unilateral cleft lip and palate have heights that are rarely above average, and sometimes they also have below-average body mass indices.

Hand-wrist radiograph studies in children with clefts show conflicting results. Menius and coworkers (1966), and Fleischer-Peters and Reicher (1981) reported delays in skeletal age in cleft lip and palate boys. Furthermore, Jensen et al (1983) reported a slight skeletal age delay in males with clefts. In contrast, Prahl-Andersen (1979) studied the skeletal and the dental maturity in a group of 189 children with cleft lip and/or cleft palate using radiographs of the wrist joint from 4 to 14 years. 486 normal children involved in the Nijmegen growth study served as control subjects. The author reported that the progression in skeletal maturity was greater in females with clefts than in females without clefts, while males with clefts did not show a remarkable difference in skeletal maturity compared with unaffected males. In a recent study Bowers (2011), studied the skeletal age patterns in children with clefts (cleft palate, unilateral cleft lip and palate, bilateral cleft lip and palate and cleft lip) using the Tanner-Whitehouse 2 method in 160 serial hand-wrist radiographs. The author concluded that skeletal age in children with clefts differed from unaffected children, where males and females showed different maturational patterns. Males with bilateral cleft lip and palate frequently had a delay in skeletal age and children with unilateral cleft lip and palate did not show a clinically significant skeletal age delay. On the other hand, some females with unilateral cleft lip and palate showed an advanced skeletal age compared with unaffected females.
f. Cervical vertebrae anomalies in patients with cleft lip and palate

The primitive embryonic cellular origins of upper cervical vertebrae, and the basilar and condylar components of the occipital bone, are similar. These all develop from parachordal cartilage that arises from the cranial end of the notochord and incorporates the fused sclerotomes of the four occipital and upper cervical somites. Consequently, it has been reported a possible association between cleft lip and palate and changes in the spheno-occipital synchondrosis (Sandham and Chen, 1988).

Ross and Lindsay (1965) compared lateral and posterior-anterior cephalometric radiographs of 342 patients with cleft lip, unilateral cleft lip and palate, bilateral cleft lip and palate and isolated cleft palate with 800 cephalometric images of patients without clefts from the Burlington Orthodontic Research Centre. They found that severe congenital synostosis of the cervical vertebrae was frequently associated with isolated cleft palate. Furthermore, mild anomalies occurred with the same frequency in cleft patients that non-cleft patients.

In a later study, Osborne et al (1971) investigated the prevalence of cervical vertebrae anomalies (CVA) in cleft patients. Their results suggest that anomalies of the cervical vertebrae occur more often in patients with cleft palate compared with a non-cleft subjects. In addition, Sandham (1986) evaluated the prevalence of CVA in 105 patients with cleft lip, cleft palate, unilateral cleft lip and palate and bilateral cleft lip and palate in comparison to 120 non-cleft patients. The results of this study confirmed that CVA occurred significantly more often in the cleft sample (13%) than in controls (0.8%). Moreover, posterior arch deficiency occurred significantly more often in cleft palate (16%) than in controls.

The prevalence of anomalies of the upper cervical vertebrae in oro-facial cleft malformations has been studied comparing different types of clefts with a noncleft group. A common finding has been
that individuals with craniofacial clefts also have a high prevalence of upper cervical spine anomalies compared with the general population (Osborne et al., 1971; Sandham, 1986; Horswell, 1991).

Cervical vertebrae anomalies are divided into posterior arch deficiency and fusions (Sandman, 1986). Posterior arch deficiencies are subdivided into spina bifida, which involves incomplete ossification of the spinous process, dehiscence, characterized by incomplete development of structure, and fusion, defined as the bone union of more than one unit with another at the articulation facets (Osborne, 1971; Sandham 1986; Ugar and Semb, 2001).

Ugar and Semb (2001) analyzed 611 lateral films of patients from the Oslo Cleft Lip and Palate Dentofacial Growth Archive, and 264 lateral cephalometric films from children without cleft. They concluded that cervical vertebral anomalies occurred more frequently in subjects with clefts than in subjects without clefts. The degree of association differs for the different cleft subtypes and CVA appear to be more closely associated with cleft palate only (CPO) and bilateral complete cleft lip and palate (BCLP).

Lima et al (2009) analyzed 600 cephalograms of 300 patients with clefts and 300 without clefts and investigated the prevalence of posterior arch deficiencies and fusion of patients with isolated cleft lip, isolated cleft palate, and complete cleft lip and palate compared with a non-cleft group. The results indicated that the prevalence of cervical vertebrae anomalies (CVA) between cleft (38.67%) and non-cleft groups (31%) was statistically significant. However, no statistically significant difference was found among the type of cleft and CVA, indicating that the occurrence of cervical vertebrae anomalies is independent of the cleft type and gender.
Other variations of the cervical vertebrae in patients with clefts include shortening of the length of the cervical spine C2 to C7. Smahel and Skavarilova (1993) measured the length of the cervical spine in 206 adult males with cleft lip and/or palate compared with a 50 aged-matched subjects in the control group. A 3mm average shortening of the spine was most marked in complete bilateral cleft lip and palate patients, less marked in unilateral cleft lip and palate patients and it was slight in isolated cleft palate patients. Complete isolated cleft palate and cleft lip was not associated with shortening of the cervical spine. Furthermore, the authors found that patients with bilateral and unilateral cleft lip and palate with short cervical spine also had a shorter mandibular ramus. In addition, Zuñiga et al (2000) found that children with unilateral cleft lip and palate presented a significant increase in the extension of the head on the neck, forward position of the cervical spine, and a decrease in the curvature of the cervical spine in comparison with children without clefts.
III. PURPOSE

The purpose of this study was to compare cervical spine maturation in children with non-syndromic complete unilateral cleft lip and palate and age- and sex-matched non-cleft individuals.
IV. RESEARCH QUESTIONS:

1. Do children with complete unilateral cleft lip and palate show a difference in cervical vertebral maturation, when compared with an age- and sex-matched non-cleft sample?

2. Is there a difference in skeletal maturation between females with UCLP and females without a cleft?

3. Is there a difference in skeletal maturation between males with UCLP and males without a cleft?

4. Is there a difference in the prevalence in cervical vertebrae anomalies between children with UCLP and children without clefts?
V. HYPOTHESES:

Null Hypothesis 1:
There is no significant difference in cervical vertebral maturation in children with UCLP and non-cleft subjects.

Alternate Hypothesis 1:
There is a significant difference in cervical vertebral maturation in children with UCLP and non-cleft subjects.

Null Hypothesis 2:
There is no significant difference in cervical vertebral maturation between males with UCLP and males without a cleft.

Alternate Hypothesis 2:
There is a significant difference in cervical vertebral maturation between males with UCLP and males without a cleft.

Null Hypothesis 3:
The is no significant difference in cervical vertebral maturation between females with UCLP and females without a cleft.

Alternate Hypothesis 3:
There is a significant difference in cervical vertebral maturation between females with UCLP and females without a cleft.
Null Hypothesis 4

There is no significant difference in the frequency of cervical vertebrae anomalies between children with UCLP and children without clefts.

Alternative Hypothesis 4

There is a significant difference in the frequency of cervical vertebrae anomalies between children with UCLP and children without clefts.
VI. MATERIALS AND METHODS:

1. Sample:

The cleft sample consisted of 62 subjects (34 males and 28 females) with complete unilateral cleft lip and palate (UCLP). The subjects were selected from the files of the Craniofacial Centre at The Hospital for Sick Children, Toronto. The sample was limited to Caucasians who had lateral cephalometric radiographs taken at 10, 12 and 14 years of age. Excluded from the study were children that were syndromic or with medical conditions suggestive of a syndrome. The mean ages for the UCLP groups were 10 years (range, 9.5 to 10.6 years), 12.2 years (range, 11.4 to 12.6 years), and 14.1 years (range, 13.5 to 14.6 years).

The control group consisted of 50 subjects (25 males and 25 females) from the Burlington Growth Centre, Discipline of Orthodontics, Faculty of Dentistry, University of Toronto matched for age, ethnicity and sex with the UCLP group. Control subjects had a lateral cephalometric radiograph taken at 10, 12 and 14 years of age. The mean ages for the groups were 10.1 years (range, 9.9 to 10.2 years), 12.0 years (range, 11.9 to 12.2 years) and 14.0 years (range, 14.0 to 14.1 years). The demographics of the study and control groups are summarized in Table 1.
Table 1. Sample Age Characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Sample size</th>
<th>Mean Age (years)</th>
<th>SD</th>
<th>Age range (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCLP</td>
<td>62</td>
<td>10</td>
<td>0.4</td>
<td>9.5 - 10.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12.2</td>
<td>0.4</td>
<td>11.4 - 12.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14.1</td>
<td>0.4</td>
<td>13.5 - 14.6</td>
</tr>
<tr>
<td>Control</td>
<td>50</td>
<td>10.1</td>
<td>0.1</td>
<td>9.9 - 10.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12.0</td>
<td>0.2</td>
<td>11.9 - 12.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14.0</td>
<td>0.1</td>
<td>14.0 - 14.1</td>
</tr>
</tbody>
</table>

2. Methodology:

This study is a retrospective chart review and radiographic analysis, approved by the Research Ethics Board Committee from the Hospital for Sick Children and the Burlington Growth Centre (University of Toronto). A total of 342 cephalometric radiographs were collected.

All cervical vertebral stages readings were done by the same investigator (CC) using the 6-stage method described Baccetti et al. in 2005. Figure 8 shows the 6-stage method of vertebral assessment. Prior to evaluating the vertebral assessments, the investigator (CC) was calibrated by Drs. Franchi and McNamara (University of Michigan). Thirty-six random cases were selected, and the investigator (CC) performed the cervical vertebral assessment in 2 different sessions. These results were compared with Dr. Franchi’s cervical vertebral assessment to determine the inter-class correlation coefficient. The same CVM readings performed by the investigator (CC) during two
different sessions, these were used to determine the reliability of the method (intra-class correlation coefficient).

3. Statistical Analysis:

The statistical analysis was performed in the Research Institute at the Hospital for Sick Children using the Statistical Analysis System (SAS) version 9.3 (SAS Institute Inc. Cary, North Carolina, USA). The Kappa test for categorical data (cervical vertebral stages, CS) was used to determine the reliability of the method. The Cochran Mantel-Hazen test was performed to compare the overall significance of categorical data between the cleft and control groups. The Chi Square test was used to compare CS between the sex- and age-matched cleft and control groups (UCLP males versus control males, UCLP females versus control females, UCLP females versus UCLP males, and control females vs control males). Due to sparseness in the categorical data (certain cervical stages were not available at a given time-point), the model did not reach convergence. For this reason, on the recommendation of the statistician, multinomial logistic regression analysis using the maximum likelihood procedure was used to adjust the model and determine odds ratio between cleft and control group. A significance level of \( p < 0.05 \) was applied to all analyses, and probabilities were modeled over the lower ordered values.
VII. RESULTS

1. Reliability

a. Inter-rater reliability for cervical vertebral stages

The Kappa test for inter-rater reliability for the cervical vertebral maturation stage assessment from the calibration session with Dr. Franchi was 0.8 for the first session and 0.9 for the second session. The results from the reliability testing showed an exact agreement for stages CS 1, CS2 and CS3 and partial agreement for stages CS4 and CS5.

b. Intra-rater reliability for cervical vertebral stages

The Kappa test for intra-rater reliability for the cervical vertebral maturation stage assessment was 0.79 with an exact agreement for stages CS 1 and CS6, and partial agreement for stages CS2, CS3, CS4 and CS5.
2. Cervical vertebral maturation stage:

Unilateral cleft lip and palate (UCLP) group versus Control group:

There was a significant difference in the CVM between children with unilateral cleft lip and palate and controls. The odds ratio was 1.9 (p=0.0005) indicating an association between a cleft and a delay in skeletal maturation (Table 2).

Table 2. Multinomial logistic regression for odds ratio in CVM between UCLP and controls

<table>
<thead>
<tr>
<th></th>
<th>p value</th>
<th>Odds Ratio</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCLP vs Control</td>
<td>0.0005***</td>
<td>1.9</td>
<td>1.3 - 2.9</td>
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</tbody>
</table>

Statistically significant at *p < 0.05; ** p < 0.01; p < 0.001***

The cervical vertebral maturation stages are tabulated by sex and age in Tables 3 and 4. The data distributions are shown in Figures 16 thorough 21. Table 5 Summarizes results from multinomial logistic regression to predict the odds ratio of the effect of a cleft in the skeletal maturation using the cervical vertebral maturation method.
Unilateral Cleft Lip and Palate Males:

Table 3. Cervical Maturation Stage (CS) for males in the UCLP group and matched un-affected controls

<table>
<thead>
<tr>
<th>CS</th>
<th>Age 10</th>
<th></th>
<th>Age 12</th>
<th></th>
<th>Age 14</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UCLP</td>
<td>Control</td>
<td>p</td>
<td>UCLP</td>
<td>Control</td>
<td>p</td>
</tr>
<tr>
<td>1</td>
<td>62% (n=21)</td>
<td>32% (n=8)</td>
<td>0.012*</td>
<td></td>
<td></td>
<td>0.023*</td>
</tr>
<tr>
<td>2</td>
<td>38% (n=13)</td>
<td>56% (n=14)</td>
<td>32% (n=11)</td>
<td>12% (n=3)</td>
<td>68% (n=23)</td>
<td>76% (n=19)</td>
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<tr>
<td>3</td>
<td>12% (n=3)</td>
<td></td>
<td>68% (n=23)</td>
<td>76% (n=19)</td>
<td></td>
<td>21% (n=7)</td>
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<td>4</td>
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<td>12% (n=3)</td>
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<td></td>
<td>60% (n=15)</td>
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<td>5</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| n  | 34 | 25 | 34 | 25 | 34 | 25 |

CVMS: Cervical vertebral maturation stage (1 to 6), UCLP: unilateral cleft lip and palate
Statistically significant at *p < 0.05; ** p < 0.01; *** p < 0.001

At 10 years of age, the cervical vertebral maturation stages (CS) in males with UCLP is 62% (CS1) and 38% (CS2). In comparison, the frequencies in the control group are 32% (CS1), 56% (CS2) and 12% (CS3).

At age 12, the distribution of CS is 32% (CS2) and 68% (CS3) for the UCLP group and 12% (CS2), 76% (CS3) and 12% (CS3) for the control group.

At 14 years of age, the distribution of CS in the UCLP group is 21% (CS2) and 79% (CS3). The frequencies in the control group are 12% (CS2), 60% (CS3) and 28% (CS4).

The odds ratios are 3.9 (p=0.012), 4.9 (p=0.023), and 5.6 (p=0.014) for ages 10, 12 and 14 years, respectively, indicating that male UCLP subjects are statistically more likely to experience a delay in cervical vertebral maturation compared with control males. These findings are summarized in Table 3 and Table 5. Distributions for males are shown in Figure 16, 17 and 18.
Figure 16. Cervical vertebral maturation stages (CS) for males in UCLP group and controls at 10 years of age.

Figure 17. Cervical vertebral maturation stages (CS) for males in UCLP group and controls at 12 years of age.
Figure 18. Cervical vertebral maturation stages (CS) for males in UCLP group and controls at age 14 years of age.
### Unilateral Cleft Lip and Palate Females:

Table 4. Cervical Maturation Stage (CS) for females in the UCLP group and matched un-affected controls

<table>
<thead>
<tr>
<th>Age 10</th>
<th>Age 12</th>
<th>Age 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS</td>
<td>UCLP (n=16)</td>
<td>Control (n=3)</td>
</tr>
<tr>
<td>1</td>
<td>57% (n=11)</td>
<td>12% (n=4)</td>
</tr>
<tr>
<td>2</td>
<td>39% (n=11)</td>
<td>16% (n=14)</td>
</tr>
<tr>
<td>3</td>
<td>4% (n=1)</td>
<td>7% (n=2)</td>
</tr>
</tbody>
</table>

CVSS: Cervical vertebral maturation stage (1 to 6), UCLP: unilateral cleft lip and palate
Statistically significant at *p < 0.05; ** p < 0.01; *** p < 0.001

At 10 years of age, the cervical vertebral maturation stages (CS) in females with UCLP were 57% (C1), 39% (CS2) and 4% (CS3). The frequencies in the control group are 12% (CS1), 72% (CS2) and 16% (CS3).

At age 12, the CS distribution for the UCLP group is 32% (CS2), 61% (CS3) and 7% (CS4). The frequencies in the control group are 60% (CS3) and 40% (CS4).

At 14 years of age, the CS distribution in the UCLP group is 25% (CS2), 50% (CS3) and 25% (CS4). The frequencies in the control group are 48% (CS3) and 52% (CS4).

The odds ratios are 8.5 (p=0.001), 14.7 (p=0.001), and 4.5 (p=0.008) for ages 10, 12 and 14 respectively, indicating that females with UCLP are statistically more likely to experience a delay in cervical vertebral maturation compared with control females. These results are summarized in Table 4 and 5. Distributions for females are shown in Figure 19, 20 and 21.
Figure 19. Cervical vertebral maturation stages (CS) for females in UCLP group and controls at 10 years of age.

Figure 20. Cervical vertebral maturation stages (CS) for females in UCLP group and controls at 12 years of age.
Figure 21. Cervical vertebral maturation stages (CS) for males in UCLP group and controls at 10 years of age.

Table 5. Odds ratios for UCLP and controls with cervical vertebral maturation stage

<table>
<thead>
<tr>
<th></th>
<th>10 years</th>
<th></th>
<th>12 years</th>
<th></th>
<th>14 years</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p</td>
<td>Odds</td>
<td>95 % CI</td>
<td>p</td>
<td>Odds</td>
<td>95 % CI</td>
</tr>
<tr>
<td>Males</td>
<td>0.012*</td>
<td>3.9</td>
<td>1.3 - 11.6</td>
<td>0.023*</td>
<td>4.9</td>
<td>1.2 - 19.3</td>
</tr>
<tr>
<td>Females</td>
<td>0.001**</td>
<td>8.5</td>
<td>2.3 - 31.1</td>
<td>0.001**</td>
<td>14.7</td>
<td>2.9 - 72.8</td>
</tr>
</tbody>
</table>

CI: Confidence Interval
Statistically significant at p < 0.05*; ** p < 0.01; p < 0.001***
Sex Differences:

Table 6. Differences between males and females in CS within the UCLP and control groups

<table>
<thead>
<tr>
<th></th>
<th>Age 10</th>
<th>Age 12</th>
<th>Age 14</th>
<th>p</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCLP</td>
<td>0.52</td>
<td>0.28</td>
<td>0.005***</td>
<td>0.125</td>
<td>1.3</td>
<td>0.9 - 1.9</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>0.23</td>
<td>0.02*</td>
<td>0.07</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CVM: Cervical vertebral maturation stage; UCLP: unilateral cleft lip and palate
Statistically significant at *p < 0.05; ** p < 0.01; p < 0.001***

There was no significant difference in CS between males and females among the 10 and 12 year-old children with UCLP, and 10 year old control children. There was, however, a significant sex difference in CS between the UCLP at 14 years of age, and at 12 of age in control subjects. Overall, when all the females from the UCLP group and controls were compared with males from the UCLP and controls, there was no significant difference in CS (p=0.125).
VIII. DISCUSSION

Stages of child maturation can be determined, or estimated in several ways and usually require special technology to accomplish. Lateral cephalometric radiographs have been used extensively to assess skeletal maturation of the craniofacial skeleton. More recently, cervical maturation has been assessed on lateral cephalometric radiographs because they are used regularly in orthodontic diagnosis (Baccetti et al., 2002).

This is the first study that evaluates skeletal maturation in patients with UCLP using the cervical vertebral maturation (CVM) method. However, from a developmental point of view, results of the present study support the idea of several studies that have pointed out that there is a close interrelationship between the presence of a cleft and alterations in craniofacial skeleton. The CVM method employed in this study was described by Baccetti et al (2005). Many researchers have reported that the CVM is a reliable maturational indicator (Lamparski, 1972; Hassel, 1995; Mito et al., 2002), although others have reported poor reproducibility (Netsman et al., 2011; Zhao et al., 2012). In our study, the reproducibility of the CVM method was excellent with high inter- and intra-examiner reliability coefficient values of 0.8 and 0.9 (inter-examiner) and 0.79 (intra-examiner). Based on these results we considered the CVM method a reliable one to determine skeletal maturation in our subjects.

Previous studies confirmed that children with clefts have marked differences in the facial skeleton, some maxillary dimensions (Smahel et al 1991), nasofrontal process and orbital width (Goyec et al., 2008), body mass index (BMI) and body height versus those without clefts (Bowers, et al., 1988). Some of these studies compared cleft populations to unmatched control subjects whose data were collected at a separate time and place (Nakamura et al, 1972; Bishara et al. 1976). Furthermore,
ethnic variations in the relationships between skeletal maturity established by cervical vertebrae have been previously reported (O’Reilly and Yannielo, 1991; Garcia-Fernandez et al., 1998, San Roman et al., 2002).

This study attempted to match, as closely as possible, the cleft subjects with normal, non-cleft subjects on the basis of age, sex, and ethnicity from the same geographical area, who were their contemporaries. The results indicate that when the CVM method is used to determine skeletal maturation, children with UCLP are significantly delayed compared with their sex-, age-, and ethnicity-matched controls (p= 0.0005). The cervical vertebral maturation of males with UCLP was significantly delayed over the controls, and this was demonstrated at ages 10, 12 and 14. Females with UCLP also showed a statistically significant delay in the same age groups. When the UCLP females and males were pooled and compared with unaffected controls, the results show that children with UCLP were 1.9 times more likely to show a delay in skeletal maturation compared with controls (p<0.001). These finding are comparable with the results of Jensen et al. (1983), who reported that skeletal maturity using the TW2 (1982) was slower in children with clefts from 6 to 20 years of age. Our findings, however, disagree with those of Bowers et al (1987), who reported that children with unilateral cleft lip and palate did not show skeletal age delay. In fact, females showed an advance skeletal maturation compared with unaffected females. Prahl-Andersen (1979) found that females with clefts showed a greater progression in skeletal maturity than females without clefts, and males with clefts did not show a remarkable difference in skeletal maturity compared to unaffected males. It is possible that part of these conflicting results may be attributable to the fact that their age estimates were made using hand-wrist radiographs, selection of the sample, which included different types of clefts, and subjects from different ethnic background. Moreover, the inclusion criteria of previous studies vary significantly from study to study thus making comparison difficult. In order
that confounding effects of different types of clefts in the sample were eliminated, our study included children with one type of cleft (UCLP).

Cephalometric studies have shown there to be differences in facial relationships in children with UCLP and children without clefts with a tendency for a relative retraction of the anterior portion of the maxilla, steeper mandibular plane, larger mandibular length and increased face height. These differences in facial morphology between cleft and non-cleft populations have been attributed to the management of the lip, palate or both, functional changes resulting from the mechanical presence of the cleft, inherited trait such as genetic influences on size and form, or a combination of these factors (Bishara et al., 1976b). Several studies report an association between UCLP and cervical vertebrae shortening (Smahel and Skavarilova, 1993), forward position and decrease in the curvature of the cervical spine (Zuñiga et al., 200). Chen et al (2008) suggested that the growth of the cervical vertebral width was almost completed during early cervical growth, and, cervical vertebrae were increased in height later in growth. It is possible that children with UCLP were generally smaller in stature that controls, with this effect shown in a difference in the cervical maturation stages.

Various explanations have been used to explain the growth lag reported in children with clefts. These include slow growth during embryogenesis, slow postnatal growth of children with clefts (Bowers et al., 1987), feeding difficulties after birth (Drillien et al., 1966), and an increased frequency of airway infections, middle ear disease and colds (Seth and Williams, 1988). There are also reports in the literature of the association of growth-hormone deficiency and cleft lip, cleft palate, or both (Laron et al., 1969; Rudman et al.1978, Seth and McWilliams, 1988). A possible explanation may lie in the embryological process by focusing on the primitive embryonic cellular origins of the upper cervical vertebrae from the parachordal cartilage that arises from the cranial end of the notochord and incorporates the scleratomes of the four occipital and upper cervical somites.
It has been postulated that the nasal capsule and the nasal septum have cellular origins in the scleratomes of this area (Wilson, 1973). Furthermore, Sandham (1986) suggests the possibility of that the mechanism involved in palatal shelf fusion during embryonic development may also have an effect on the development of the first cervical vertebrae.

Conflicting results exist regarding the effect of clefting in skeletal maturation in females and males. Some studies have shown different effects for females and males with clefts. The present study noted sex differences in the UCLP group 14 years of age (p =0.005) and at 12 years of age for the control group (p< 0.05). These finding are in accordance with the results reported by Björk (1972), Fishman (1979) and Hägg (1980), who observed a sexual divergence in the growth patterns in non-cleft subjects. When examined sex differences between females and males, the results show a trend toward females developing skeletally 30% faster than males. This difference, however, was not statistically significant (p=0.125). This might be possibly due to combining the data from the cleft and noncleft subjects, and not having enough power.

A finding of the present study was that of the 6 cervical vertebral stages, the highest cervical vertebral maturation stage (CS) for the UCLP groups was CS4 and CS5 for the controls. Baccetti et al. (2005) report in their results a mean chronological age of 165.1 months (13.7 years) for CS6. However, the literature demonstrates that chronological age cannot be used as a parameter for the appraisal of individual skeletal maturation and our data is not directly comparable with previous studies performed by Baccetti and coworkers (2000, 2002, 2005).

In the present study, two of 64 cases (3%) were excluded from the UCLP sample due to fusion of two cervical vertebrae (C2 and C3). Comparatively, we did not find cervical vertebrae anomalies (CVA) in the control sample. This result agrees with Ross and Lindsay (1965) who reported that mild cervical vertebrae defects in which one vertebra was involved or there was fusion of only two
vertebrae did not occur more frequent in unilateral clefts than non-cleft controls. On the other hand, Lima et al (2009) reported a CVA prevalence in children with clefts of 38% with no statistical difference among the cleft types. It is reasonable to suggest that differences in frequency with other studies can be attributed to the inclusion/exclusion criteria for the cleft type in this study.

This study found a significant difference in skeletal maturation between children with UCLP and sex-matched non-cleft controls. This skeletal delay should be considered when planning treatment and timing of surgeries.

One limitation of this study was the absence of continuing records to assess cervical vertebral maturation over time until full skeletal maturation was achieved. Because the records were collected at three discrete time points (ages 10, 12 and 14 years), no comment can be made on whether children with unilateral cleft lip and palate exhibit a catch-up of skeletal maturity during early adolescence as has been suggested by other growth studies on CLP. This study is the first to investigate the difference in skeletal maturation using the CVM method between children with UCLP and children without a cleft lip and/or palate. These findings may be helpful for the determination of the expected delay in skeletal maturity in children with UCLP. However, to have a better understanding of the interrelation between skeletal maturation and orofacial clefts, further investigations should be performed to evaluate other types of clefts using longitudinal cephalometric records. In addition, determining the exact socioeconomic level for each subject was not possible, since this factor may influence development and growth generally.
IX. STUDY LIMITATIONS

- It was not possible to evaluate skeletal maturation in patients with UCLP beyond age 14. Thus, it was not possible to determine if a skeletal catch-up exists in children with UCLP, as it has been found in studies on other maturation indices.

- In this study, the investigator was able to achieve a high reliability coefficient in identifying the cervical vertebral maturation stages. Skeletal maturation, however, is a continuous process and each stage of maturation blends into the next stage, making the 6-stage CVM method sometimes difficult to differentiate borderline cases.
X. CONCLUSION

At age 10, 12 and 14, the cervical vertebral maturation stages for children with unilateral cleft lip and palate were significantly delayed compared with children without a cleft. This was true for both males and females.
XI. References


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Rose GJ. A Cross-Sectional Study Of The Relationship Of Facial Areas With Several Body Dimensions. Angle Orthod. 1960 01/01; 2012/07;30(1):6-13


Ross RB, Lindsay WK. The Cervical Vertebrae as a Factor in Etiology of Cleft Palate. Cleft Palate J. 1965 Jul;36:273-81


## XII. Appendix

### 1. Appendix A

#### a. Reliability of the Method

The SAS System 21:47 Sunday, May 6, 2012 1

The FREQ Procedure

Table of morningCVM by afternoonCVM

<table>
<thead>
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The SAS System 21:47 Sunday, May 6, 2012 2

The FREQ Procedure

Statistics for Table of morningCVM by afternoonCVM

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Kappa Statistics

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Sample Size = 36

The SAS System 21:47 Sunday, May 6, 2012 3

The FREQ Procedure

Table of CVM1_camila1 by CVM_GS1

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The SAS System 21:47 Sunday, May 6, 2012 4

The FREQ Procedure

Statistics for Table of CVM1_camila1 by CVM_GS1

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Kappa Statistics

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Sample Size = 36


The FREQ Procedure

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The SAS System 21:47 Sunday, May 6, 2012 6

The FREQ Procedure

Statistics for Table of CVM_camila2 by CVM_GS2

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