Université de Montréal

A comparative retrospective clinical study of hypodontia in Pierre Robin sequence and isolated cleft palate: distribution, number and sites affected

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A comparative retrospective clinical study of hypodontia in Pierre Robin sequence and isolated cleft palate: distribution, number and sites affected

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RÉSUMÉ

La séquence de Pierre Robin (SPR) représente une triade de symptômes distinctifs d'expression simultanée: micrognatie, glossoptose – causant une obstruction respiratoire – et fissure palatine. Le but de cette étude rétrospective est d'étudier l'hypodontie (absence congénitale d'au moins une dent), particulièrement l'agénésie de la deuxième prémolaire inférieure, chez les patients présentant la SPR, selon la distribution, le nombre et les sites affectés. Le groupe étudié comprenait 39 patients (17 garçons et 22 filles) souffrant de la forme non syndromique (isolée) de la SPR. Le groupe contrôle fut composé de 47 patients (19 garçons et 28 filles) ayant une fente palatine isolée (FP). Les deux groupes furent sélectionnés parmi les patients des cliniques de fente palatine et craniofaciale de l'Hôpital Sainte-Justine de Montréal du CHUM. Tous les sujets avaient, au moins, une radiographie panoramique dont l'âge moyen était de 7,97 ans pour le groupe SPR et de 7,65 ans pour le groupe FP. Les analyses statistiques réalisées sont les tests de Chi-carré (McNemar et test exact de Fisher). Le seuil de signification statistique a été établi à : $p \leq 0,05$. La prévalence de l'hypodontie est hautement significative dans le groupe SPR (46%) comparativement au groupe FP (19%). Le maxillaire inférieur est plus affecté dans le groupe SPR (41%) que dans le groupe FP (15%). Les deuxièmes prémolaires inférieures sont plus souvent absentes dans les deux groupes (SPR 33%, FP 13%). Aucune différence statistique ne fut observée entre l'agénésie dentaire gauche ou droite dans les deux groupes. Aucune corrélation statistique n'a été détectée entre l'agénésie des prémolaires inférieures et le degré de sévérité d'obstruction respiratoire dans des sujets de SPR. Une prépondérance chez les filles était observée dans les deux groupes (56% pour les SPR, 60% pour les FP). Avec un « odds ratio » de 3,4, cette étude permet d'établir une association clinique et statistique entre la SPR et l'agénésie de la deuxième prémolaire inférieure.

Mots clés : Pierre Robin, obstruction respiratoire, hypodontie, deuxième prémolaire inférieure, agénésie.

ABSTRACT

Pierre Robin Sequence (PRS) consists of a triad of distinctive symptoms that are expressed concurrently: micrognathia, glossoptosis – causing respiratory distress – and cleft palate. The purpose of this retrospective clinical study was to investigate hypodontia in general, and lower second premolar agenesis in particular, in male and female patients with PRS: distribution, number, and sites affected. The experimental group consisted of 39 patients (17 males and 22 females) with the non-syndromic, "isolated" form of PRS. The control group consisted of 47 patients (19 males and 28 females) with isolated cleft palates (CP). Both groups were selected from the patient database of the Craniofacial and Cleft Palate Clinics at the Sainte-Justine Hospital. All subjects had at least one panoramic radiograph (at a mean age of 7.97 years for the PRS group and a mean age of 7.65 years for the CP group). Statistical comparisons were made using Chi-square (X^2) tests (McNemar and Fisher's Exact tests); the significance level was set at $p \leq 0.05$. The prevalence of hypodontia was significantly higher in PRS (46%) compared with CP (19%). The lower jaw was more affected in the PRS group (41%) and the CP group (15%). Lower second premolars were the most frequently missing teeth in both groups (PRS 33%, CP 13%). No statistical difference was observed between right and left side tooth agenesis in either group. No statistical correlation was detected between lower premolar agenesis and the degree of severity of respiratory obstruction in PRS subjects. A female preponderance was seen in both groups (56% in PRS, 60% in CP). With an odds ratio of lower second premolar agenesis for PRS/CP of 3.4, a clinical and statistical association between Pierre Robin sequence and mandibular second premolar agenesis can therefore be established.

Key words: Pierre Robin, respiratory obstruction, hypodontia, lower second premolar, agenesis.

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LIST OF ABREVIATIONS

CEJ	Cemento-enamel junction
CP	Cleft palate
PRS	Pierre Robin sequence
%	Percentage
Vs.	Versus
≤	Less than, or equal to
"	Inches (when followed by a number)
PEG tube	Percutaneous Endoscopic Gastrostomy tube

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I hope that this work will contribute to the continued development of our specialty.

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"I love you from here to the moon,…and back".

CHAPTER ONE

INTRODUCTION

1. Introduction

Normal human craniofacial development is a complex process, requiring a number of timely and well-coordinated interactions between genetically controlled components. Interference with any one of these critical morphogenetic events leads to craniofacial malformations, the severity of which depends on the affected tissue and the timing of the interference. One such malformation has come to be known as Pierre Robin sequence.

Previously known as the "Pierre Robin syndrome" (1923), the nomenclature of this clinical entity evolved to "Robin anomalad" (1975), followed by "Robin malformation complex" (1978), and then "Robin sequence" (1982), the currently accepted term (Sadewitz, 1992) (Figure 1).

The Pierre Robin sequence (PRS) consists of a triad of distinctive symptoms that are expressed concurrently—micrognathia, glossoptosis, and cleft palate. Fewer than 20 percent of all Robin cases are "isolated"—not coupled with another symptom (Sher, 1992); other associated anomalies often exist, involving the eye, ear, heart, and limbs. In the neonatal period, feeding and respiratory problems caused by glossoptosis may be severe enough to require immediate medical attention for serious complications – even death – arising from hypoxia, aspiration, bronchopneumonia, and malnutrition (Pruzansky, 1971; Poupard and Rivoalan, 1987; Freed et al., 1988). Duhamel and Eliachar (1968) stated that the mortality rate in that group was as high as 50 %, whereas more recently, Delorme, Larocque, and Laberge (1989) reported a 10 to 30 % mortality rate.

The Craniofacial and Cleft Palate Clinics of the Sainte-Justine Hospital (comprised of a multidisciplinary team — including specialists in

orthodontics, genetics, and plastic surgery), is one of the largest medical units in the country to treat PRS patients in the first weeks of life and provide follow-up support to the patients and their families. These specialists observed that mandibular second premolars were often congenitally missing in these patients, data that is sparse and anecdotal in the medical literature. Moreover, they noticed that PRS patients with this specific type of tooth agenesis did not exhibit the occasional "catch-up growth" of the mandible that could accompany the prepubertal and pubertal growth spurts, a fact that could be neither confirmed nor denied in the medical literature.

This observation led the geneticists at the Sainte-Justine Hospital to infer that a link may exist between the genes responsible for the growth of the mandible and those implicated in the formation of mandibular second premolars. Similar theories have been previously put forth in the field of genetics; as Thesleff (2000) noted, ***"So far, all genes that have been linked with early tooth morphogenesis have developmental regulatory functions in other organs, too."***

The current research is the **initial step** in a sequence of projects intended to investigate the existence of a possible link or a common etiology between lower second premolars and mandibular catch-up growth. To establish such an association, we propose to first explore the conjecture that, indeed, hypodontia is a common occurrence and that mandibular second premolars, in particular, are the most frequently missing teeth in PRS patients. In addition, we intend to gather and analyze data on sexual incidence in patients inflicted with PRS, and present a comprehensive review of the literature on Pierre Robin sequence. Since PRS functional anomalies are transient, whereby glossoptosis and retrognathia progressively resolve or improve between 2 and 4 years of age (Abadie et al., 2002) – the age at

which lower second premolars first develop – we plan to investigate a possible correlation between the severity grade of glossoptosis and lower second premolar agenesis (an original exploration).

By examining the records of PRS patients of the Craniofacial and Cleft Palate Clinics of the Sainte-Justine Hospital (experimental group) and comparing them with "isolated" cleft palate patients (control group), we wish to put together a retrospective study that will shed some light on the topic and provide new information, contribute to what is known, and pave the way for future research opportunities.

Should our results establish a statistically significant higher rate of mandibular second premolar agenesis in PRS patients, as compared to isolated cleft palate patients, then, hopefully, a future project will examine the possible connection between this particular type of tooth agenesis and the hypothesized mandibular "catch-up" growth theory.

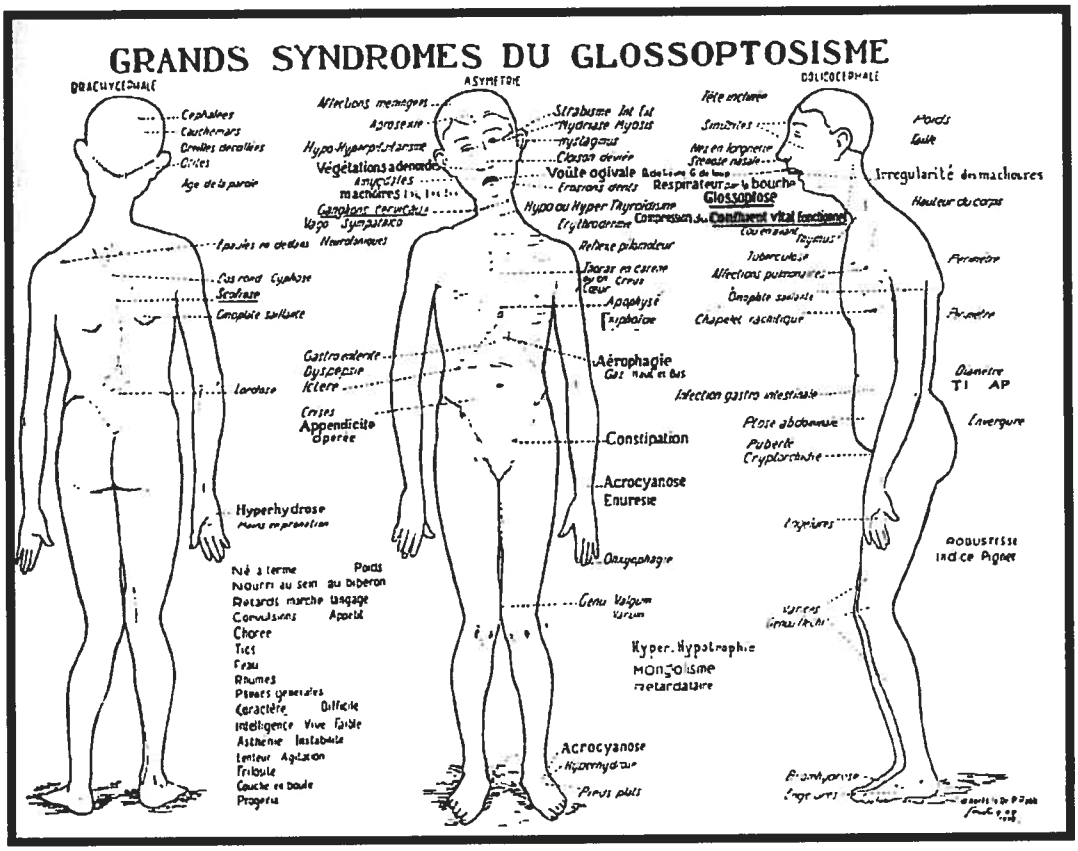

Figure 1: *"Pierre Robin syndrome" as published in 1923 (Robin).*

CHAPTER TWO

REVIEW OF THE LITERATURE

2. REVIEW OF THE LITERATURE

2.1 Introduction

Pierre Robin (1867-1950), a French stomatologist, professor, and editor-in-chief of the journal *Revue de Stomatologie*, may not have been the first to recognize the syndrome that came to bear his name, but he is generally acknowledged by researchers as being the first one responsible for calling attention to it. In a series of articles and a monograph published in the 1920s, he raised concerns among physicians about its possible effects on newborns.

Since then, Pierre Robin's combination of the conditions that he characterized as a *syndrome*—small jaw (micrognathia), abnormal positioning of the tongue so that it "falls back" and obstructs the upper airway (glossoptosis), and the co-occurrence of cleft palate (Figure 2)—has lingered in the minds of subsequent investigators and clinicians, despite a substantial accumulation of empirical work that has called into question the idea that the simultaneous presence of these conditions in a newborn constitutes a syndrome.

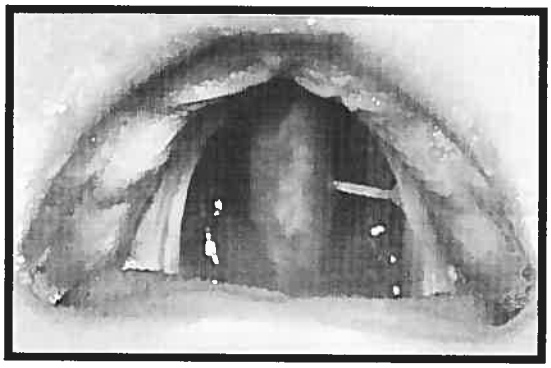

Figure 2: *U-shaped cleft palate (Tewfik, 1997).*

2.2 Terminology

2.2.1 Pierre Robin Syndrome

Over time, as researchers have continued exploring the relationship between these conditions and their possible etiologies, the terminology used to describe abnormalities present, at birth, in the jaw, tongue, and palate has changed, reflecting a shift away from thinking of these conditions as a "syndrome". For example, in the 1960s, Randall and colleagues were among those who accepted the traditional description of Robin syndrome, but in an article appearing in *Cleft Palate Journal* they reported that about a third of the patients in their sample had distorted, malpositioned mandibles, but not abnormally small ones, suggesting to these investigators that a posterior displacement of the mandible (retrognathia) was a rather more accurate way of describing mandibular abnormalities in Robin Syndrome than the term micrognathia (Randall, Krogman, & Jahina, 1965). In the 1960s and 1970s, investigators continued to question the etiology and embryology of the individual components of the syndrome and the relationships among them.

2.2.2 Pierre Robin Anomalad

By the mid-1970s, a National Institutes of Health conference on "Classification and Nomenclature of Non-Pathological Defects" adopted the term *Robin anomalad*. At that time, investigators assumed that the development of the mandible had been somehow arrested before birth, and that it was abnormal mandibular development that was preventing the tongue from descending between the developing shelves of the palate, thus preventing the palatal shelves from fusing (Edwards & Newall, 1985).

2.2.3 Pierre Robin Sequence

More recently, investigators have shown a preference for the term *Robin sequence*, preserving the role of Pierre Robin in the recognition of the clinical conditions that constituted a particular birth defect or set of defects, but suggesting at the same time that the conditions are causally related to other syndromes and factors. Olney, Kolodziej, MacDonald, and Schaefer (1997), for example, are among those who have focused on etiology, describing Robin sequence as "***a cascade of events***" caused primarily by mandibular hypoplasia, which they see as occurring early in pregnancy.

2.2.4 Terminology and diagnostic criteria

The standard triad of diagnostic criteria described by Robin continues to be questioned, further complicating the use of a term to denote what Pierre Robin originally attempted to describe. Ricks, Ryder, Bridgewater et al. (2002), for example, require the presence of U-shaped cleft palate specifically, along with mandibular retrognathia. In addition, these authors have suggested that Robin sequence may include pseudomacroglossia, a condition in which the tongue is of normal size but the oronasal cavity is abnormally small, so that the result is obstruction. Figueroa, Glupker, Fitz, and BeGole (1991), however, found that the tongue of the Pierre Robin sequence (PRS) infants in their study tended to be smaller than normal. Other investigators have linked Robin sequence with a variety of other conditions that appear to be coincidental; Handžic, Bagatin, Subotic, and Cuk (1995), for example, found frequent hearing impairment in infants with the sequence.

Twenty years prior to the work of Ricks, et al. (2002), Carey, Fineman, and Ziter, (1982) had also associated the U-shaped cleft (wide, inverted "U"

shape cleft), rather than the V-shaped cleft (narrower, inverted "V" shape cleft), with Pierre Robin, but were ambiguous about the etiology. Their focus on the palatal consequences led them to conclude that it was an "***isolated defect or one feature of many different syndromes.***"

As Cohen commented, "***A person with a syndrome is defined as having multiple anomalies all with a single pathogenesis***" (1981), while in a sequence, an individual may have multiple anomalies, only one of which is responsible for causing all or most of the others. Shprintzen (1992) considers the anomaly as a sequence because it is the primary anomaly, namely micrognathia, which subsequently leads to cleft palate and obstruction of the upper airway in newborns. While these latter anomalies are well documented consequences of mandibular abnormalities, they themselves may have many potential etiological factors—genetic, chromosomal, teratogenic, mechanical, or a combination of such factors.

As Sadewitz (1992) concluded, there is little justification for regarding PRS as a "disease", because its diagnosis depends on the effects of a series of events, prominent among which is the primary defect of the mandible, and that alone may have hundreds of causes. Nor is the presence of cleft palate conclusive or sufficient to establish PRS. As Sadewitz pointed out, while "***in 1976, there were fewer than 150 recognized syndromes with clefting***," by 1992 that number had exceeded four hundred, and may be continuing to rise today.

The differences in the research literature represented by the use of "**syndrome**," "**anomalad**," or "**sequence**" are not merely a matter of terminology, but have a significant effect on many other aspects of the topic, as discussed below. The terminology chosen by an investigator or group of investigators signals, for example, the diagnostic criteria used to

qualify research participants in a study; the diagnostic criteria used, in turn, influence assessments of the incidence of the syndrome, anomalad, or sequence, and so on through the research process.

2.3 Incidence

2.3.1 Prevalence in live births

An analysis of admissions over a 23-year period to a regional cleft palate facility in the United Kingdom led Bush and Williams (1983) to estimate an incidence of Pierre Robin syndrome at **one in 8,500** live births. They were prompted to conduct the study because of the wide range of variation in previous reported estimates, from **one in 2000** to **one in 30,000** (Poswillo, 1968; Rubin, 1969; Salmon, 1978). In the view of Bush and Williams (1983), inconsistency in diagnoses and the inclusion of isolated cleft palate data may have led to over- or under-reporting. They also observed that reporting of congenital abnormalities was not required by law in the UK and most other Western nations, pointing out that in Hungary, where reporting of birth defects was required, the rate of PRS had been reported to be **0.05 per 1000 live births, or one in 20,000**, between 1970 and 1976. To date, there is no reliable incidence data, primarily because no study has been designed to assure that consistent diagnostic criteria and reporting requirements are implemented.

2.3.2 Gender

While it is common in research on specific disease entities to consider the influence of gender, PRS investigators have paid scant attention to this factor. Bush and Williams (1983) found in their review of 23 years of

records a predominance of males born with PRS, which they were unable to explain. The data were of interest to them, because it had been previously reported that the incidence of isolated cleft palate is higher in females (Oldfield, 1959). The cleft palate data only indirectly relates to the PRS data. Later on, Dulude and Payette (1991) concluded that 60 percent of isolated cleft palate patients (sample = 53) and 73 percent of PRS patients (sample = 15) were **females**. Caouette-Laberge et al. (1994) reported an almost even distribution between the sexes whereby 64 of the 125 PRS experimental group subjects were **females** (51.2%). Perhaps more typically, the work of Amaratunga (1989) found that 59.5 percent of the patients diagnosed with PRS group and 58 percent of those diagnosed with isolated cleft palate group were **females**. It is impossible to draw any conclusions from any of these references, despite their indication that gender is not a salient factor in PRS.

Note: In this review, the abbreviation *PRS* will be used to denote Pierre Robin syndrome, the Robin anomalad, or Robin sequence in references to research where patients identified diagnostically have been included in the samples.

2.4 Craniofacial Embryogenesis

2.4.1 The branchial apparatus

The pharyngeal (branchial) arches, which give rise to considerable structures of the head and neck, begin their development during the fourth week *in utero*, as a result of migration of neural crest cells into the head and neck region. Six bilateral branchial arches (I to VI) appear in a gradual cephalocaudal sequence, of which the fifth arch is short-lived and

completely degenerates without giving rise to any structure, while the sixth arch is thought to fuse with the fourth (Bishara, 2001). The arches are segregated by branchial clefts externally and branchial pouches internally. Each arch (supported by a specific cartilage) has skeletal, muscular, nervous, and vascular derivatives that contribute to the head and neck formation (Ferguson, 1991).

Arch I, also known as the mandibular arch, forms two separate processes: the maxillary and the mandibular prominences. The maxillary process differentiates into the maxilla, zygoma and the zygomatic process. The mandibular process gives rise to *Meckel's* cartilage (and its derivatives: the sphenomandibular ligament, malleus, and incus) and the mandible (Bishara, 2001). Additionally, the muscles of mastication, the anterior digastric muscle, and the mylohyoid muscles are all derivatives of the first branchial arch. What is noteworthy is that the mandible is not a bony replacement for *Meckel's* cartilage; rather, mesenchymal tissue condensation lateral to this cartilage undergoes intramembranous ossification to produce the body of the mandible. Ultimately, *Meckel's* cartilage degenerates as its remnants form the sphenomandibular ligament and two of the ossicles of the middle ear—incus and malleus (Proffit and Fields, 2000).

2.4.2 Development of the face

The development of the human face takes place, for the most part, between weeks 4 and 10 *in utero* (Ferguson, 1991; Johnston, 1997). Essentially, the face starts to form when the five prominences, namely the frontonasal, the right and left maxillary and mandibular prominences, which surround the primitive oral cavity (the stomodeum), enlarge and move in a predetermined fashion. First, the distal ends of the paired mandibular prominences grow forward and eventually fuse in the midline to form the

chin and lower lip (Johnston, 1997). Concomitantly or shortly thereafter, the epithelium covering the frontonasal prominence thickens into large bilateral circular areas called nasal discs (placodes). The placodes then gradually thin out to finally disappear, leading to the formation of nasal pits (O'Rahilly and Muller, 1987). The surrounding mesenchymal tissues protrude at the rim, forming the medial and the lateral nasal prominences. Subsequently, the maxillary prominences proliferate and grow toward each other and toward the medial nasal prominences to finally fuse. In turn, the right and left medial nasal prominences approach each other to fuse in the midline, hence forming the intermaxillary segment. The intermaxillary segment gives rise to the philtrum of the upper lip, the four incisors and their periodontium, as well as the primary palate (the premaxilla). Finally, the corner of the mouth is delineated by the fusion of the maxillary and mandibular prominences laterally (Johnston, 1997) (Figure 3).

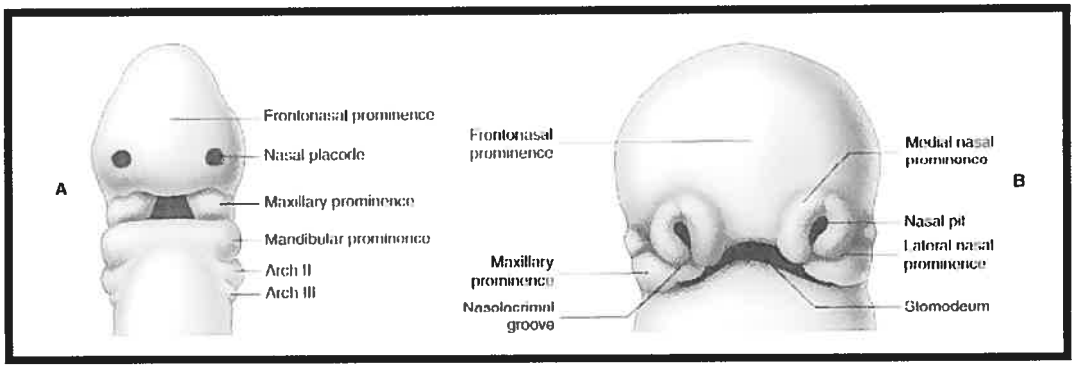

Figure 3: *Human embryo.* ***A****: 41/2 weeks.* ***B****: 6 weeks. (Bishara, 2001).*

It is noteworthy that the process of fusion between the various facial processes involves adherence of the opposing epithelial cells (which display surface specialization) to form an "epithelial seam," which then degenerates by cell death and epitheliomesenchymal transformation. Contacting

epithelial cells transform into mesenchyme cells and actively participate in the fusion (Ferguson, 1988).

2.4.3 Development of the palate

Early in week 6 *in utero,* bilateral prominences extend from the ventral ends of the medial nasal processes (the intermaxillary segment) to eventually unite and fuse in the midline to form the primary or premaxillary palate (Ferguson, 1991). The primary palate is the portion of the palate anterior to the incisive foramen. Failure of primary palate formation leads to clefts of the lip with or without cleft palate (Dioniopoulos & Williams, 1997).

The secondary (hard and soft) palate formation begins early in week 7 *in utero* as bilateral projections from the maxillary processes (the palatal shelves), which initially grow vertically down the sides of the tongue. During week 8 *in utero*, the palatal shelves rapidly elevate to a horizontal position, approach one another, and then fuse in the midline (forming the median palatine raphe) above the dorsum of the tongue, and anteriorly with the nasal septum and the primary palate. Ferguson (1991) also described an ***"intrinsic shelf-elevating force"*** normally large enough to overcome the resistance factors, such as the force required to displace the tongue, responsible for the rapid elevation of the shelves. Any interference with, or delay in, palatal shelf elevation can lead to clefting of the secondary palate.

At or around the same time, the elongation of *Meckel's* cartilages facilitates the sinking of the tongue into the developing mandible, while the maxilla develops and moves forward, thus lifting the head upwards from the mandible and further facilitating the retreat of the tongue away from the palatal shelves and into the developing mandible (Diewert, 1983).

2.4.4 Development of the tongue

The tongue arises from a midline swelling (termed *tuberculum impar*) in the floor of the pharynx and from two lateral lingual swellings adjacent to it. The paired lingual swellings enlarge and fuse posteriorly with the hypobranchial eminence (from the third branchial arch, caudal to the foramen cecum), and anteriorly with each other (Bishara, 2001). Thus, the body of the tongue (anterior 2/3) originates from the first branchial arch, whereas the base of the tongue (posterior 1/3) is derived from the third branchial arch. The *terminal sulcus* (passing through the foramen cecum) demarcates the separation between the body and base. Foramen cecum denotes the invagination of the endodermal primordium of the thyroid gland (Johnston, 1997).

As for its innervation, the tongue has sensory and motor input from several cranial nerves: the mucosa covering the body of the tongue is derived from the nerve of the first branchial arch, the 5th cranial nerve (the trigeminal nerve); the mucosa covering the base of the tongue is derived from the nerve of the third branchial arch, the 9th cranial nerve (the glossopharyngeal nerve), whereas the skeletal muscles of the tongue are innervated by the 12th cranial nerve—the hypoglossal nerve (Bishara, 2001). Interestingly, the skeletal muscles of the tongue and their nerve supply, the hypoglossal nerve, develop from myoblasts that migrate into the tongue from occipital somites, and not from any of the branchial arches (Gorlin & Slavkin, 1997).

2.4.5 Development of the dentition

Tooth development begins with the migration of neural crest cells into the region of the upper and lower jaws (Carlson, 2004). Both the ectodermal and mesodermal germ layers contribute to the formation of the tooth germ.

Enamel is a by-product of the oral ectoderm, whereas dentin, cementum, periodontal membrane, and pulp tissue arise from the mesoderm (Graber, 1966). This sophisticated and continuous ectodermal-mesenchymal interaction is responsible for teeth formation (Carlson, 2004). During the sixth week of gestation, the overlying oral ectoderm thickens into C-shaped bands, known as the **dental lamina**, in the upper and lower jaw (Carlson, 2004), and by the seventh week, the dental lamina becomes apparent along the perimeter of both maxillary and mandibular alveolar processes (Moyers, 1975).

As the dental lamina proliferates into the underlying neural crest mesenchyme, and through ectodermal-mesenchymal inductive interactions, a series of buds develop (Thesleff, 2000). These **tooth buds**, which expand rapidly, are the precursors of the deciduous dentition. By differential growth, the swelling of the tooth bud goes through a mushroom-shaped **cap stage** prior to entering the **bell stage** (Carlson, 2004). Through the process of histodifferentiation, the ameloblasts (enamel-forming cells) and odontoblasts (dentin-forming cells) begin to secrete precursors of dentin and enamel in the late bell stage. The pulp is formed by the **dental papilla**, which is an invagination in the enamel organ containing neural crest mesenchyme cells (Carlson, 2004). Attached to the dental lamina and close to the enamel organ is a small bud of the permanent tooth, which, at a later age, goes through the same developmental stages as the primary tooth (Carlson, 2004).

When enamel and dentin formation reaches the future cemento-enamel junction (CEJ), root formation begins. The shape of the root is determined by **Hertwig's sheath**, which is the merged outer and inner layers of the enamel organ that extends beyond the CEJ. As the root is formed, Hertwig's sheath atrophies, but when any of the cells persist, they receive

the name "**Epithelial rests of Malassez**". All these prenatal activities occur between the 6th and 14th week of intrauterine life. Thereafter, calcification begins (Graber, 1966) (Figure 4).

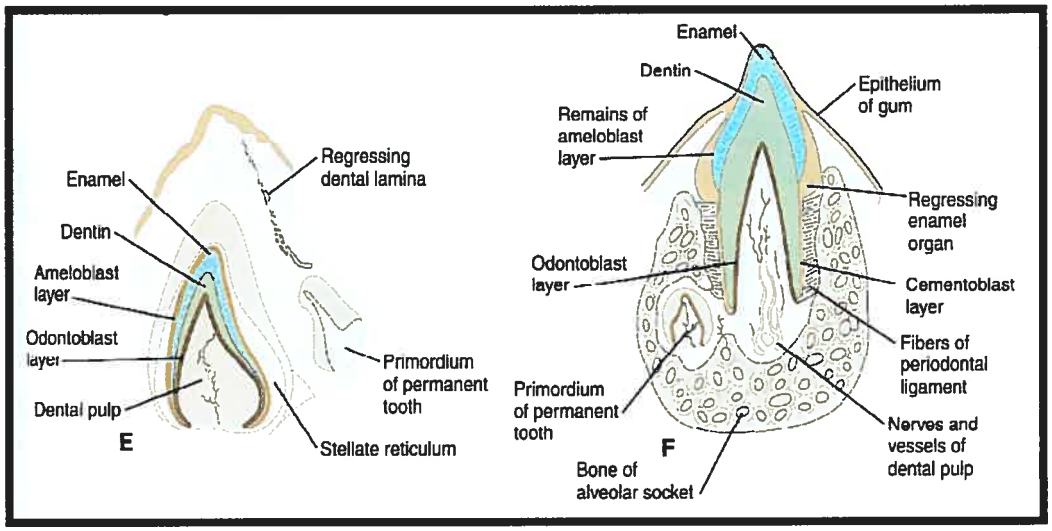

Figure 4: E: *Unerupted tooth in a fetus,* ***F:*** *partially erupted tooth in a newborn (Carlson, 2004).*

2.4.6 Conclusion

Understanding fundamental developmental mechanisms and their timing during normal head and neck embryogenesis allows for better understanding of pathogenesis and etiology. The opposite is also true; clinical cases of malformation, called ***"experiments of Nature"*** by Poswillo (1988), help shed some light on the stages of embryological and fetal development.

It is agreed upon by researchers that interference with any of the critical morphogenetic events *in utero* can lead to malformations and abnormalities. However, movements of the craniofacial complex are also considered important, even necessary, for the healthy development and differentiation of facial structures. Mouth opening, tongue protrusion, swallowing, hiccup movements and digit sucking have all been recorded, requiring the embryo to be loose and free to move in the amniotic fluid (Ferguson, 1991).

2.5 Postnatal Development

2.5.1 The Permanent dentition

Given the significant variations in the timing of dental development between individuals of the same sex and age, an ***average range*** (in months or years) is typically used to demarcate the separate stages of tooth mineralization and eruption. Nonetheless, an approximation of averages can be a very valuable asset in diagnosis during the developmental years. Tables I and II, adopted from *Wheeler's Dental Anatomy, Physiology, and Occlusion* (Ash, 1984), represent a summary of each individual tooth developmental stage. Knowledge of average mineralization times and eruption patterns can be helpful in determining congenitally absent versus late developing teeth.

Permanent Maxillary Teeth	1st Evidence of Calcification	Enamel Completed	Eruption	Root Completed
Central incisor	3 -4 months	4 -5 years	7 – 8 years	10 years
Lateral incisor	1 year	4 - 5 years	8 – 9 years	11 years
Canine	4 – 5 months	6 – 7 years	11 – 12 years	13 – 15 years
First premolar	1 ½ - 1 ¾ years	5 – 6 years	10 – 11 years	12 – 13 years
Second premolar	2 – 2 ¼ years	6 – 7 years	10 – 12 years	12 – 14 years
First molar	At birth	3 – 4 years	6 years	9 – 10 years
Second molar	2 ½ - 3 years	7 – 8 years	12 – 13 years	14 – 16 years
Third molar	7 – 9 years	12 – 16 years	17 – 21 years	18 – 25 years

Table I: *Developmental stages of permanent maxillary teeth (adopted from Ash, 1984).*

Permanent Mandibular Teeth	1st Evidence of Calcification	Enamel Completed	Eruption	Root Completed
Central incisor	3 – 4 months	4 – 5 years	6 – 7 years	9 years
Lateral incisor	3 – 4 months	4 – 5 years	7 – 8 years	10 years
Canine	4 – 5 months	6 – 7 years	9 – 10 years	12 – 14 years
First premolar	1 ¾ - 2 years	5 – 6 years	10 – 12 years	12 – 13 years
Second premolar	2 ¼ - 2 ½ years	6 – 7 years	11 – 12 years	13 – 14 years
First molar	At birth	2 ½ - 3 years	6 – 7 years	9 – 10 years
Second molar	2 ½ - 3 years	7 – 8 years	11 – 13 years	14 – 15 years
Third molar	8 – 10 years	12 – 16 years	17 – 21 years	18 – 25 years

Table II: *Developmental stages of permanent mandibular teeth (adopted from Ash, 1984).*

2.5.2 Growth and development of the mandible

Mandibular postnatal growth occurs mainly at the condyle and along the posterior surface of the ramus; the body of the mandible grows longer by apposition of bone on the posterior surface of the ramus, while large bone quantities are resorbed from its anterior surface. Essentially, the body of the mandible grows by remodelling (Figure 5).

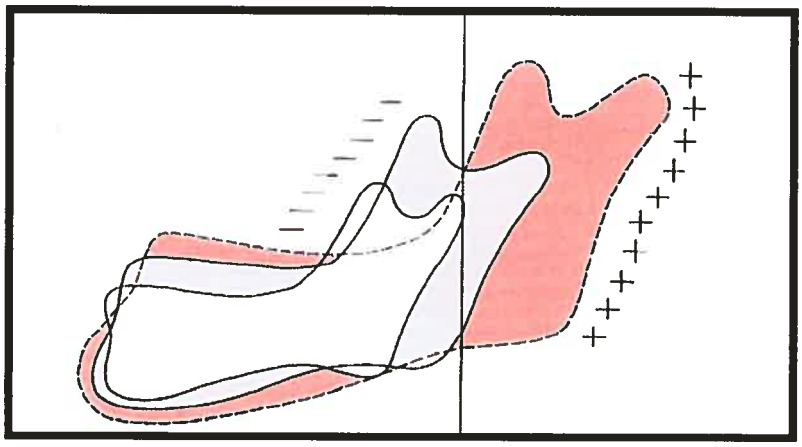

Figure 5: *Anteroposterior growth of the mandible by remodeling of the ramus (Proffit & Fields, 2000).*

Unlike other areas of the mandible, growth at the condyles is possible due to its cartilaginous covering at the temporomandibular joint. This secondary cartilage is capable of hyperplasia, hypertrophy, and endochondral replacement (conversion of cartilage into bone) (Proffit & Fields, 2000). Basically, the growth at the head of the condyle takes place in an upward and backward direction, leading to "translation" or displacement of the mandible downward and forward, thus maintaining condylar contact with the skull (Bishara, 2001) (Figure 6).

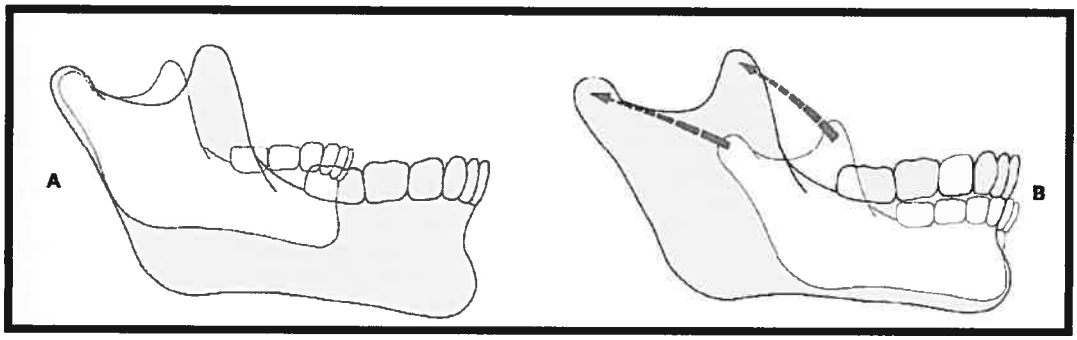

Figure 6: *Growth at the condylar head and translation (Proffit & Fields, 2000).*

While acknowledging the genetic growth potential of mandibular condyle cartilage, Moss and Salentijn's functional matrix theory (1969) claims that the major determinant of growth of the maxillo-mandibular complex is basically the enlargement of the oral and nasal cavities which, in turn, grow in response to functional needs. The authors clearly state that ***"growth of the face occurs as a response to functional needs and is mediated by the soft tissue in which the jaws are embedded"*** (Moss & Salentijn, 1969). In short, the soft tissues grow, and bone and cartilage react.

It is believed that a combination of both theories regulates mandibular growth: while proliferative growth occurs at the condylar heads and appositional growth at the posterior surface of the ramus, this growth is stimulated by the growth of the muscles and other neighboring soft tissues (Proffit & Fields, 2000). Muscles and tendons act directly upon the skeletal unit via the periosteum, leading to bone apposition and resorption and, ultimately, growth and/or remodeling (Bishara, 2001).

2.5.3 Morphologic characteristic

At birth, the **mandible** of the PRS infant is different from normal and cleft palate infants in both shape and size. Its body is shorter (symmetrically receded), the gonial angle is more obtuse (Ranta, Laatikainen, & Laitinen, 1985), the ramus length reduced (Laitinen, Heliövaara, & Ranta, 1997), and the chin underdeveloped (Dulude & Payette, 1991). Significantly greater horizontal and vertical overbites also occur in PRS patients as compared to isolated cleft palate patients. Moreover, the bony maxilla of the PRS subjects is more retrusive in relation to the cranial base than in normal individuals, but the "soft-tissue maxilla" is more prognathic, leading to a more convex profile (Ranta, Laatikainen, & Laitinen, 1985) (Figure 7).

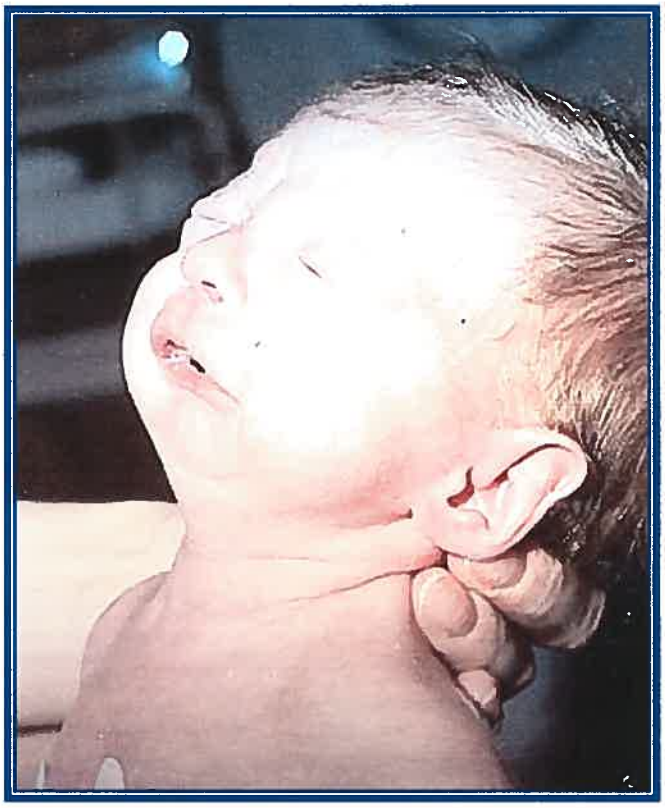

Figure 7: *Retrognathia in a PRS baby*
(Courtesy of Dr Louise Caouette-Laberge).

Glossoptosis (backward falling of the tongue into the pharynx), which varies in severity at birth, is a transient phenomenon that progressively resolves between 2 and 4 years of age (Figure 8). Minor glossoptosis can be found in 27% of newborns, moderate glossoptosis in 56%, and major glossoptosis in 17% of newborns (Abadie, Morisseau-Durand, Beyler, Manach, & Couly, 2002). Glossoptosis was classified according to tongue position and tongue-tip elevation at rest, in the aforementioned study. In another study by Caouette-Laberge et al. (1994), airway obstruction caused by glossoptosis was divided into three groups according to the severity of the symptoms: **Group I:** adequate respiration in the prone position and regular bottle feeding; **Group II:** adequate respiration in the prone position but with feeding difficulties requiring gavage (forced feeding by stomach tube, also known as PEG tube); and **Group III:** children with respiratory distress with endotracheal intubation and gavage. Of the 125 PRS children in the study, 44.8% belonged in group I, 32% in group II, and 13.6% in group III.

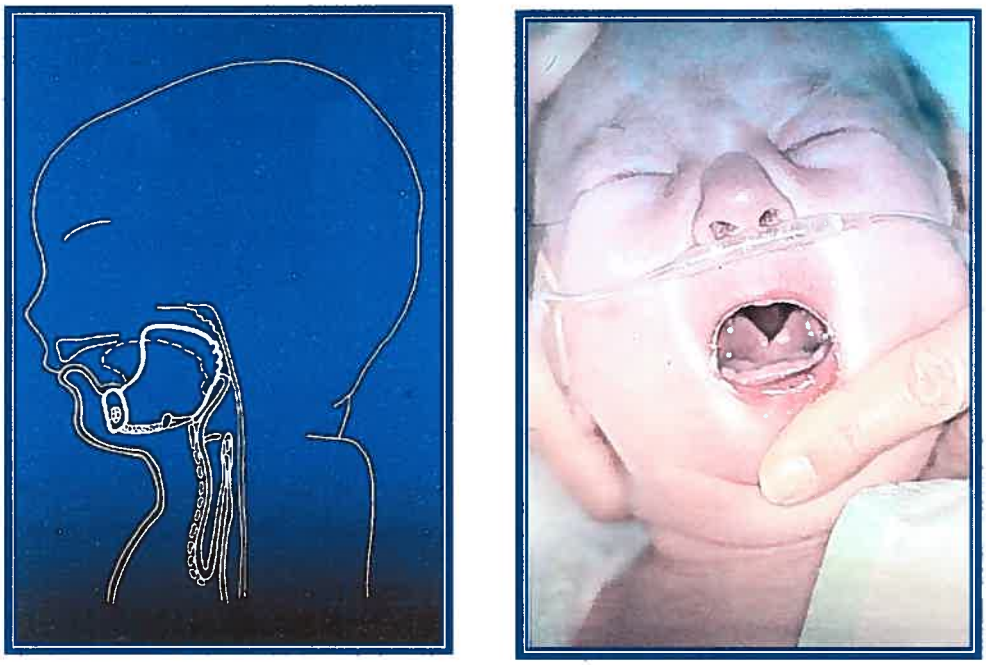

Figure 8: *Glossoptosis in a newborn with PRS (Courtesy of Dr Louise Caouette-Laberge).*

Cleft palate, usually present in 90.4 % of PRS subjects (Caouette-Laberge, Bayet, & Larocque, 1994), affects the secondary palate (posterior to the incisive foramen), and can either affect the soft palate alone or both soft and hard palate simultaneously (Dulude & Payette, 1991). On average, PRS clefts are slightly wider than isolated clefts (Figure 9) (Rintala, Ranta, & Stegars, 1984; Marques, Barbieri, & Bettiol, 1998). A bifid uvula may or may not be present (Dulude & Payette, 1991).

Figure 9: *U-shaped cleft palate in a newborn with PRS (Courtesy of Dr Louise Caouette-Laberge).*

Noteworthy, PRS can exist either as an isolated clinical entity (**non-syndromic PRS**) or associated with other anomalies and syndromes (**syndromic PRS**). However, no consensus exists in the literature as to the ratio of syndromic PRS to non-syndromic PRS, with percentages of isolated PRS ranging from 17 % (Shprintzen, 1992) to 48 % (Holder-Espinasse et al., 2001), to 63.5 % of total PRS cases (Van den Elzen et al., 2001).

2.6 Etiology

Cohen (1976) was one of the earliest investigators to question the designation of PRS as a specific syndrome. Instead, he suggested that it was a complex of symptoms that could occur alone, as part of a known syndrome, or associated with other birth defects which were not known to be part of a specific syndrome. Amaratunga (1989) has perhaps summarized the whole history of the etiology arguments by commenting, "***No single theory provides all the answers.***"

The various theories that have been advanced to explain the appearance of the PRS conditions at birth can be approximately categorized as mechanical or teratogenic, with the additional influence of some genetic factor. Prows and Bender (1999) found genetic causes in about 80 percent of PRS patients, and Ricks et al. (2002) suggested that etiologies may overlap. It is therefore an understatement to say that there is no consensus among researchers about the etiology of PRS or any of its components.

2.6.1 Mechanical theory

In the mid-1960s, Randall et al. (1965) observed that there was probably no exact cause, citing a lack of conclusive evidence for the role of a genetic

factor and the theoretical nature of arguments for the role of intrauterine pressure, which has been referred to as the mechanical theory of etiology or the fetal malposition theory. This theory proposes that the fetal head is at some point pressed against the chest so that the chin is pushed up and back; if the head does not lift up at exactly the right time in the fetal developmental process, the tongue stays in between the soft palate shelves and prevents them from fusing. This theory is intended, in part, to account for the presumed higher incidence of U-shaped cleft palate, as opposed to the V-shaped palate, in newborns with PRS. It does not claim to explain the mandibular abnormalities that appear as part of PRS.

Hypoplasia, or abnormal mandibular development, has been a focus of etiological research in the context of PRS for a number of years. Embryologists have argued that a critical time in fetal development appears to be a period approximately 7 to 11 weeks after conception, when it is thought that the tongue descends from between the palatal shelves as they begin to grow toward each other, eventually to fuse, which is usually accomplished by about 11 weeks (Sadewitz, 1992).

A number of possible causes for lack of mandibular growth have been advanced, including the constricted position of the fetal chin on the chest. This constriction itself could have any number of physical causes, such as crowding from twins or triplets, some physical abnormality of the uterus or the implantation, or a neuromuscular disorder affecting uterine size or flexibility. Another possibility is the presence of connective tissue disorders that influence the position of the fetus or its ability to move in the uterus, like having unstretched uterine muscles within a structurally small uterus (Cohen, 1976; Sadewitz, 1992).

2.6.2 Genetics

Rintala, Ranta, and Stegars (1984) tested the fetal malposition theory by comparing experimental groups of patients diagnosed with PRS and those with isolated cleft palate (without micrognathia or upper airway obstruction). They found that U- and V-shaped cleft palates occurred with the same frequency in both the PRS and the isolated cleft palate groups, suggesting that genetic factors were responsible, rather than an abnormal position of the fetal chin, and that they had therefore seen indirect evidence contradicting the role of the fetal position.

Earlier, Ranta and Rintala (1983) had also suggested that the etiology of the cleft palate in PRS patients was not due to the position of the tongue at a particular development time, but to the same factor that influenced the abnormal development of the mandible. Ranta and Rintala (1983) considered the fetal position theory too limiting, hypothesizing a broader cause for disruption in fetal developmental processes. They were early advocates of the theory that the primary abnormality in PRS was the disturbance in the development of the mandible, and that the cleft palate was a secondary abnormality due to the resulting position of the tongue or by some unknown factor that stopped or delayed the growth of the mandible.

Amaratunga (1989) conducted a comparative study to determine whether PRS and isolated cleft palate were associated etiologically or embryologically, and concluded that his findings support both the fetal compression (mechanical restriction) of mandibular growth theory and the primary growth disturbance of the mandible and the maxilla theory.

While no single gene has been associated with the non-syndromic form of PRS, Stickler and velocardiofacial syndromes (VCFS) are the most commonly associated conditions with the syndromic form of PRS. Stickler syndrome is due to autosomal dominant COL11A2 mutations while velocardiofacial syndrome is due to an interstitial deletion of chromosome 22q11 (Van den Elzen et al., 2001).

In a study by Marques, Barbieri and Bettiol (1998), the authors state that heredity could be a possible factor in the etiopathogenesis of isolated PRS. In a sample of 36 non-syndromic PRS patients, isolated cleft palate among distant relatives occurred in 6 cases. No cases of PRS among relatives were reported. The authors admit that the association could simply be anecdotal, but that they could not exclude multifactorial polygenic inheritance.

The fact remains that no single gene has been identified as the etiological factor responsible for PRS; however, recent sporadic and unrelated publications associate PRS with a chromosomal translocation. In 2001, Houdayer et al. published their findings in the *American Journal of Medical Genetics* stating that an unbalanced reciprocal translocation 46,XX, t(2;21), del 2(q32.3q33.2) in a PRS proband confirms the role of genetics in Pierre Robin sequence. Specifically, the deletions encompass the 2q31-q33 region which is recognized to be nonrandomly associated with known clinical manifestations of cleft palate and micrognathia, among other symptoms. The authors proceed to suggest a locus for PRS maps in the interval between markers D2S369 and D2S315, stating ***"this observation supports the hypothesis for the genetic bases of nonsyndromic PRS, strengthens its possible genetic association with isolated CP, and provides a candidate PRS locus".*** To date, this has been the only reported case in the literature of nonsyndromic PRS implicating 2q32.

More recently, Jamshidi et al. (2004) identified a chromosomal translocation between chromosomes 2 and 17 in a PRS family for three generations. Using the fluorescent in situ hybridization (FISH) technique, the authors identified a balanced reciprocal t(2;17)(q23;q23.3) chromosomal translocation in all six family members with isolated PRS, and in none of the unaffected members. Three other papers have been published that describe translocations involving the 17q23.3-17q25 region (Vintinier et al., 1991; Luke et al., 1992; Stalker et al., 2001).

As research in genetics intensifies in an attempt to identify a gene specifically responsible for PRS, while the debate over the role of genetics all-together in the etiology of PRS continues in the research community, the multifactorial nature of the etiology of PRS remains the accepted theory among researchers.

2.6.3 Environment

Ricks et al. (2002) have more recently observed that various external events may be responsible for the PRS conditions in newborns. Some external event, for example, may prevent the flattening of the tongue and its move away from the palatal shelves, another event may cause the head to drop to the chest, and yet another may prevent its rising again at the appropriate developmental time. Among the possible events, Ricks et al. include oligohydramnios (deficiency in the amount of the amniotic fluid), which could cause the dropping of the head and, subsequently, depression of the mandible. These authors have also suggested, based on animal studies, some teratogenic effect that inhibits the growth of the mandible so that it cannot accommodate the tongue in a flattened position in time for the growth and fusion of the palatal shelves. Edwards and Newall (1985) found that this was "improbable" in humans, though it may be accurate in rodents.

Some of the teratogenic factors known to cause, or be associated with, PRS are **1)** ethyl alcohol, **2)** hydantoin (medication used for treatment of grand mal epileptic seizures), and **3)** trimethadione (medication used for treatment of petit mal epileptic seizures) (Cohen, 1999). Other teratogens associated with clefting of the palate include **1)** 6-Mercaptopurine (antineoplastic agent), **2)** Aspirin, **3)** cigarette smoke (hypoxia), **4)** Dilantin, and **5)** Valium (Proffit & Fields, 2000).

2.6.4 Brainstem dysfunction: neuroembryological pathogenesis

Another hypothesis put forth recently implicates a brainstem dysfunction that originates from neuroembryological pathology in the prenatal stage (Abadie, Morisseau-Durand, Beyler, Manash, & Couly, 2002). Neural projections from the brainstem to the organs associated with feeding, breathing, and cardiac regularity were inspected. Esophageal manometry, systemic respiratory and cardiac monitoring were performed and recorded for 66 isolated PRS patients. Feeding and respiratory disorders were present in all of these patients to varying degrees (including, but not limited to, the following cranial nerves: IX, X, & XII). The authors (Abadie et al., 2002) concluded that the presence of esophageal hypertonia (increased muscular tension) and failure to relax, along with pharyngolaryngeal collapse, even in the absence of severe anatomical malformations associated with PRS, would certainly implicate a brainstem dysfunction. A feeble intrauterine sucking and swallowing reflex could be the cause of the mandibular retrognathia, since normal movements of the craniofacial complex are considered necessary for the healthy development and differentiation of facial structures.

2.6.5 Meckel's cartilage aberration

Yet another possibility advanced by Ricks et al. (2002) is the occurrence of some alteration in the growth of Meckel's cartilage and the subsequent effect of that alteration on palate closure. Their work in mice showed that when the growth of Meckel's cartilage was retarded before palate closure, the result was micrognathia. Meckel's cartilage is thought to be instrumental in the eventual length of the mandible. Because an appropriate length in the lower jaw is necessary before the tongue can descend from between the palatal shelves, any abnormality in the development of Meckel's cartilage is thought to contribute to cleft palate. Earlier, Edwards and Newall (1985) had also implicated, in cleft palate, damage to Meckel's cartilage or inhibition of its growth. At that time, they hypothesized that if the damage *in utero* was minor, a normal facial profile could gradually be achieved by infantile swallowing, eating, and similar actions, but if the damage were severe, the mandible would be abnormally small and perhaps distorted in shape (Diewert, 1981).

2.6.6 Syndromic PRS

Further complicating the etiological picture of PRS is its association with other syndromes. Carey, Fineman, and Ziter (1982), for one, list numerous syndromes that can cause fetal malformations or disruptions of fetal development, such as fetal alcohol syndrome and Möbius sequence (periodic oculomotor paralysis), osteochondrodysplasia (including Stickler syndrome), and a number of congenital neuromuscular conditions. They reported on two cases of siblings who had a generalized neuromuscular condition in which Robin sequence appeared as only one feature.

Olney, Kolodziej, MacDonald, and Schaefer (1997) have also commented on the association of PRS with other syndromes, including single-gene conditions such as Stickler syndrome, the most common genetic syndrome associated with PRS and also associated with mandibular hypoplasia, which in turn has been associated with various genetic, chromosomal, and teratogenic syndromes. Olney et al. also cite the association of PRS with cerebro-costo-mandibular syndrome (a rare and serious congenital disorder characterized by the association of posterior rib malformations, micrognathia, and mental deficiency), and mandibulofacial dysostosis (Treacher-Collins syndrome).

Holder-Espinasse et al. (2001) refer to a "*helpful*" classification of PRS as (1) Isolated PRS, (2) Syndromic PRS, and (3) PRS with associated anomalies. Although the classification was not original, the results were intriguing; in the isolated PRS subgroup, at least one feature of the triad (cleft palate, glossoptosis, and/or micrognathia) was found in a relative in 13% of the cases. Twinning was also noted in 9% of the cases. While no deductions or rationalizations were attempted by the authors to explain these occurrences, heterogeneity of PRS can only be confirmed (Cohen, Jr., 1999). Twinning may confirm the mechanical constriction etiopathogenesis, whereas familial tendencies may imply a genetic involvement, whether syndromic or non-syndromic PRS.

Table III (adopted from Shprintzen, 1992) summarizes the primary diagnoses associated with syndromic PRS and their prevalence. The most commonly associated diagnosis is Stickler syndrome (Shprintzen, 1992; Van den Elzen et al., 2001):

Primary Diagnosis	%
Stickler syndrome	34
del(22q11.2) syndrome (formerly velocardiofacial syndrome)	11
Fetal alcohol syndrome	10
Provisionally unique pattern syndrome	10
Treacher Collins syndrome	5
Bilateral femoral dysgenesis syndrome	2
Distal arthrogryposis	2
Larsen syndrome	2
Miller-Dieker syndrome	1
Spondyloepiphyseal dysplasia syndrome	1
Diastrophic dysplasia syndrome	1
Popliteal pterygium syndrome	1
ADAM sequence (amnion rupture syndrome)	1
Beckwith-Wiedemann syndrome	1
Nager syndrome	1
Isolated (non-syndromic) PRS	17

Table III: *Primary syndromic diagnoses in a sample of 100 consecutive PRS children (adopted from Shprintzen, 1992).*

2.7 Diagnosis

As has already been suggested in this review, a major factor in any attempt to establish PRS as a distinct clinical entity or to determine its etiology is the diagnostic process and the subsequent difficulties presented by existing data, particularly when retrospective data based on hospital admissions or birth records are used. In addition, researchers have tended to be highly selective in the diagnostic criteria they use to include and exclude patients from studies.

In their retrospective study, Bush and Williams (1983) used the following criteria to examine the data on admissions over a 23-year period (1960-1982) to select patients with PR syndrome: presence of U-shaped cleft palate; hospitalization for a minimum of 28 days with respiratory compromise and feeding problems (i.e., upper airway obstruction); and confirmation of the diagnosis by two orthodontists and a pediatrician. They excluded patients with mandibular retrognathia or micrognathia without cleft palate, because they considered those conditions to be separate clinical entities, thus eliminating what some researchers consider one of the major features of PRS.

Pasyayan and Lewis (1984) eliminated what some consider another prominent feature of PRS, cleft palate, in a clinical trial they conducted among a group of newborns diagnosed with Robin sequence based on retrognathia and glossoptosis with or without cleft palate, all with upper airway obstruction and feeding problems. They further distinguished between those with "isolated" Robin sequence (non-syndromic PRS) and those with Robin sequence as part of another syndrome or with one or more birth defects (syndromic PRS). Daskalogiannakis, Ross, and Tompson (2001) also found that in assembling their sample, many patients labeled

PRS also had other syndromes that have been associated with micrognathia that could have been genetically induced.

In some cases, the researchers' basic definition of PRS determines which diagnostic criteria will apply. Shprintzen (1992) attempted to develop a more accurate diagnosis for the congenital abnormalities that might be attributed to PRS, in order to improve treatment and clinical management of these conditions, based on his essential assumption that PRS is a sequence, rather than a syndrome. He refers to the "***classic triad of Robin findings***" (micrognathia, U-shaped cleft palate, and upper airway obstruction), but argues that they need not be the only diagnostic criteria applied: "***If Robin sequence is not a specific disorder of known cause, does it make sense to discuss specific physical findings***?" He argues that, rather than a final diagnosis, PRS should be the point at which clinicians begin their search for the associated syndromes that in all probability led to the physical findings of PRS.

2.8 The Theory of "Catch-Up Growth"

Randall et al. (1965) introduced, or were at least among the earliest investigators to have introduced, what has since become known as the "catch-up growth" issue in PRS. They studied a sample of 22 patients who had a clinical diagnosis of micrognathia (small jaw) as newborns and cleft palate. At one year, less than 70 percent of these patients could still be classified as micrognathic. Evaluating the growth of these patients' mandibles showed three distinct growth patterns. In one group (three patients), the jaw was of nearly normal size and position. Persistent micrognathia occurred in the second group (six patients), and although these patients were followed for several years, one to the age of nearly

nine, Randall et al. thought it unlikely that normal jaw size would be achieved. In the third group, the children's mandibles remained underdeveloped, but possibly because the mandibles tended to protrude forward, their facial profiles were not severely affected.

There is as yet no real consensus among investigators as to the likelihood of mandibular growth to a normal size after birth in children with PRS. Olney et al. (1997) stated that good catch-up growth of the jaw was typical by age eight or nine, but Shprintzen (1992), in exploring the complexities of diagnosis in PRS, has argued that misdiagnosis may result in a prognosis for normal mandibular growth within a few years of birth. In his view, catch-up growth can only be expected if the mandibular abnormality has affected its position (retrognathia), rather than its size (micrognathia), since that would indicate a positional or mechanical etiology rather than some kind of congenital growth defect. In addition, Shprintzen points out that when PRS is accompanied by another syndrome that features mandibular hypoplasia, there will probably be no further growth of the mandible.

In an early study, Ranta, Laatikainen, and Laitinen (1985) found an abnormal relationship between the mandible and the maxilla in PRS subjects that was readjusted somewhat in the first few years after birth, but subsequently, growth slowed, so that the mandible continued to be micrognathic. In a later study of young adults with PRS or isolated cleft palate (Laitinen, Heliövaara, & Ranta, 1997), the research group found that while the size and shape of the maxilla were essentially the same in both groups, the PRS patients had significantly more retrognathia in the mandible.

Daskalogiannakis et al. (2001) recently reported on a retrospective study of craniofacial and mandibular morphology in patients with Robin sequence

and isolated cleft palate. They acknowledge a continuing debate over the etiology of the micrognathia, and the persistence of the intrauterine compression or positional theory of etiology. As they observed, "***if this theory is accurate, it [would be] logical to expect some rebound growth of the mandible shortly after birth, reducing the facial convexity and perhaps allowing the mandible to catch up with the maxilla.***" They found, however, that after the age of five, mandibular catch-up growth does not occur. The length of the PRS patients' mandibles, measured at three different stages, was 4 to 5 percent shorter than those of the cleft palate patients. For the PRS patients, measurements were taken at 5.5 years, 10.3 years, and 16.8 years. While these authors acknowledge that soon after birth there may be an immediate growth spurt, it would most likely be limited, and insufficient to achieve a normal profile. Overall, they concluded that in PRS children, even those who experience some growth of the mandible, the facial profile never achieves real harmony, because the relationship of the lower jaw to the upper jaw and to the cranial base remains essentially the same.

2.9 Treatment

2.9.1 Conservative treatment

Depending on the severity of the glossoptosis and airway obstruction at birth, treatment may vary from a conservative approach to a surgical intervention. In mild glossoptosis cases, conservative treatment could include intubation to ensure a patent airway, prone positioning of the newborn to prevent any respiratory obstruction by the tongue (Figure 10), mandibular traction and advancement appliances that serve to advance the mandible, thereby alleviating respiratory distress.

Figure 10: *Bed adapted for prone positioning (Courtesy of Dr Louise Caouette-Laberge).*

2.9.2 Surgical treatment

Conservative management alone, however, is sometimes insufficient in severe glossoptosis circumstances, and surgical intervention is indicated. Tracheostomy (Figure 11), distraction osteogenesis of the mandible (Figures 12 A-C), subperiosteal release of the floor of the mouth (Figures 13 and 14), and tongue-lip adhesion are the most commonly performed procedures on PRS infants. Surgical repair of the cleft palate may be done as either a two-stage procedure whereby the velum is closed initially at 18 months of age and the hard palate is closed between 5 and 8 years of age (Perko, 1979), or a single-stage procedure whereby both soft and hard palate closure is done when the child is between 6 and 18 months of age (Dionisopoulos & Williams, 1997). The one-stage approach is the more

common practice in North America. Surgery to lengthen the mandible may be performed in the neonatal period as early as 14 days of age (distraction osteogenesis) to alleviate respiratory obstruction (Figures 12-A, 12-B, 12-C), or at a later time (orthognathic surgical advancement of the mandible) when growth has stabilized to minimize relapse. According to Proffit, the timing of surgery ***"is not so clear-cut"*** (Proffit, White & Sarver, 2003).

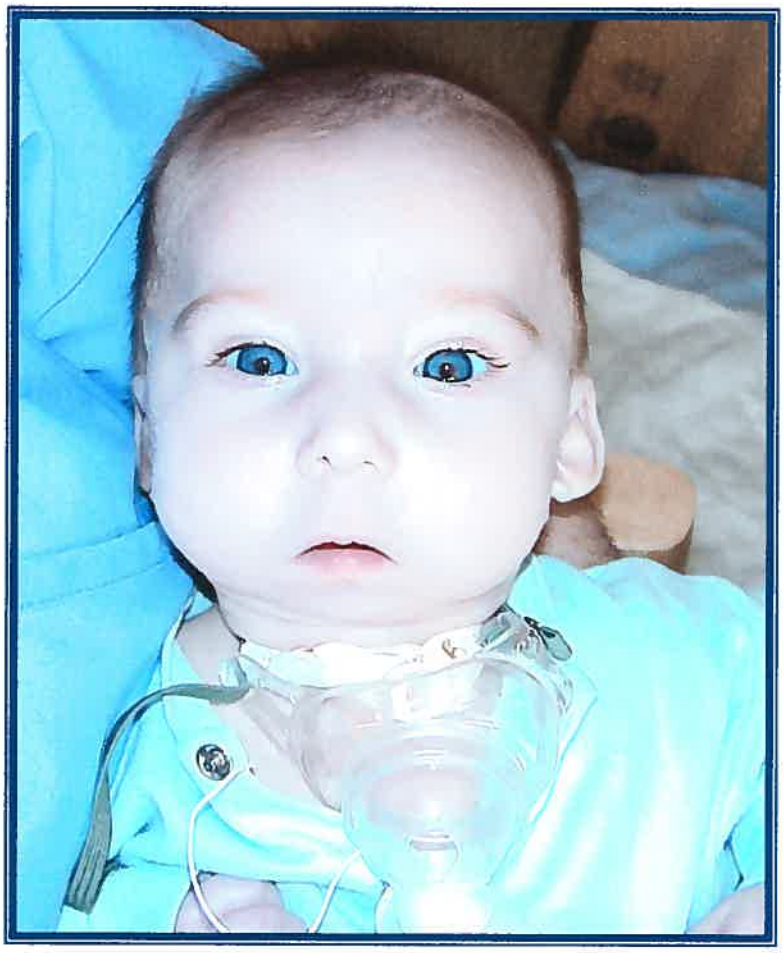

Figure 11: *PRS baby with tracheostomy*
(Courtesy of Dr Patricia Bortoluzzi).

Figure 12-A

Figure 12-B

Figure 12-C

Figures 12-A, 12-B, 12-C: *Distraction osteogenesis of the mandible (Courtesy of Dr Patricia Bortoluzzi).*

2.9.3 Release of the floor of the mouth musculature

A longstanding belief in the science community that the suprahyoid musculature of PRS patients is under reduced tension leading to a diminished ability to hold the base of the tongue forward, thus causing it to "fall back" (Randall, 1977) has been challenged recently by a team of plastic surgeons at the Sainte-Justine Hospital in Montreal. Delorme, Larocque, and Caouette-Laberge (1989) described a novel surgical approach that consists of a subperiosteal release of the musculature of the floor of the mouth (i.e., the suprahyoid muscles) through a 2-cm submental incision (Delorme et al., 1989) (Figures 13 A-C, and 14 A-C). In fact, this

unique methodology is based on the concept that the suprahyoid muscles are, instead, under increased tension, pushing the tongue upward and backward with secondary retrognathia and respiratory obstruction. Moreover, this restrictive muscle traction is detrimental to mandibular growth. The approach, used by Delorme and his colleagues on PRS patients with severe obstruction at Sainte-Justine Hospital, has led to significant postoperative improvement: ***"This operative method is simple and is associated with little morbidity. The dissection is subperiosteal with minimal blood loss,"*** write the authors (Delorme, Larocque, & Caouette-Laberge, 1989).

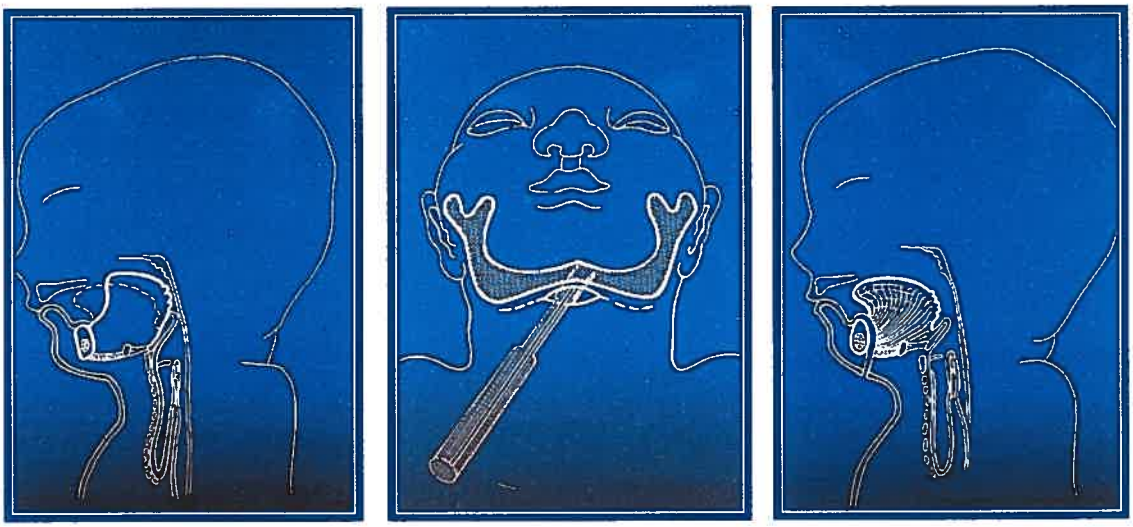

Figure 13: *Diagrammatic outline of the subperiosteal release of the floor of the mouth showing severe glossoptosis (A), submental incision and release of the musculature of the mouth (B), leading to correction of the glossoptosis (C) (Courtesy of Dr Louise Caouette-Laberge).*

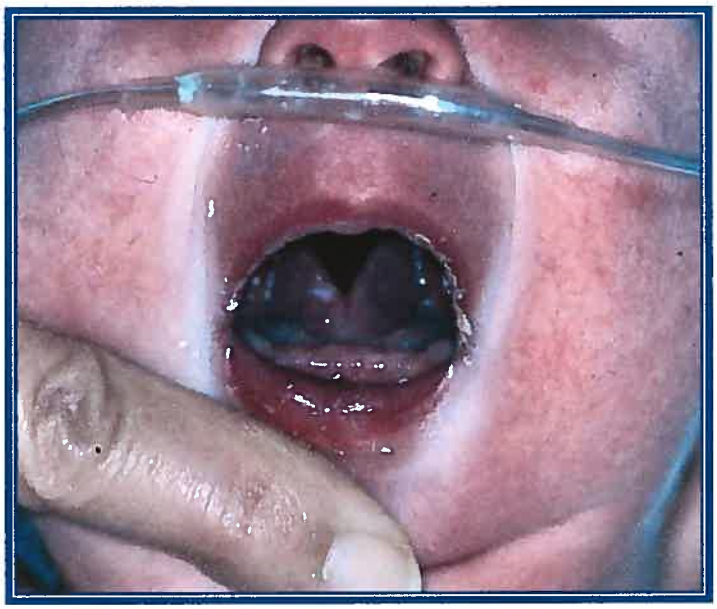

Figure 14-A: *Glossoptosis (corresponds to Figure 13-A) (Courtesy of Dr Louise Caouette-Laberge).*

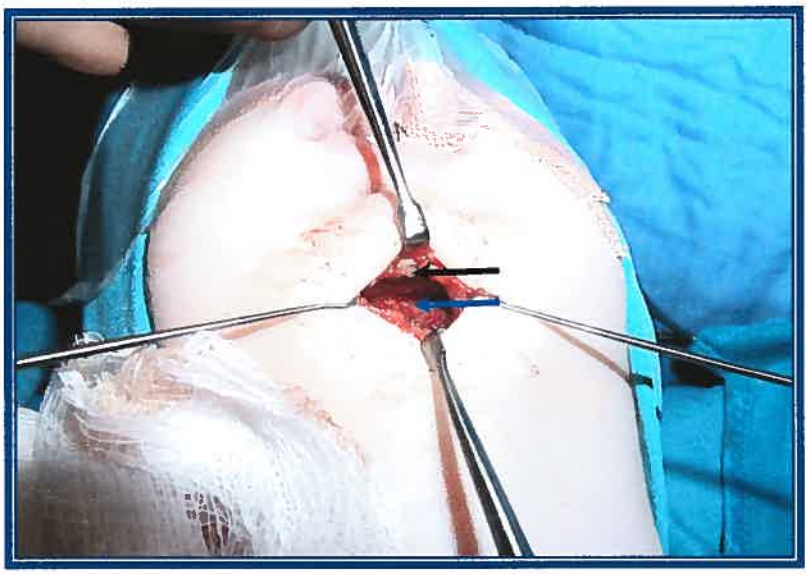

Figure 14-B: *Submental incision during surgery (corresponds to 13-B). Black arrow indicates the mandible. Blue arrow indicates the released musculature attached to periosteum. (Courtesy of Dr Louise Caouette-Laberge).*

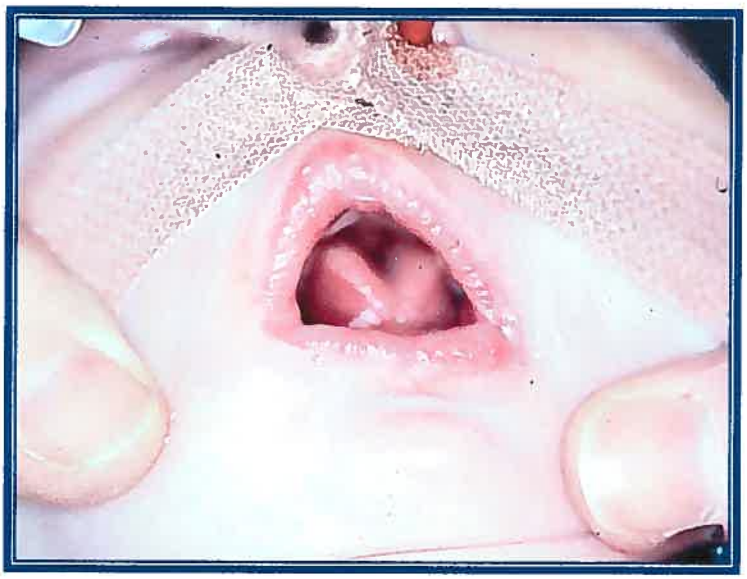

Figure 14-C: *Same patient as 14-A and 14-B with improved tongue position following surgery (corresponds to 13-C)*
(Courtesy of Dr Louise Caouette-Laberge).

2.10 Hypodontia

While tooth **agenesis** refers to absence or lack of formation of teeth due to a developmental defect, **hypodontia** indicates an anomaly in number, size, and shape of teeth, as well as abnormalities in the overall rate of dental development and time of eruption (Vastardis, 2000). Numerous theories have been postulated in an attempt to explain tooth agenesis (Butler, 1939; Clayton, 1956; Sofaer et al., 1971; Svinhufvud et al., 1988; Kjaer, 1997). Of these, the theory of Svinhufvud and his colleagues (1988) attributes the selectivity of tooth agenesis to anatomic and embryonic factors. These researchers suggested that areas of embryonic fusion are more susceptible to epigenetic influences, leading to agenesis. The upper lateral incisor, the most frequently missing tooth in the maxilla, develops in the area of the

embryonic fusion between the lateral maxillary and medial nasal processes. In the mandible, the *"fragile"* site is the area of the second premolar; this corresponds to the distal end of the primary dental lamina (Vastardis, 2000).

Normal tooth development seems particularly sensitive to defects in craniofacial development (Gaunt & Miles, 1967). According to Vastardis (2000), tooth agenesis may actually serve as an indicator of developmental jaw defects, since early craniofacial defects are often masked by bone remodeling, leading to agenesis.

Much of the work on dental aberrations and cleft palate has been carried out by Scandinavian investigators. Ranta and Rintala (1983) may have been the first (and only) investigators to focus on hypodontia and other dental abnormalities in patients with the Robin sequence, to confirm that this is one of the structural changes that could definitely be associated with the condition. They also looked at the timing of tooth formation and the form of the lower lip. Their sample included 56 children with Robin *anomalad.* The results were compared with the corresponding data on isolated cleft palate and non-cleft palate groups. Results showed that hypodontia (excluding third molars) was more prevalent in the Robin *anomalad* group (50%) than in the cleft palate control group (31.5%) and non-cleft control patients (8%). **Hypodontia was more prevalent in girls than in boys**. The lower jaws were generally missing **twice** as many teeth as the upper jaws, and the distribution of the missing teeth in both jaws was significantly different for the Robin *anomalad* and the cleft palate groups. **Among the Robin anomalad patients, the lower second premolars were missing in 20.5 percent of the patients**, the upper lateral incisors in 10.7 percent, upper second premolars (5.4%); other teeth (especially lower incisors and lower canines) were missing in 1% of the patients. In the cleft palate group,

10.4 percent were missing the lower second premolars and 11.2 percent the upper lateral incisors. As for the form of the lower lip, a median depression was noted in 54% of the PRS subjects, in 39% of the CP subjects and only 0.7% of the non-cleft control subjects.

In a related study, Ranta, Stegars, and Rintala (1983) observed that cleft palate has a significant genetic etiology, although heredity does not appear to contribute to hypodontia in children with cleft lip or palate. However, they suggested that the prevalence of hypodontia in children with clefts was probably related to the factors that caused the clefting, rather than to the clefting itself. This recalls the earlier arguments for defining PRS as a sequence rather than a syndrome and for separating the causes and consequences involved in the classic triad of micrognathia, cleft palate, and upper airway obstruction.

2.10.1 Arch perimeter

Laitinen and Ranta (1998) found that the dental arches, both maxillary and mandibular, were significantly smaller in young adults who had been born with PRS than in young adults born with isolated cleft palates. Despite the possibility that the original diagnosis of PRS was flawed in some way, these results are intriguing. In an attempt to explain, but not to explore, the possible etiology of these findings, the authors suggest that the smaller arches might be the result of some congenital growth disturbance or defect, or even the hypodontia. There have been no subsequent studies of the relationship between the hypodontia found in PRS and dental arch size.

Ranta and Rintala (1983) suggested that congenitally missing teeth in the lower jaw may be explained by the fact that in cleft palate, deficient facial mesenchyme may be unable to support developing teeth (Ross & Johnson,

1972). This hypothesized facial mesenchyme deficiency may also explain the diminished size of the jaws in addition to the number of missing mandibular teeth, the latter being attributed to poor support for the developing tooth germ epithelium. As Thesleff (2000) has recently pointed out, "***tooth development is under strict genetic control***," a statement that is supported by research that has identified the specific genes involved. Investigators have also learned that the genes that regulate tooth development in the embryo are also used for many other purposes, so that dental defects may also be related to other birth defects and syndromes.

2.10.2 Delayed tooth development

Shapira, Lubit, and Kuftinec (1999) acknowledged the association of missing permanent teeth with the presence of cleft lip, cleft palate, or both, supporting Ranta's earlier work in determining that the lower second premolars outside the cleft region appear to be missing most frequently (Ranta, 1982; Ranta, 1983). Ranta (1983) had found that in cleft palate children 33.7% had late developing maxillary second premolars and 26.9% had late developing mandibular premolars; overall, the incidence of hypodontia was just over 11% in the upper and just over 9% in the lower jaws. These incidence figures are normally much lower in children without cleft lip or palate, as Shapira et al. pointed out. Ranta believed that his research supported the conclusion that children with cleft palates have marked delays in the development of second premolars as well as higher numbers of congenitally missing second premolars in both arches.

In a 1984 study, Ranta confirmed that hypodontia in PRS children was a significant factor in delayed tooth development, and also suggested that the delay increased when the number of missing teeth per child increased. This convinced Ranta of the involvement of a genetic abnormality rather than an

anomalous intrauterine position of the chin. One year earlier, Ranta and Rintala (1983) published a study involving 56 children with PRS and concluded that tooth formation in PRS and cleft palate children was delayed approximately 0.6 year, compared to normal, non-cleft children.

2.10.3 Lower second premolar agenesis

It has been suggested by researchers that delayed tooth formation is but a milder expression of hypodontia (Ranta, 1983). Ranta (1986) later provided, as part of a concise overview of dentition in children with cleft lip or cleft palate, an analysis of hypodontia outside of the cleft region. He proceeded on the assumption that in children with clefts, the upper second premolars are more frequently missing than the lower second premolars. He also suggested that the severity of the cleft was related to the degree of hypodontia. Ranta cites a study showing that in children with PRS, hypodontia is generally more pronounced in the lower jaw (Ranta & Rintala, 1983).

Shapira et al. (2000) conducted their study in order to reassess the frequency of missing second premolars in cleft lip/palate patients and, further, to see whether the missing premolars were on the left side of the upper and lower dental arches. The patients in their sample were five to 18 years of age, with a mean age of 10.4 years. Patients under the age of five were excluded because initial crown calcification for second premolars is usually found at three and completed at about six years. Perhaps significantly, the investigators also excluded patients in whom another syndrome possibly related to cleft palate or lip was implicated. They found that 18 percent of the children in their sample were missing second premolars, and that these teeth were missing three times as often in the maxilla than in the mandible.

2.11 Summary

Historically, when PRS patients were compared to a control group in the literature, "isolated cleft palate" patients were invariably chosen as the control group. In our literature review of the Pierre Robin sequence, this trend was always encountered (Ranta & Rintala, (1983); Rintala, Ranta, & Stegars, (1984); Ranta, Laatikainen, & Laitinen, (1985); Amaratunga, (1989); Figueroa, Glupker, Fitz, & BeGole, (1991); Dulude & Payette, (1991); Laitinen, Heliövaara, & Ranta, (1997); Laitinen, & Ranta, (1998); Daskalogiannakis, Ross, & Tompson, (2001)). Statistical data would be comparable between the various studies and therefore applicable and useful.

The approach of researchers to Pierre Robin sequence (PRS) has undergone significant changes in the approximately 80 years since Robin named a group of clinical conditions present in newborns as a "syndrome". As each of the conditions — micrognathia, cleft palate, and glossoptosis with upper airway obstruction — has been investigated separately by researchers seeking to determine the etiology, embryology, and pathogenesis of the conditions involved, the integrated concept Robin established has gradually been eroded.

Current thinking tends to view the coincident presence of these conditions as a "sequence" in which the micrognathia is the primary birth defect, from which other abnormalities follow or "cascade" (Olney et al., 1997). There is a general, but not entirely unanimous, consensus that cleft palate and upper airway obstruction are either unrelated to the primary defect or that they are consequences of the defect.

Currently, there is nothing approaching a consensus among researchers regarding the possible etiology of even the micrognathia featured in PRS;

the cleft palate has been associated with at least 400 different syndromes (Sadewitz, 1992). It has been suggested that the etiology of the primary defect is genetic, chromosomal, teratogenic, mechanical, or a combination of one or more of these causes. While researchers have not yet subscribed to any one etiology, a review of the literature indicates that opinions tend to point **1)** toward the theory of intrauterine pressure, a mechanical etiology, **2)** toward the implication of a genetic or chromosomal defect, or **3)** toward a disruption of fetal development by some external event, such as fetal exposure to alcohol.

Part of the difficulty that researchers face in investigating PRS, particularly in retrospective studies that rely on data recorded at birth, is that there has been no universal agreement among physicians on what constitutes PRS. Some researchers have relied on cleft palate data, but have not always been sure that micrognathia has been noted. Reporting of birth defects of this sort is not required in all countries, so that incidence of PRS has been difficult to determine.

In addition to diagnostic ambiguities and the problems they pose for researchers attempting to assemble valid clinical samples, the research literature has been confounded over the prognosis for children born with PRS. It is not yet known whether the micrognathia that characterizes PRS is a "permanent" defect. Studies can be found that support the contention that children born with small mandibles have them for life; studies can also be found that support the idea that the growth of these children's mandibles "catches up" in the first few years of life, so that a normal facial profile is eventually achieved.

Of particular interest to the current research is the work that has been done on the dental abnormalities that have been associated with PRS, particularly

the occurrence of hypodontia, the congenital absence of permanent teeth. There is as of yet no consensus regarding the etiology of these dental abnormalities, but there is a growing body of research that suggests that they are related to the micrognathia associated with PRS and that they may be related to the cleft palate. It is not yet known whether the two conditions share a common etiology or whether a correlation between glossoptosis (respiratory obstruction) and hypodontia exists. It is hoped that the current research will contribute to what is known, as well as point the way toward future research that will help to clear up some of the current controversy surrounding PRS.

CHAPTER THREE

MATERIALS & METHODS

3. Materials and Methods

3.1 Design

The study used a clinical retrospective, case control design, approved by the Ethics Committee for Research at the Sainte-Justine Hospital in Montreal. The aim of the study was to investigate the association between PRS and hypodontia, using information on distribution, sites affected (right vs. left, upper vs. lower), and teeth affected (excluding third molars), as well as gender distribution. Correlation between severity of respiratory obstruction in newborn PRS children and lower premolar agenesis was also investigated. The source of the data used in the study was the patient database of the Craniofacial and Cleft Palate Clinics of the Sainte- Justine Hospital in Montreal (CHUM).

3.2 Investigators

All records (charts and radiographs) were reviewed and analyzed by two investigators: Wissam Daher (WD), senior resident at the Université de Montréal, Faculty of Dentistry, Section of Graduate Orthodontics, and Hicham El-Khatib (HK), an orthodontist and associate professor of orthodontics at the Université de Montréal, Faculty of Dentistry, and the Sainte-Justine Hospital (CHUM).

3.3 Sampling

Two patient samples were identified, an experimental (PRS) group and a control (CP) group, from a retrospective review of the Craniofacial and Cleft Palate Clinics database compiled between 1988 and 2003. Most of our subjects in both groups were of French-Canadian descent, and inter-group racial diversity was proportionate across both the experimental (PRS) and control (CP) groups.

Because the second premolars and second molars are the last teeth to develop in the dental arch (excepting the third molars), and because the mean age for initial crown calcification for second premolars and second molars has been established at 2.5 years and 3 years, respectively (Ash, 1984), the investigator's assumption was that it should be possible to detect the agenesis of any tooth radiographically by the age of 6.17 years (the age of the youngest subject in our study). Even accounting for a possible 0.6 year delay in the formation of teeth in PRS and CP patients (Rintala, 1983), we believe that it is still reasonably possible to detect agenesis in the youngest patient in this sample.

To avoid sample selection bias, the criteria for intrusion and exclusion for both experimental and control groups were determined prior to the examination of records of the database. All patients who met the criteria were selected and included in the study (Table IV).

Samples	Females	Males	Total
PRS	22	17	n=39
CP	28	19	n=47
Total	50	36	n=86

Table IV: *Experimental group (PRS) vs. control group (CP) samples.*

3.3.1 Experimental group (PRS) subjects

A search through the archives and records of the Sainte-Justine Hospital Craniofacial and Cleft Palate Clinics resulted in an initial identification of 230 PRS patients admitted between 1988 and 2003. When the criteria for inclusion and exclusion from the study were applied, the initial list was reduced to 39 eligible patients (22 females and 17 males).

The following criteria were used to support **inclusion** in the experimental (PRS) group:

1 A diagnosis of isolated PRS as confirmed by a geneticist, a plastic surgeon, and at least one orthodontist at the Sainte-Justine Hospital;
2 Retrognathia, clefting of the secondary palate (posterior to the incisive foramen), and glossoptosis with or without a history of respiratory distress;
3 At least one well-identified, dated panoramic radiograph of good diagnostic clarity, taken no earlier than the age of six; and
4 No orthodontic treatment and no dental extractions performed prior to taking the initial panoramic radiograph.

The following criteria were used to support **exclusion** from the experimental (PRS) group:

1 Any patients with other syndromes associated with PRS;
2 Children diagnosed with PRS but whose records lacked panoramic radiographs; and
3 Children younger than six years of age at the time of the study.

The records of all 39 subjects in the experimental group included an initial panoramic radiograph (taken at time T1) and a follow-up panoramic radiograph (taken at time T2). At time T1, the age range of the patients was 6.17 to 11.25 years, with a mean age of 7.97 years and median age of 8.00. The records of 29 of the 39 subjects contained panoramic radiographs taken at time T2. The age range in this case was 8.00 to 14.00 years (Table V), with a mean age of 10.18 years and a median age of 10.25 years. When available, the panoramic radiograph taken at T2 was examined for further evidence of possible tooth formation. When tooth agenesis was determined to be present at T1, and in all cases examined, evidence of agenesis at T1 always corresponded with agenesis at T2.

PRS (n=44)	T1	T2
Number of subjects	39	29
Mean age (years)	7.97	10.18
Median age (years)	8.00	10.25
Minimum age (years)	6.17	8.00
Maximum age (years)	11.25	14.00

***Table V**: Frequency table for PRS. **T1**= first panoramic radiograph; **T2**= second panoramic radiograph.*

Non-syndromic, or isolated, PRS patients were selected in an attempt to explore the link between PRS and hypodontia without the confounding effect of other clinical entities that may be associated with PRS.

3.3.2 Control group (CP) subjects

The subjects selected for this group, identified from a review of the patient database of the Craniofacial and Cleft Palate Clinics of the Sainte-Justine Hospital in Montreal, totaled 47 patients (28 females and 19 males). All of the selected subjects had been diagnosed with isolated cleft of the secondary palate, all had had at least one panoramic radiograph taken, and all were born between 1990 and 1995. The investigators in this study chose 1995 as the cut-off year in order to ensure that all subjects had at least one panoramic radiograph at or after the age of six.

Children whose cleft was part of a craniofacial syndrome and children whose radiographs were lacking or were of poor diagnostic clarity were excluded from the sample. Also excluded from the control group were cases with clefting of the lip and/or the primary palate (anterior to the incisive foramen), and cases in which dental extractions had been performed prior to the first panoramic radiograph. An essential criterion for inclusion in the control group was the presence of a well-documented cleft of the secondary palate in the dental chart, including a written description coupled with a diagrammatic depiction of the cleft on a standardized form designed by the Craniofacial and Cleft Palate Clinic for this purpose (Figure 15).

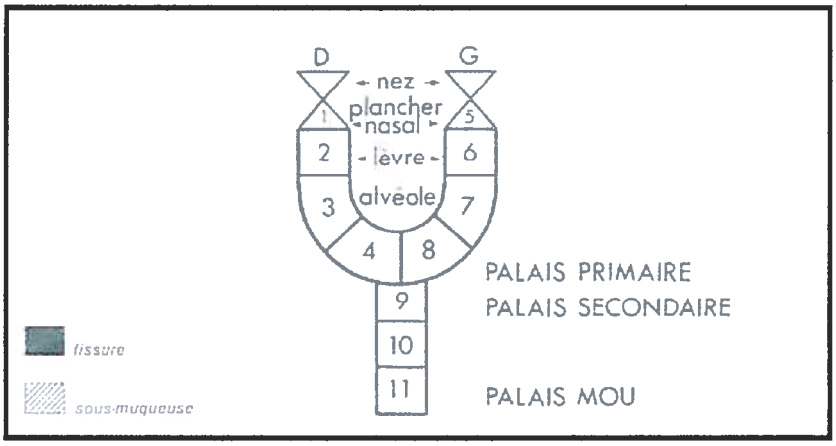

Figure 15: *"Striped **Y** of Kernahan" diagram used by the orthodontists at Sainte-Justine Hospital to indicate type and location of cleft (adopted from Kernahan and Stark, 1958).*

All 47 subjects had had a panoramic radiograph taken at time T1. The age range was 6.00 years to 10.00 years, with a mean age of 7.65 years and a median age of 7.42 years. At T2, 29 of the 47 subjects had had panoramic radiographs taken. Among this subgroup, the age range was 8.25 years to 13.25 years, with a mean age of 9.88 years and a median age of 9.75 years (Table VI).

CP (n=47)	T1	T2
Number of subjects	47	29
Mean age (years)	7.65	9.88
Median age (years)	7.42	9.75
Minimum age (years)	6.00	8.25
Maximum age (years)	10.00	13.25

Table VI*: Frequency table for CP.* ***T1****= first panoramic radiograph;* ***T2****= second panoramic radiograph.*

3.4 Severity Grade of Respiratory Obstruction

All children admitted to the Sainte-Justine Hospital with a diagnosis of PRS were divided into four groups according to the severity of their symptoms: **group I**: adequate respiration in prone position and bottle feeding; **group IIa**: adequate respiration in prone position but with feeding difficulties requiring gavage for more than 5 days; **group IIb**: children with respiratory distress requiring gavage and endotracheal intubation for more than 5 days; and **group III**: severe respiratory obstruction requiring a surgical intervention procedure, such as a glossopexy or a subperiosteal release of the floor of the mouth musculature. These severity grades were accurately documented in the medical charts of PRS patients by the plastic surgeon of the craniofacial team.

3.5 Materials

The primary source of the data for this study were the panoramic radiographs, all of which had been taken on-site, using the same x-ray machine—"***Siemens***" (Munich, Germany) — at the Craniofacial and Cleft Palate Clinics. All radiographs were viewed by the same two investigators (WD and HK) using a "***Densply Rinn***" (Pennsylvania, USA) 10" x 13.5" view box. A magnifying loop was used, when necessary, to thoroughly inspect the presence of a tooth bud.

3.6 Data Analysis

All study data were analyzed by means of the statistical software ***SPSS 12.0 for Windows*** (SPSS Inc., Chicago, Illinois). Since our data are nominal

(sex, tooth type, side), statistical comparisons were made using the Chi-square (X^2) test. Intra-group comparisons (i.e., right vs. left side, maxillary vs. mandibular agenesis within each group) were analyzed with the X^2 McNemar test. Inter-group comparisons (i.e., hypodontia in PRS subjects vs. CP subjects) were analyzed with the X^2 Fisher's Exact test. The significance level was set at $p \leq 0.05$ and a two-sided test adopted. Wherever applicable, odds ratio and 95% confidence levels were calculated to evaluate the strength of the association between the risk factor (agenesis) and the groups studied (PRS and CP).

CHAPTER FOUR

RESULTS

4. Results

4.1 Age Distribution

There were slight, but statistically insignificant differences in the age range, median age, and mean age between the subjects in the PRS group and those in the CP group. The mean age for the panoramic radiograph at T1 was 7.97 years for the PRS group with a range of 6.17 – 11.25 years, and a median at 8.00 years. The CP group had a panoramic radiograph at T1 at a mean age of 7.65 years, a range of 8.25 – 13.25 years, and a median of 9.88 years. At T2, 29 of the 47 CP subjects had panoramic radiographs with a mean age of 9.88 years, median at 9.75 years, and a range of 8.25 – 13.25 years, whereas 29 of the 39 PRS subjects had panoramic radiographs with a mean age of 10.18 years, median at 10.25 years, and a range of 8.00 – 14.00 years.

Whenever available, the panoramic radiograph that had been taken at T2 was examined by both investigators (WD and HK) for further evidence of possible tooth formation when tooth agenesis was deemed present at T1. In all cases examined, an agenesis at T1 always corresponded with agenesis at T2.

Both groups were selected retrospectively from the patient database pool of the Craniofacial and Cleft Palate Clinics of the Sainte-Justine Hospital in Montreal. As mentioned in the Materials and Methods, most of our subjects in both groups were of French-Canadian descent, and inter-group racial diversity was proportionate across both the experimental (PRS) and control (CP) groups.

4.2 Gender Distribution

The experimental (PRS) and the control (CP) groups were comparable in composition and distribution (PRS: n = 39; 22 females and 17 males. CP: n = 47; 28 females, 19 males) (Table VII). Despite a female preponderance of 56.4 % in the PRS group and 59.6% in the CP group, no statistically significant difference was noted between boys and girls in either group. A Fisher's Exact test showed p = 0.748, and an odds ratio of 1.429 with a 95 percent confidence interval of [0.398 – 5.124].

Gender	**PRS**		**CP**	
	Number	***%***	***Number***	***%***
Male	17	43.6	19	40.4
Female	22	56.4	28	59.6
Total	**39**	**100**	**47**	**100**

Table VII: *PRS & CP subject distribution by gender.*

4.3 Rate of Hypodontia

The congenital absence of at least one tooth (excluding third molars) in either arch was examined in both the PRS and CP groups. A statistical significance in the rate of hypodontia of 53.8 % in the PRS group was confirmed by means of a Fisher's Exact test, p = 0.01 ($\leq$ 0.05), an odds ratio for PRS/CP of 3.619, and a 95% confidence interval of [1.384 – 9.465]. No statistical significance in the rate of hypodontia was found in the control (CP) group.

Hypodontia	PRS		CP	
	Number	*%*	*Number*	*%*
Generalized	18/**39**	46.2	9/**47**	19.1
Maxillary	4/**39**	10.3	2/**47**	4.3
Mandibular	16/**39**	41.0	7/**47**	14.9
Right	14/**39**	35.9	6/**47**	12.8
Left	13/**39**	33.3	5/**47**	10.6

Table VIII: *Hypodontia distribution in PRS & CP subjects.*

The prevalence of hypodontia was significantly higher in PRS patients (46.2%) compared to the CP patients (19.1%). Lower jaw hypodontia in the PRS group was statistically significant with 41.0 % [using McNemar Symmetry Chi-square test, $p = 0.0027$ (≤ 0.05)]. Hypodontia in the lower jaw in the CP group was also higher than the upper jaw (14.9% lower vs. 4.3% upper) but the results were not statistically significant ($p = 0.1573 > 0.05$). No statistical difference was noted between right-hand side and left-hand side agenesis in either group (Table VIII).

The incidence of hypodontia in the female subjects in both PRS and CP groups was also slightly higher than in the male subjects, although the difference in the rate of hypodontia between the genders was not statistically significant (hypodontia in PRS: 50% females vs. 41.2% males; hypodontia in CP: 21.4% females vs. 15.5% males; Table IX)

Gender	PRS			CP		
	Total Number	*Hypodontia*		*Total Number*	*Hypodontia*	
		n	*%*		*n*	*%*
Male	17	7	41.2	19	3	15.8
Female	22	11	50.0	28	6	21.4
Total	**39**	**18**	**46.2**	**47**	**9**	**19.1**

Table IX: *Hypodontia distribution in PRS & CP subjects by gender.*

4.4 Premolar Agenesis

The only statistically significant tooth agenesis was that of lower second premolars in both our groups (PRS 33.3 %, CP 12.8%. Figure 17). A Fisher's Exact test showed a significance level $p = 0.035$ (≤ 0.05), and an odds ratio of PRS/CP of 3.417, and a 95% confidence interval of [1.155 – 10.111]. In other words, PRS patients have 3.4 times the risk of having lower second premolars agenesis as compared to isolated CP patients.

Furthermore, an equal distribution was noted between subjects missing one of the lower second premolars and those missing both lower second premolars among the PRS subjects (17.9%).

Table X details the agenesis of individual second premolars in the experimental and study groups, and Figure 16 is a comparative histogram between lower second premolar versus other teeth agenesis in both PRS and CP groups:

Agenesis	Tooth #15		Tooth #25		Tooth #35		Tooth #45	
	n	%	n	%	n	%	n	%
PRS (n=39)	1/39	2.6	2/39	5.1	9/39	23.1	10/39	25.6
CP(n=47)	1/47	2.1	1/47	2.1	4/47	8.5	4/47	8.5

Table X: *PRS vs. CP 2nd premolars agenesis.*

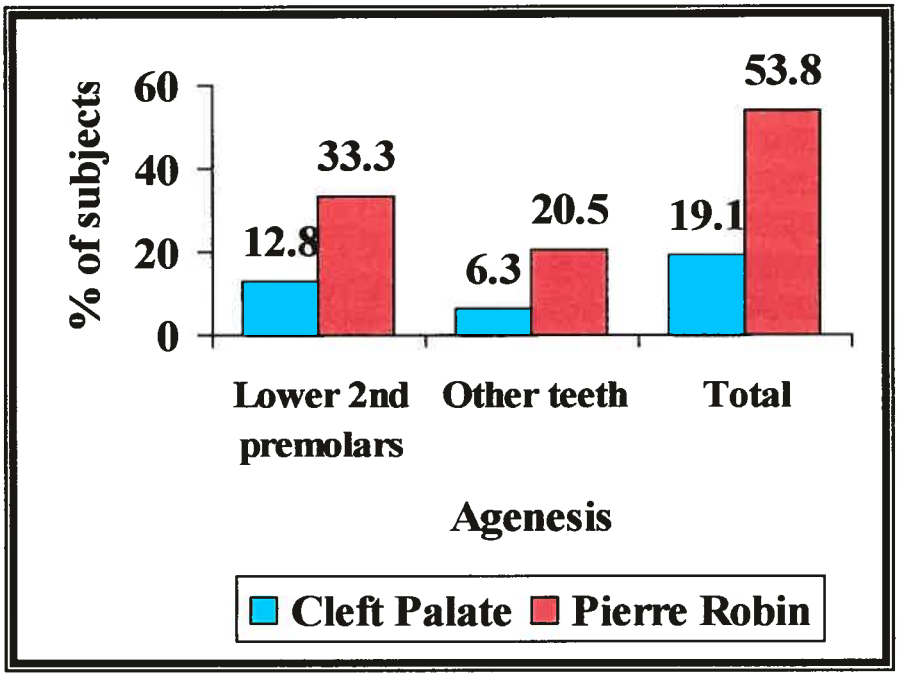

Figure 16: *Lower 2nd premolar vs. other teeth agenesis in PRS &CP subjects.*

4.5 Severity Grade of Respiratory Obstruction

Group I: adequate respiration in prone position and bottle feeding;

Group IIa: adequate respiration in prone position but with feeding difficulties requiring gavage for more than 5 days;

Group IIb: children with respiratory distress requiring gavage and endotracheal intubation for more than 5 days; and

Group III: severe respiratory obstruction requiring a surgical intervention procedure, such as a glossopexy or a subperiosteal release of the floor of the mouth musculature.

The 39 PRS subjects in our study group were distributed as follows (Table XI):

Severity	I	IIa	IIb	III	Total
No lower premolar agenesis	13	5	0	7	**25**
Lower premolar agenesis	6	2	3	3	**14**
Total	**19**	**7**	**3**	**10**	**39**

Table XI: *Classification of PRS subjects according to severity grade of the respiratory obstruction and lower 2nd premolar agenesis.*

Lower second premolar agenesis and the four degrees of severity of respiratory obstruction in PRS subjects were compared using Pearson's Chi-square test. No statistical correlation between these two variables was noted, as $p = 0.1204 > (0.05)$; no increase in the prevalence of lower second

premolar agenesis paralleled the increase in the severity grades of respiratory obstruction. Furthermore, groups I (mild form) and III (severe form) have nearly the same prevalence of lower second premolar agenesis: 6/19 (31.6%) for group I versus 3/10 (30%) for group III.

CHAPTER FIVE

DISCUSSION

5. Discussion

A number of the design considerations in the current research study were based on a review of the previous clinical literature, in order to determine which parameters would combine to give the most accurate picture possible of hypodontia in children born with Pierre Robin sequence.

As discussed earlier in the review of the literature, the diagnostic criteria for PRS have been evolving since the 1920s, when the condition was first identified. There is some evidence in the recent literature, in fact, that descriptions of the primary features continue to evolve, as investigators attempt to confirm associations between, for example, PRS and hypodontia.

Some decisions regarding sampling were necessary for the investigators in the current study to make in order to ensure a valid sampling, including the ages of the patients chosen for inclusion in the PRS and CP groups. Taking a cue from Ranta (1986), whose comprehensive review of the research literature suggested that the evidence was compelling that the delay in tooth development was more pronounced in children with Pierre Robin sequence and cleft palate as they grew older, we selected subjects for inclusion in the sample who were at least six years of age, with a mean age of 8.25 among PRS subjects and a mean age of 7.65 among isolated cleft palate subjects at the time of the first panoramic radiograph.

In their study, Shapira et al. (1999) included subjects as young as five years of age, based on the assumption that the first and second premolars are calcified by a mean age of three years and completed by mean ages of 5.2 and 6.2 years, respectively. Nevertheless, since it has been established that a delay in dental development is closely associated with both Robin sequence and cleft palate, we chose the more conservative cut-off age of six

years, and the higher mean ages at first panoramic radiograph for inclusion in the experimental and control groups, to ensure that the results would be representative of the patients with PRS and cleft palate, and that the study parameters would be consistent with most of the previous research.

5.1 Gender Distribution

5.1.1 Gender and PRS

The findings in this study showed no statistically significant difference attributable to gender, despite a female preponderance in both the PRS (56.4%) and the cleft palate (59.6%) groups. These findings are consistent with what previous researchers have found (Amaratunga, 1989; Dulude & Payette, 1991; Caouette-Laberge et al., 1994).

5.1.2 Gender and hypodontia

Our data indicate that despite a somewhat higher prevalence of hypodontia among females (50%) compared to male PRS patients (41.2%), no statistically significant difference in the incidence of hypodontia between the genders could be ascertained, a finding which is in accordance with the published literature (Randall et al., 1965; Ranta & Rintala, 1983; Rintala, Ranta, & Stegars, 1984; Ranta, 1986; Amaratunga, 1989). In a comprehensive review of the research into tooth formation abnormalities in children with isolated cleft palate or Pierre Robin sequence that had been conducted up to the late 1980s, Ranta (1986) could find no study showing a statistical difference in formation based solely on gender. Earlier, Ranta and Rintala (1983) had found that while hypodontia was more prevalent among the female subjects in their study sample (PRS), that prevalence was

not statistically significant.

While it is highly likely that future investigators will continue to include gender as a variable in research on the many aspects of PRS, data is gradually accumulating to support the hypothesis that gender is not a significant influence on the hypodontia associated with Pierre Robin sequence. The gender variable may be clearly significant in studies of genetic precursors or influences on the initial diagnosis of PRS and in studies of subsequent growth of the jaws and other relevant structures.

5.2 Hypodontia

Agenesis of the permanent teeth in the general population has been reported to be between 1.6 percent and 9.6 percent (Shapira, Lubit, & Kuftinec, 1999; Vastardis, 2000), and the incidence of severe cases, meaning the absence of four or more permanent teeth, to be about 0.25 percent (Vastardis, 2000). As the findings in the current research suggest, the incidence of hypodontia among children born with Pierre Robin sequence or isolated cleft palate is much higher than it is in the general population, supporting the prevailing view among researchers that hypodontia is a definite feature of these conditions (Ranta, 1983; Ranta & Rintala, 1983; Ranta, Stegars, & Rintala, 1983; Ranta, 1984; Edwards & Newall, 1985; Amaratunga, 1989; Shapira et al., 1999).

The work of Ranta and colleagues in the 1980's (Ranta, 1983; Ranta et al., 1983; Ranta & Rintala, 1983; Rintala et al., 1984; Ranta et al., 1985; Laitinen et al., 1997; Laitinen & Ranta, 1998), conducted primarily among Scandinavian children, has firmly established the association of hypodontia, among other dental abnormalities, in children with Pierre Robin sequence,

with or without cleft palate. In addition to establishing hypodontia as a feature of the sequence, these researchers also looked at the timing of tooth formation, the distribution of missing teeth between the maxilla and mandible, the size of the dental arches, and the numbers of missing teeth, thus providing a firm foundation for further research into these factors.

In the sample of children investigated in the current research, the incidence of hypodontia in those children with Pierre Robin sequence was significantly higher (46.2% of the PRS group), compared with the incidence among children with isolated cleft palate (19.1% of the CP group). These findings are consistent with earlier research, such as the work of Rintala, Ranta, and Stegars (1984), which found an incidence of hypodontia in 50% of the PRS patients they examined. The study of Rintala et al. (1984) confirmed an earlier study by Ranta and Rintala (1983), which also found hypodontia in half of their sample of Robin sequence patients.

In terms of the location of absent teeth, we found no statistical difference between right-hand and left-hand side hypodontia in the study (PRS) group. This finding is in accordance with previously published data (Ranta, 1983).

Previous research has suggested that in PRS children, hypodontia is more apparent in the lower jaw than the upper (Ranta & Rintala, 1983; Ranta, 1986). In the current study as well, 41% of the subjects in the PRS group had lower jaw hypodontia. There are a number of possible explanations for the prevalence of hypodontia in the lower jaw in patients with Robin sequence that have been advanced by previous researchers. While there is as yet no consensus among researchers as to the etiology of PRS, they have tended to advocate either a mechanical (teratogenic) cause or a genetic cause, when they have taken a position at all; some have suggested that both causes may be implicated in the etiology of PRS (Ricks et al., 2002).

The mechanical theory of etiology, sometimes referred to as the fetal malposition theory, was advanced in the 1960s (Randall et al., 1965, among others), primarily to explain the prevalence of cleft palate among newborns diagnosed with PRS. Rintala et al. (1984), in an attempt to test the mechanical etiological hypothesis, found that genetic factors were a more likely explanation, since cleft palates occurred with equal frequency in the relatives of PRS and isolated CP patients. That finding led these investigators to suggest that a more prominent feature of PRS was the abnormal development of the mandible, rather than the presence of cleft palate.

5.3 Premolar Agenesis

In terms of the general population, it has been suggested that hypodontia occurs for at least one tooth in about a 25 percent of the population (Shalish, Peck, Wasserstein et al., 2002). Ranta (1986), in a comprehensive review of the research into tooth development abnormalities, concluded that there was some evidence to support an association between the delay in tooth development and the number of missing teeth in PRS children. In addition, Ranta concluded that in older children, aged six to nine years, the delay was significantly longer than in younger children.

Rintala et al. (1984) found more missing teeth in the lower jaw of PRS subjects, hypothesizing that ***"The high incidence of hypodontia in the PRS speaks for the action of genetic etiological factors and can hardly be explained to be due to the anomalous intrauterine position of the chin."*** As discussed above, the current research also supports the higher incidence of mandibular hypodontia in PRS. However, we made no attempt to trace etiology in the patients who were included in either the PRS or CP groups.

In a 1983 study, Ranta and Rintala found that, in addition to a greater prevalence of hypodontia in PRS patients compared with isolated cleft palate patients, a significantly different pattern of distribution between these two groups of patients exists. In PRS patients, the second premolars were missing in almost twice the number of patients as in the isolated cleft palate patients included in their study (20.5% vs. 10.4%). These findings led Ranta and colleagues to pursue a genetic etiology, but not all researchers have taken this course (Shapira et al., 2000).

It was in part the assertion of Ranta (1986) about developmental dental abnormalities, including delays in development and the number of missing teeth in children born with Pierre Robin sequence, upon which the current investigation proceeded, with a focus on the development of second premolars. Perhaps the greatest contribution derived from the data collected in the course of our study was to reveal that the risk of missing lower second premolars in PRS patients was three-and-one-half times that of patients born with isolated cleft palate (33.3% in PRS vs. 12.8% in CP, with an odds ratio of PRS/CP of 3.4).

Further investigation into mandibular second premolar agenesis revealed an equal distribution between PRS patients with only one lower second premolar agenesis and those with both lower second premolar agenesis. No comparable data was found in the literature.

Moreover, in all cases of lower second premolar agenesis in our PRS group, the **primary** mandibular second molars were present in the arch. This new data could not be compared to findings from other studies, since tooth agenesis in the primary dentition, as associated with PRS, was never previously reported in the literature.

5.4 Respiratory Obstruction

Previous studies in PRS children dealt mainly with etiology and treatment of PRS with very limited data on respiratory distress and feeding difficulties. In most cases, mortality correlates significantly with the severity of airway obstruction (Sadewitz, 1992). Until recently, glossoptosis due to micrognathia was assumed to be the main factor responsible for upper airway distress (Sher, 1986); more recent endoscopic evaluation of the pharyngeal airway reveals both the origin and mechanism of airway obstruction to be multifactorial (Van den Elzen et al., 2001). Tightness or shortness of the genioglossus muscle and other musculature of the floor of the mouth has also been reported to contribute to glossoptosis leading to secondary respiratory obstruction (Delorme et al., 1989; Caouette-Laberge et al., 1994).

In our study, lower second premolar agenesis was not statistically correlated with the severity grades of respiratory obstruction in the study (PRS) group. By the same token, the group with the mildest form of respiratory obstruction in the PRS group and the group with the most severe form had a similar incidence of lower second premolar agenesis. This finding could not be compared to data from other PRS studies given that such correlation has never been previously reported in the literature. Based on the accepted belief that glossoptosis and respiratory distress are transient phenomena that disappear, or at least greatly improve between the ages of 2 and 4, the age at which mandibular second premolar formation begins, our objective was to investigate the correlation between these two clinical entities for a possible connection.

5.5 Summary

In general, the current research appears to confirm the findings of previous researchers who have investigated developmental dental abnormalities in patients born with Pierre Robin sequence. New and original data pertaining to PRS has also been collected and discussed in the hopes that future research would further contribute to this new knowledge.

We were able to confirm, for example, that despite a female preponderance among the PRS subjects in the current research, the factor of gender appears to have no statistical significance with regard to the prevalence of PRS. Likewise, the factor of gender appears to have no statistical significance with regard to hypodontia in either Robin sequence or isolated cleft palate patients. While we make no claim that this is a definitive finding with regard to the role of gender, we do believe that these findings make a much-needed contribution to the growing data supporting this conclusion.

The current study was also able to confirm that hypodontia is clearly more prevalent in patients born with Pierre Robin sequence than in patients born with isolated cleft palate. In addition to this important finding, we were also able to confirm that the risk of missing lower second premolars is also much greater in PRS patients than in isolated cleft palate patients. With the affirmation that PRS patients have a 3.4 times the risk of having lower second premolars agenesis as compared to isolated CP patients, a clinical and statistical association between PRS and lower second premolar agenesis can now be established. Such an original input will certainly make a significant contribution to the body of research on dental development in Pierre Robin sequence. There have been a number of suggestions about the etiology of the dental abnormalities found in Pierre Robin sequence, but

there is as yet no consensus among researchers, who have found conflicting or inconclusive results. Thesleff (2000) has recently reminded the research community that tooth development is genetically controlled, and that the controlling genes are known. Because these genes are also implicated in many other functions in developing embryos, there is still a great deal of work to be done to determine how they are associated with PRS in general and mandibular growth in particular.

Consequently, another area of research that offers great promise is a focus on abnormal mandibular development (hypoplasia) and the theory of "catch-up growth." The possible association between lower second premolar agenesis and postnatal mandibular catch-up growth in PRS patients would certainly imply the presence of a genetic link, which in turn may support future research into etiological avenues beyond the fetal compression hypothesis.

Mechanisms of airway obstructions are known to have different origins; our investigation into a possible link between lower second premolar agenesis and airway obstruction showed no clinical or statistical correlation. Since the impact of respiratory obstruction on hypodontia in PRS patients has not been previously studied, we were not able to find any comparable data in the literature.

In any interpretation of findings regarding hypodontia, it is well to keep in mind the caution expressed by Alexander-Abt (1999). This author, among others, has recommended that investigators consider the extraordinarily wide variation in the timing of dental development among individuals. The incidence of missing teeth can also vary in different geographic areas and among individual members of racial and ethnic groups (Shapira et al., 1999). While Alexander-Abt pointed out that the mineralization of second

premolars may be atypically delayed in some rare cases, it has been suggested by other researchers that delayed tooth formation is nothing more than a minor form of hypodontia (Ranta, 1983).

Despite the focus of the current study on developmental dental abnormalities associated with PRS, it has not been possible to escape some of the diagnostic ambiguities entirely. The patients selected for inclusion in the experimental (PRS) and control (CP) groups for the current study were identified from a large clinical database which, by its very nature, may be assumed to contain inconsistencies and even inaccuracies. These occurrences could not be controlled, nor could the investigators assume that a completely consistent set of diagnostic criteria were used in every single case to determine a diagnosis of Pierre Robin sequence when the clinical data were entered into the records that formed the database. Nonetheless, every effort was made to ensure that the records of the patients selected for inclusion in the study were as complete and as accurate as possible.

CHAPTER SIX

CONCLUSIONS

6. Conclusions

1. The prevalence of hypodontia was greater in the PRS group (46.2%) than in the CP group (19.1%).

2. PRS patients have 3.6 times the risk of having hypodontia as compared to isolated CP patients.

3. Female preponderance was higher in both the experimental and study groups (56.4% in the PRS group; 59.6% in the CP group), although the differences between the sexes were not statistically different.

4. Hypodontia was more prevalent in girls than in boys in the PRS group (50% in females; 41.2% in males); however the differences were not statistically different.

5. Lower jaw hypodontia (41.0%) in the PRS group was more prevalent than the upper jaw.

6. We found no statistical difference in prevalence between right-hand side and left-hand side hypodontia in the study (PRS) group.

7. Lower second premolars were the most frequently missing teeth in both our groups (PRS 33.3 %, CP 12.8%).

8. PRS patients have 3.4 times the risk of having lower second premolars agenesis as compared to isolated CP patients.

9. An equal distribution was noted between subjects missing one of the lower second premolars and those missing both lower second premolars among the PRS subjects (17.9%).

10. In all cases of lower second premolar agenesis in our PRS group, the **primary** mandibular second molars were present in the arch.

11. Lastly, we found no statistical correlation between lower second premolar agenesis and the degree of severity of respiratory obstruction in PRS subjects.

As a final point, we **recommend** improving the method of follow-up of patients diagnosed with PRS to ensure periodic examinations of these patients at Sainte-Justine Hospital. Clinical and, when necessary, radiographic records should be taken at regular intervals, as agreed upon by the team of specialists of the Craniofacial and Cleft Palate Clinics.

It is hoped that the contribution of this study will move the research community forward in work not only on developing new techniques for treatment and intervention, but also on refining diagnostic criteria and exploring the possible genetic link between lower premolar agenesis and postnatal mandibular growth in PRS patients.

CHAPTER SEVEN

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CHAPTER EIGHT

ANNEX

Université de Montréal

Faculté des études supérieures
Vice-décanat

Le 20 avril 2004

Monsieur Wissam Daher
2187, du Souvenir
Montréal (Québec) H3H 1R9

Objet : Rédaction d'un mémoire en anglais

Monsieur,

Pour faire suite à votre demande relative à la rédaction de votre mémoire en anglais, la Faculté des études supérieures vous autorise à le rédiger en langue anglaise.

Veuillez agréer, Monsieur, l'expression de mes sentiments les meilleurs.

Le vice-doyen,

[redacted]

Fernand A. Roberge
Secteur Santé

FAR/vs

c.c. : M. Claude Remise, Coordonnateur du prog. d'orthodontie
M. Jean Barbeau, resp. des études supérieures - FMD

C.P. 6128, succursale Centre-ville Téléphone : (514) 343-5891 Télécopieur : (514) 343-2252

Le 02 septembre 2004

Dr Hicham El-Khatib
Médecine dentaire
Étage B Bloc 5

HÔPITAL
SAINTE-JUSTINE
Le centre hospitalier universitaire mère-enfant

Pour l'amour des enfants

OBJET: Titre du projet: ÉTUDE RÉTROSPECTIVE SUR LES AGÉNÉSIES DENTAIRES ET LES FISSURES PALATINES CHEZ LES PATIENTS ATTEINTS DU SYNDROME DE PIERRE-MARIE ROBIN

Responsables du projet: Hicham El-Khatib D.M.D. , Dr Claude Remise, Dr Wissam Daher

Cher Docteur,

Votre projet cité en rubrique a été approuvé par le Comité d'éthique de la recherche en date d'aujourd'hui. Vous trouverez ci-joint la lettre d'approbation du Comité.

Tous les projets de recherche impliquant des sujets humains doivent être réexaminés annuellement et la durée de l'approbation de votre projet sera effective jusqu'au 2 septembre 2005. Notez qu'il est de votre responsabilité de soumettre une demande au Comité pour que votre projet soit renouvelé avant la date d'expiration mentionnée. Il est également de votre responsabilité d'aviser le Comité de toute modification au projet ainsi que de tout effet secondaire survenu dans le cadre de la présente étude.

Votre projet a été envoyé au directeur du Centre pour approbation finale.

Nous vous souhaitons bonne chance dans la réalisation de votre projet et vous prions de recevoir nos meilleures salutations.

[redacted]

Jean-Marie Therrien, Ph.D., éthicien
Président du Comité d'éthique de la recherche,

JMT/ic

Université de Montréal

3175, Côte-Sainte-Catherine
Montréal (Québec)
H3T 1C5

Un comité de l'Hôpital Sainte-Justine formé des membres suivants:

Jean-Marie Therrien, éthicien et président
Anne-Claude Bernard-Bonnin, pédiatre
Geneviève Cardinal, juriste
Michel Duval, hémato-oncologue
Françoise Grambin, représentante du public
Maja Krajinovic, scientifique
Lyne Pedneault, pharmacienne
Jean-François Saucier, psychiatre
Valérie Tremblay, infirmière de recherche
Chantal Van de Voorde

HÔPITAL SAINTE-JUSTINE
Le centre hospitalier universitaire mère-enfant

Pour l'amour des enfants

Approbation valide jusqu'au 2 septembre 2005

Les membres du comité d'éthique de la recherche ont étudié le projet de recherche clinique intitulé:

Étude rétrospective sur les agénésies dentaires et les fissures palatines chez les patients atteints du syndrome de Pierre-Marie Robin

soumis par: *Hicham El-Khatib D.M.D. , Dr Claude Remise, Dr Wissam Daher*

et l'ont trouvé conforme aux normes établies par le comité d'éthique de la recherche de l'Hôpital Sainte-Justine. Le projet est donc accepté par le Comité.

[redacted]

Jean-Marie Therrien, Ph.D., éthicien
Président du Comité d'éthique de la recherche

Date d'approbation: 02 septembre 2004