From the DEPARTMENT OF DENTAL MEDICINE
Karolinska Institutet, Stockholm, Sweden

CRANIOFACIAL DEVELOPMENT AFTER THREE DIFFERENT PALATOPLASTIES IN CHILDREN BORN WITH ISOLATED CLEFT PALATE

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Karolinska Institutet

Stockholm 2018

Published by Karolinska Institutet
Printed by Eprint AB 2018

ISBN 978-91-7831-277-1

Craniofacial development after three different palatoplasties in children born with isolated cleft palate

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To Christina, little Anastasios and…forthcoming Vassilios

“Wherever the art of Medicine is loved,
there is also a love of Humanity”

Hippocrates of Kos, c.460-370 B.C.

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ABSTRACT

Introduction: Different palatoplasties are applied for the surgical correction of children born with an isolated cleft in the palate (ICP). During the last decades the Veau-Wardill-Kilner (VWK), Minimal Incision (MI) and Minimal Incision with radical muscle reconstruction (MMI) palatoplasties were performed by the Stockholm Craniofacial Team.

Aims: To compare the VWK, MI and MMI techniques for repair of isolated clefts of the soft and/or hard palate regarding surgical complications, dentoalveolar outcome at 5 years, facial growth at 5 and 10 years, and to compare patients with ICP with children born without a cleft at 10 and 16 years of age.

Materials: A consecutive series of 247 Caucasian non-syndromic children born with isolated cleft palate between 1980 and 2007 and treated surgically at 13 months were studied. Children with Pierre Robin Sequence (PRS) were included in the study. The patients were divided into six groups: three groups regarding the three surgical techniques and two groups regarding cleft length (extending in the soft, or hard and soft palate). A control group of 55 children (25 boys and 30 girls) without a cleft registered at 10 years and another 55 (25 boys and 30 girls) at 16 years of age was used.

Methods: Retrospective study of:

A. *medical records* of patients treated with MI or MMI concerning time for surgery, blood loss, complications in the immediate postoperative period, frequency of fistulas and additional pharyngeal flap surgery.

B. *study models* of patients treated with MI or MMI at 5 years concerning dental relations, structure of the palatal mucosa, and height of the palatal vault.

C1. *lateral cephalograms* of patients treated with VWK, MMI or MMI at 5, 10 and 16 years of age calculating fourteen skeletal and one soft tissue measurement.

C2. *lateral cephalograms* of patients born without a cleft at 10 and 16 years calculating fourteen skeletal and one soft tissue measurement.

Results:

A. surgical complications: The MMI, compared to the MI, technique resulted in statistically significant increased operation time, less need for pharyngeal flaps, and to shallower palatal vault. Big clefts result in statistically significant increased operation time and need for pharyngeal flaps.

B. dentoalveolar outcome: Dental relations and the structure of the palatal mucosa were the same in all groups. The palatal height was reduced in the MMI group distal of the first primary molars.

C1. facial growth: Only minor differences in cephalometric morphology were found between the techniques at 5 years and 10 years. Comparing VWK to MI, the only statistically significant difference was at 5 years, where a shorter mandible in the MI big cleft group ($p<0.01$) was found. Comparing MI to MMI, at 5 years, statistically significant increased inclination of the palatal plane in the big MMI cleft group ($p<0.01$), increased posterior upper face height ($p<0.01$) and longer mandibular length ($p<0.001$) in the small MI cleft group was observed. Comparing MI to MMI, at 10 years, statistically significant increased inclination of the palatal plane ($p<0.001$), decreased posterior upper face height ($p<0.001$) and longer palatal length ($p<0.01$) was seen in the big MMI group. Similar results were found independent of cleft length or the inclusion of children with PRS in the sample.

C2. Facial growth after MI or MMI versus matched children without a cleft: Comparing children operated with MI to a group without cleft, at both 10 and 16 years of age, a retrognathic, smaller and with a posteriorly inclined maxilla and a retrognathic mandible was measured in treated patients born with a palatal cleft compared to the control group. Additionally, at 10 years of age a smaller mandible and reduced posterior face heights were recorded.

Conclusions: The muscle reconstruction has been shown to result in less need for pharyngeal flaps, but to shallower palatal vault and demand for almost double operation time. Dental relations were the same with or without performed the muscle reconstruction. The craniofacial cephalometric morphology at 5 and 10 years of age in patients with isolated cleft palate is similar between the three surgical groups. The craniofacial morphology at 10 and 16 years of age in treated patients born with an isolated cleft in the palate differs compared to the morphology of a normal control group born without an isolated cleft in the palate: both the maxilla and the mandible are retrognathic, and the maxilla is smaller and posteriorly inclined.

LIST OF SCIENTIFIC PAPERS

I. Facial growth at five and ten years after Veau-Wardill-Kilner versus Minimal-Incision Technique Repair of Isolated Cleft Palate
Parikakis K, Larson O, Larson M, Karsten A
The Cleft Palate-Craniofacial Journal (2018); 55: 79-87

II. Minimal Incision Palatoplasty with or without muscle reconstruction in patients with isolated cleft palate – A cast and medical records analysis
Parikakis K, Larson O, Larson M, Karsten A
European journal of orthodontics (2018); 40: 504-511

III. Minimal Incision Palatoplasty with or without muscle reconstruction in patients with isolated cleft palate – A cephalometric study at 5 and 10 years
Parikakis K, Larson O, Karsten A
European journal of orthodontics (2018); doi: 10.1093/ejo/cjy077

IV. Facial growth in patients with treated isolated cleft palate compared to a normal population – A cephalometric study at 10 and 16 years of age
Parikakis K, Larson O, Karsten A
Submitted

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LIST OF ABBREVIATIONS

3D	Three-dimensional
ANOVA	Analysis of variance
CBCT	Cone Beam Computed Tomography
CP	Cleft palate
CT	Computed Tomography
FH	Face height
ICD	International Classification of Diseases
ICP	Isolated cleft in the palate
MHB	Modified Huddart and Bodenham
MI	Minimal Incision
MMI	Minimal Incision with muscle reconstruction
PRS	Pierre Robin Sequence
VPI	Velopharyngeal insufficiency
VWK	Veau-Wardill-Kilner
C (group)	Control group: children born without a cleft
T (group)	Treated group (of children born with ICP)
1 (group)	Small (short) cleft: cleft extending only within the soft palate and a notch less than 3 mm in the posterior border of the hard palate
2 (group)	Big (long) cleft: cleft extending in the soft and hard palate
points:	
Ar	(articulare): a mid-planed point located at the intersection of the posterior border of the ramus with the inferior surface of the cranial base
Ba	(basion): the most inferior point on the anterior margin of foramen magnum
Cd	(condylion): the midpoint point on the contour of the glenoid fossa where the line indicating maximum mandibular length intercepts the contour of the fossa
Gn	(gnathion): the most inferior point on the bony chin
mlp	(inferior gonion): a mid-planed point at a tangent to the inferior border of the mandible near gonion

n	(nasion): junction of the frontal and nasal bones at the naso-frontal suture
pg	(pogonion): the most anterior point on the bony chin
pgn	(prognathion): the point on the contour of the bony chin indicating maximum mandibular length measured from the temporomandibular joint
pm	(pterygomaxillare): the posterior limit of the floor of the nose at the tip of the posterior nasal spine
pm´	constructed point at the perpendicular projection of pm on HP
rli	(posterior gonion): a mid-planed point at a tangent to the posterior border of the ramus near gonion
s	(sella): the midpoint of the sella turcica
sm	(supramentale): the deepest point in the concavity of the anterior mandible between the alveolar crest and pogonion
sp	(spinal point): the anterior limit of the floor of the nose at the tip of the anterior nasal spine
sp´	constructed point at the perpendicular projection of sp on n-gn line
ss	(subspinale): the deepest point in the concavity of the anterior maxilla between the anterior nasal spine and the alveolar crest
tgo	constructed point at the intersection between RL and ML
G	(Glabella): the most anterior point on the forehead, in the region of the supra-orbital ridges
Pg´	(Soft Tissue Pogonion): the most anterior point on the soft tissue chin
Sn	(Subnasale): the junction of the columella of the nose with the philtrum of the upper lip

planes (lines):

HP	(contructed Horizontal Plane): a line -7^{o} from NSL passing through s
ML	(Mandibular Line): gn-mlp
NL	(Nasal Line): sp-pm
NSL	(Nasion Sella Line): n-s
RL	(Ramus Line): ar-rli

variables (measurements):

NSBa	n-s-ba angle
SNA	s-n-ss angle
SNB	s-n-sm angle
ANB	ss-n-sm angle
NSL / NL	NSL/NL angle
NSL / ML	NSL/ML angle
NL / ML	NL/ML angle
ML / RL	ML/RL angle
NAPg	n-ss-pg angle
Palatal plane length	sp-pm distance
Mandibular length	cd-pgn distance
n-sp´/n- gn	n-sp´/n- gn ratio
sp´-gn/n- gn	sp´-gn/n- gn ratio
Posterior upper FH	(posterior upper face height): pm-pm´ distance
Posterior FH	(posterior face height): s-tgo distance
Facial convexity	G-Sn-Pg´ angle

1 INTRODUCTION

1.1 ISOLATED CLEFT IN THE PALATE

1.1.1 General - Epidemiology

The most common birth defect is the presence of a cleft and 27-34.3% of the clefts in the face are those found only in the palate (1-3). The prevalence of ICP varies from 0.17 to 0.7 out of 1000 live births (1-8). Females are equally or more affected by a ratio of 1.5-1.6/1 than males (1, 9, 10). In recent years a small decline in prevalence (2), which is mainly attributed to prenatal screening, no change (but decline in syndromic cases) (6), or even a raise of 13,4% (in Shanghai) (9) were reported. Seasonal trends in infants with ICP born in Sweden were found with a peak in April (11).

A cleft only in the palate is associated with a syndrome in 21-33% of the cases (1, 12). The incidence of a congenital malformation didn't differ according to various socio-economic status (e.g. occupation of the mother, type and income of the family, housing standard) (13).

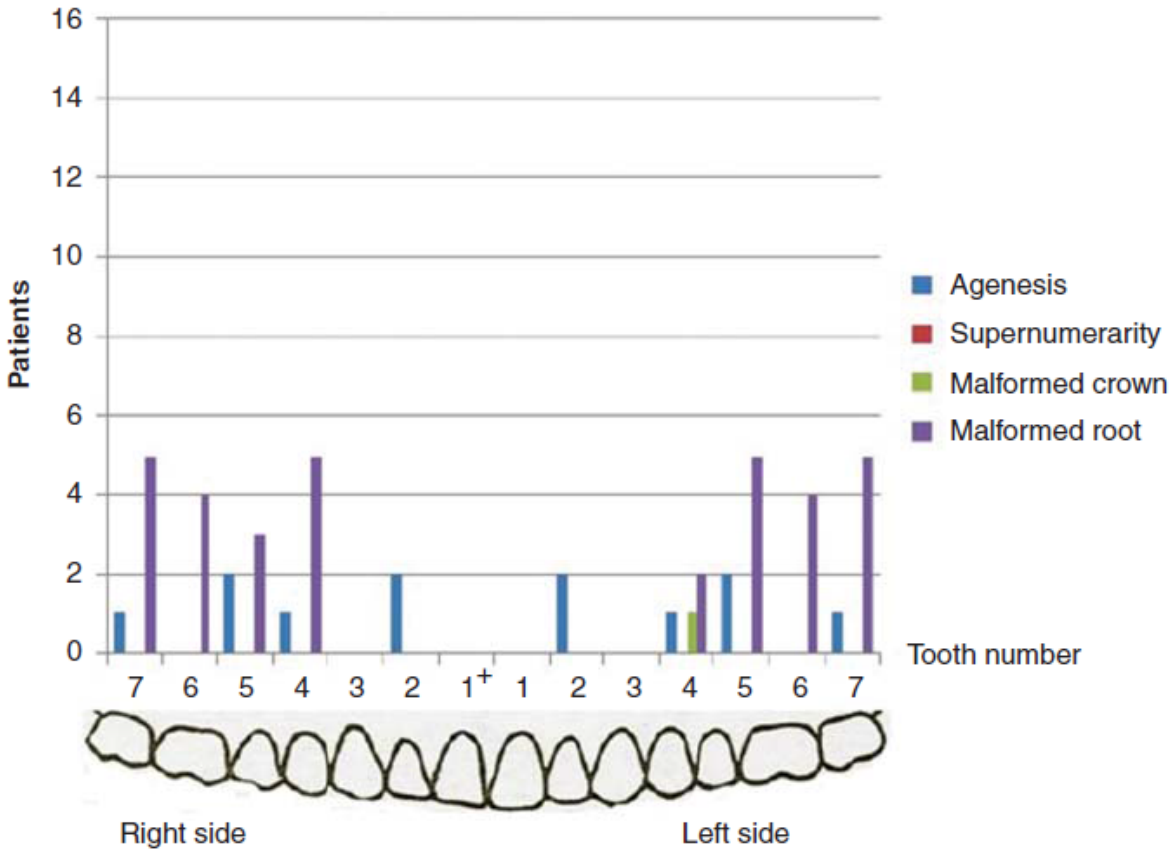

Fig. 1. The distribution of dental deviations in patients with ICP. The dental deviations are located primarily in the premolar/molar region, where few agenesis and more malformed roots were observed (Reprinted with kind permission from Riis et al. (14), Journal of plastic surgery and hand surgery, Taylor & Francis)

In children born with an ICP aplasia is more often present (31.5-43.8 %) (15, 16), as compared to the total population (6.4%) (17) when excluding the 3rd molars. The aplasia

mainly concerns the mandibular second premolars, maxillary lateral incisors, maxillary second premolars, mandibular lateral incisors and second molars (15, 16, 18). In the total population agenesis occurs more often in the mandibular second premolars followed by maxillary lateral incisors and maxillary second premolars. Malformed root of some teeth is a usual finding (Fig. 1) (14). Ectopically erupted, impacted and even supernumerary teeth may be present (19-21). Tooth formation is delayed and in case of hypodontia this delay is more severe (22). Cervical vertebral anomalies occur twice more often in children with ICP (23).

1.1.2 Embryology

The two palatal shelves (mesodermal projections, also called lateral palatine processes), derived from the maxillary prominences, are formed initially vertical on both sides of the tongue. At the beginning of the 8th embryonic week, the tongue is pulled out from the space between the vertical shelves due to growth of the stomodeum and the initiation of the reflexes of mouth opening. Functioning of the hyoglossus muscle is required for the pulling of the tongue and neuromuscular and jaw joint activity are needed. Those procedures are initiated by genes, influenced by the environment and should be synchronized and happen on critical timing (24). Then, as space is provided from the movement of the tongue, the palatal shelves can elevate to a horizontal position, dorsal to the tongue, meet, and start fusing in the midline at the end of the 8^{th} to the beginning of the 9^{th} embryonic week, forming the secondary palate. The fusion starts approximately in the middle of the anterior part of the palatal shelves, continuous both anteriorly and posteriorly like a zipper, and ends around the 11^{th} embryonic week (24-27).

Failure of the palatal shelves to meet leads to a *cleft in the palate*. If the failure happens early the child is born with an anteroposteriorly *long* cleft (in part or the complete hard and all of the soft palate) and if it happens late the child has got a *short* cleft (in part or all of the soft palate). Adhesion and fusion of the palatal shelves in the midline guide to the formation of the secondary palate and later to normal intramembranous bone formation. Apoptosis of the medial edge epithelia takes place during fusion (28). If adhesion of the epithelia enveloping the palatal shelves occurs, but complete removal of the epithelial seam fails, then a *submucous* cleft is formed, where the mucosa is continuous, non-keratinized but the bone and the muscles of the palate are discontinuous (24, 27).

1.1.3 Classification

The main distinguish is if a syndrome co-exists with the cleft in the palate or not, characterizing the cleft as *syndromic* or *non-syndromic* respectively.

A cleft in the palate can vary significantly in width and extension. A cleft in the palate can be narrow or very wide, extended in the soft palate only or in both the hard and soft palate. There may also be clefts in the muscular layer of the soft palate only (submucous) or minor clefts localized only in the uvula (bifid uvula). Usually no palatal process is attached to the nasal septum and there is complete communication of the nasal with the oral cavity, but there are rare cases where one of the palatal shelves is connected to the nasal septum (27).

In early attempts to classify facial clefts, ICP was identified and consisted of a special category. According to Shprintzen all defects of the palate consisted of one group (group 2). Veau defined two types of ICP, Type I, clefts of the soft palate posterior to the hard palate, and type 2, complete clefts of the palate from the incisive foramen posteriorly through the soft palate. Fogh-Andersen defined one group: the cleft palate group, were the defect is in the midline and does not extend anteriorly beyond the incisive foramen (29).

Later Kernahan and Stark introduced the striped Y diagram (30, 31), providing three areas for ICP: areas 7 and 8 for the hard palate, and area 9 for the soft palate (Fig. 2). Following decades more anatomical classifications were proposed and later the integration of pathogenic and etiologic classifications lead to different approaches (29). Nowadays, apart from the etiologic classifications, the system from Ross and Johnston, proposing group CP for clefts involving the hard and soft palate only, seems most used.

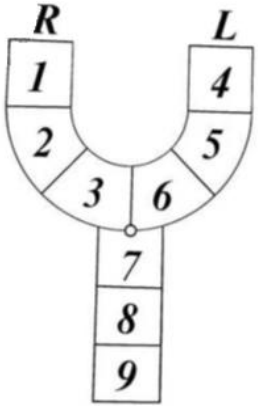

Fig. 2. The stripped Y. The hard palate is represented by areas 7 and 8, while the soft palate by area 9. The hole in the middle represents the incisive foramen (Reprinted with kind permission from Kernahan (31), Plastic and reconstructive surgery, Wolters Kluwen, https://journals.lww.com/plasreconsurg/pages/default.aspx).

According to the international health information standards, the index from WHO (ICD: International Classification of Diseases) is widely accepted and used for registration of the diagnosis in many countries. Mainly two out of five codes for ICP in ICD-10 are in use: Q35.3 for cleft soft palate, and Q35.5 for cleft hard palate with cleft soft palate. Since June 2018 a new version was released (ICD-11) with the new codes: LA42.0 for cleft hard palate, and LA42.1 for cleft soft palate (32).

1.1.4 Genetic background

1.1.4.1 Genes / Syndromes

There is an important genetic factor in the creation of a palatal cleft. Cleft palate seems to be caused by a disorder in neural crest migration to the maxillary and palatal fields (14). The last decades more than 30 genes are associated with cleft palate and presently examined as possible contributors: MSX1, NECTIN1, IRF6, TP63, LOXL3, TBX22, SPECC1L, PHF8, SOX9, TGDS, CDH1, TBX1, SF3B4, SLC17A8, SLC6A9, SLC6A3, BMP4, GABRB3, PRSS12, TAS2R16, FGF8, ACTL6A, ALX1, ALX3, MTHFR, FREM1, FGFR1, ALX4 genes and Chromosomes 2 and 22 (33).

Many syndromes may be present together with a cleft in the palate (Table 1). The most common ones are: Stickler syndrome, 22q11.2 deletion (DiGeorge syndrome, velocardiofacial syndrome), Facio-aurico-vertebral/oculo-auricolo-vertebral spectrum, Kabuki syndrome, Treacher Collins syndrome, Fetal alcohol syndrome, Diabetic embryopathy, Down syndrome, Spondyloepiphyseal dysplasia congenital and Kniest dysplasia, and Van der Woude syndrome (34).

Syndrome	Cause (Gene)	Prominent Features
Stickler syndrome	Autosomal dominant (COL2A1, COL11A1, COL11A2)	Flat face, Pierre Robin sequence (more than half of cases), myopia
	Autosomal recessive (COL9A1, COL9A2)	Spondyloepiphyseal dysplasia
22q11.2 deletion (velocardiofacial syndrome, DiGeorge syndrome)	22q11.2 deletion	Short palpebral fissures, conotruncal cardiac defect, alar hypoplasia, small ears
Facio-aurico-vertebral/oculo-auricolo-vertebral spectrum	Usually sporadic	Microtia, ear tags, cardiac defects, Pierre Robin sequence (occasionally), epibulbar dermoid
Kabuki syndrome	Autosomal dominant (KMT2D); X-linked (KDM6A)	Large palpebral fissures, cardiac defects, Pierre Robin sequence (occasional), fetal finger pads
Treacher Collins syndrome	Autosomal dominant (TCOF1, POLR1D); autosomal recessive (POLR1C)	Microtia, micrognathia, Pierre Robin sequence (common), zygomatic hypoplasia
Fetal alcohol	Alcohol exposure	Microcephaly, smooth philtrum, short palpebral fissures
Diabetic embryopathy	Poorly controlled maternal diabetes	Cardiac defects, ear tags, caudal regression
Down syndrome	Trisomy 21 (nondisjunction, translocation, mosaic)	Flat face, cardiac defects, small ears, single transverse palmar creases
Spondyloepiphyseal dysplasia congenita and Kniest dysplasia	Autosomal dominant (COL2A1)	Short-limb dwarfing, Pierre Robin sequence (more than half of cases), pulmonary hypoplasia, myopia

Van der Woude syndrome	Autosomal dominant (IRF6,GRHL3)	Lower lip pits, cleft lip and/or palate, hypodontia
Popliteal pterygium syndrome	Autosomal dominant (IRF6)	Lip pits, popliteal web genital anomalies, cleft lip and/or palate, hypodontia, syndactyly, webs of skin
Anticonvulsant embryopathy	Exposure to carbamazepine, hydantoin, mysoline, phenobarbital, valproic acid,	Microcephaly, cardiac defect, nail hypoplasia, coarse facies
CHARGE syndrome	Autosomal dominant (CDH7)	Ocular colobomas, cardiac defects, choanal atresia, micropenis
Diastrophic dysplasia	Autosomal recessive (SLC26A2)	Short-limb dwarfing, Pierre Robin sequence (common), scoliosis, hitchhiker thumb
Distal arthrogryposis	Autosomal dominant	Camptodactyly, dimples
Orofacial digital syndrome type I	X-linked dominant (OFD1)	Lobulated tongue, alopecia, oral frenuli, milia
Beckwith syndrome	Multiple mechanisms affecting imprinted loci 11p	Overgrowth, Pierre Robin sequence (common), Macroglossia, omphalocele, hemihypertrophy
Branchio-oto-renal syndrome	Autosomal dominant (EYA1, SIX5, SIX1)	Cup ears, branchial arch remnants, Mondini defect, ear pits
Campomelic dysplasia	Autosomal dominant (SOX9)	Short bowed tibias with dimpling, sex reversal, flat face
de Lange syndrome	Autosomal dominant (NIPBL, SMC3, RAD21); X-linked (SMC1A, HDAC8)	Growth deficiency, Pierre Robin sequence (common), limb defects, hirsuitism, cardiac defects
Fragile X syndrome	X-linked (FMR1)	Intellectual disability, large ears, lax joints, autistic behavior
Mandibulofacial dysostosis with microcephaly	Autosomal dominant (EFTUD2)	Microcephaly, Pierre Robin sequence (common), ear tags, microtia, micrognathia

Marshall syndrome	Autosomal dominant (COL11A1)	Flat face, Pierre Robin sequence, myopia, sensorineural hearing loss
Möbius sequence	Sporadic	Sixth and seventh cranial nerve palsy, other cranial nerve palsy, clubfoot
Nager syndrome	Autosomal dominant (SF3B4)	Radial limb defects, Pierre Robin sequence (common), ear malformation, zygomatic hypoplasia
Otopalatodigital syndrome type 1	X-linked recessive (FLNA)	Broad nasal root, Pierre Robin sequence (common), broad distal phalanges, deafness
Prader-Willi syndrome	15q11.2-q13 deletion; maternal uniparental disomy at chromosome 15	Hypotonia (neonatal), obesity (later)
Rapp-Hodgkin ectodermal dysplasia	Autosomal dominant (TP63)	Coarse dry hair, anhidrosis alopecia
Cleft palate ankyloglossia	X-linked recessive (TBX22)	Ankyloglossia
Distichiasis lymphedema syndrome	Autosomal dominant (FOXC2)	Double row of eyelashes, cardiac defects, peripheral edema
Multiple pterygium syndrome	Autosomal recessive (CHRNG)	Multiple pterygia, scoliosis with vertebral defects, short neck
Retinoic acid embryopathy	Isotretinoin exposure	Anotia, brain defects, conotruncal cardiac defects,
Saethre-Chotzen syndrome	Autosomal dominant (TWIST1)	Craniosynostosis, hallux duplication, ear anomalies, brachydactyly
Smith-Lemli-Opitz syndrome	Autosomal recessive (DHCR7)	Ptosis, second-third toe syndactyly, hypospadias
Wildervanck syndrome	Sporadic, mostly females	Klippel-Feil anomaly, sensorineural deafness, Duane anomaly
Williams syndrome	Deletion of elastin locus 7q11.23	Intellectual disability, supravalvular aortic stenosis, hypercalcemia

Table 1. Syndromes associated with cleft palate in descending order of appearance.

1.1.4.2 Pierre Robin Sequence

The Pierre Robin Sequence was previously mentioned as a syndrome. It is now mostly considered a sequence of three main phenotypes: micrognathia (hypoplastic mandible), glossoptosis and upper airway obstruction (35-37). Its prevalence varies from 0.5 to 3.7 in 10000 births (8, 38-40) probably due to various diagnostic criteria applied and heterogeneity of characteristics (41-43). About 90% of the cases with PRS present also a cleft in the palate (44).

In the majority of patients an operation for upper airway obstruction for the treatment of children with PRS is not required, as the obstruction improves with time (45-47). The hypoplastic mandible in children with PRS was reported to increase more in childhood and access an almost normal size in adolescence, which was considered a "catch-up" effect (48-51). Recent studies put into doubt this concept (52-56). Some objective studies suggest increased mandibular growth rates while fewer suggest that the maxillomandibular discrepancy in PRS completely resolves later on (37).

1.1.5 Environmental background

Mechanical impendence and influence of chemical factors may contribute to formation of an ICP. According to the mechanical theory an obstacle, such as a big tongue, does not provide adequate free space for the palatal shelves to elevate. So, as they are kept in distance in a vertical orientation, there is no possibility for them to meet and fuse.

Many environmental factors, pre-existing or present during the closure of the secondary palate, are associated with ICP, although the association of some of them is rather weak. Maternal use of medications (mainly retinoids, anticonvulsants and folate antagonists), maternal diseases (diabetes, gestational diabetes, fever not controlled by antipyretics), behavior (smoking, heavy alcohol consumption, obesity, high stress) and nutrition (absence of folic acid, very high dose of vitamin A), as well as environmental exposures (contaminants in drinking water, occupational exposure to toxicants (e.g. work as a janitor)) increase the risk for the birth of a child with ICP (57).

1.1.6 Occlusion

According to Angle, the father of modern orthodontics, a *normal* occlusion was defined as one where the mesiobuccal cusps of the upper first molars occlude at the buccal grooves of the lower first molars (*Angle's class I*), and all teeth are well arranged in a smoothly curving line (58). In 1972 Andrews introduced the 6 keys to normal occlusion (correct molar relationship, crown angulation and inclination, absence of teeth rotations and spaces, and almost flat occlusal plane) after observing orthodontic patients (59), while later it was added that the normal occlusion shouldn't cause any functional or aesthetic problems.

A normal occlusion in the permanent dentition is described as:

In the *sagittal* dimension: the horizontal distance of the tip of the upper central incisors from the labial surface of the lower central incisors (overjet) is about 2 mm, and the mesiobuccal cusp of the upper first molars occludes at the buccal groove of the lower first molars (Angle's class I),

In the *vertical* dimension: the vertical distance of the tip of the upper central incisors from the tip of the lower central incisors (ovebite) is about 2 mm, and

In the *transverse* dimension: The buccal surfaces of the upper teeth are harmonically outside the buccal surfaces of the lower teeth (no crossbites exist).

Angle also described 3 main types of *malocclusion* (58):

- Class I: Normal relationship of the molars, but line of occlusion incorrect because of malposed teeth, rotations, or other causes.
- Class II: Lower molar distally positioned relative to upper molar.
- Class III: Lower molar mesially positioned relative to upper molar.

In *unoperated* individuals with CP a shorter maxillary arch length and larger posterior dental arch widths in both jaws were reported (60). On the contrary, smaller maxillary arch width was found when comparing *treated* to unoperated children with ICP, or to children with submucous cleft (61-64). Measuring posteroanterior lateral cephalograms, no difference in transversal growth between individuals with repaired ICP and without a cleft was found (65).

1.1.7 Additional surgery related to treatment of ICP

1.1.7.1 Fistulas

After a palatoplasty a small hole in the corrected palate, called fistula, permitting communication between the oral and nasal cavities may occur. They are ascribed to breakdown of the wound due to tension, infection, flap trauma, hematoma or tissue ischemia (66). In small sizes fistulas may not constitute a clinical problem, but in increased sizes they may lead to escape of nasal air, distortion of speech, loss of hearing and regurgitation of food (67). A new surgery may be needed to eliminate them.

For the correction of a postoperative fistula many alternatives exist from elevation of local flaps to transfer of free tissue. As management of palatal fistulas is very difficult, the selection of a palatoplasty to decrease the possibility of the creation of fistulas is of high importance (66). Nowadays, one-stage palatoplasty is associated with less risk of fistula formation than two-stage repair, and the Furlow palatoplasty with less risk of fistula formation than the von Langenbeck or Veau-Wardill-Kilner techniques (68). An increased fistula rate is also associated with longer extension of the cleft and low experience of the surgeon (69).

1.1.7.2 Velopharyngeal flap surgery

In some cases, after a palatoplasty the velopharyngeal sphincter cannot isolate completely the nasopharynx from the oropharynx, leading to velopharyngeal insufficiency (VPI). The child doesn't articulate well and speech is strange. Hypernasal speech, nasal air emission, reduced pressure for oral consonants and articulation errors are symptoms of VPI. So, final evaluation of speech after a palatoplasty, usually around the age of 4 years, may distinguish VPI and then an additional operation (usually velopharyngeal flap surgery) should be performed to correct VPI and, consequently, improve speech. About 10-36% of children will need an additional surgery for VPI (70-76).

The final decision for surgical intervention depends on patient age and intellectual capability, cause, severity and duration of VPI, comorbidities, and the presence of obstructive sleep apnea (70). The Furlow repair was associated with lower rate of VPI compared to the Bardach palatoplasty, and the one-stage repair with less VPI compared to two-stage repair (68).

1.1.7.3 Orthognathic surgery

Some children born with ICP may require an orthognathic surgery at cease of growth for the correction of a disharmony of the jaws. The rate varies between studies from 0 to 40 % (77-80) and confirms a rather harmonious profile and an adequate growth in most of the cases, despite the retrognathic maxillas. Orthognathic surgery in patients born with ICP concerns both correction of skeletal class II and class III malocclusions (81).

1.2 LIVING WITH A PALATAL CLEFT

Children born with an ICP present anatomical defects influencing mainly the function of the soft palate (sling). For example, the tensor palatini and levator palatini muscles of the soft palate, on each side, are not attached to the contralateral ones, but they are attached to the posterior part of the hard palate, close to the midline. Due to the communication of the oral and nasal cavity through the palate, the function of suction is missing and food may enter the nostrils. Special care and instruction, mainly concerning feeding, should be given from birth till at least the surgical correction of the deformity. Speech is also influenced. It can be difficult to produce clear sounds and the main problem, in some cases even after the operation, is hypernasality. Further surgical improvement or assistance may be needed. Additionally, due to malfunction of the muscles of the soft palate, the Eustachian tube may also malfunction. Then liquid remains in the middle ear and infections are usual, influencing hearing and guiding to the use of grommets in both ears. As ICP is influencing directly only structures inside the mouth, mainly speech problems may influence social life. Sometimes a long treatment is needed to follow speech development, solve occlusal problems or presence of another problem, such as appearance of fistulas.

1.3 CARE OF PATIENTS WITH ICP

1.3.1 Multidisciplinary treatment

The best treatment for children with ICP is a multidisciplinary one, provided by a specialized team (82). The main care is provided by a plastic surgeon, orthodontist, speech and language pathologist and psychologist. Additionally the team consists of an ENT specialist, maxillofacial surgeon, pediatrician, geneticist, nurse, phonetician and radiologist.

1.3.2 Protocol at the Stockholm Craniofacial Team

Care of all children born in the Stockholm region is provided by a specialized team, the Stockholm Craniofacial Team. The same national guidelines are followed throughout the years concerning care and registration of every child born in the region. Cephalograms and casts are taken at the ages of 5, 10, 16 and 19 years. Selected data is reported to the National Registry for Care of Patients with clefts (83). The applied surgical procedure is decided from the team. The same technique was used simultaneously, till it was replaced by another one. In 1986 the VWK technique was replaced by MI, which provided better transversal development of the palate (84). In 1997 a muscle reconstruction was added to MI leading to a modification of the technique (MMI) aiming to improve the speech and dentofacial growth (Table 2).

1.3.2.1 till 1986: VWK

One-stage palatoplasty, according to Veau-Wardill-Kilner (85), a more radical procedure than the original V-Y retropositioning one, was the standard operation for ICP (Fig. 3). According to this technique the whole mucoperiosteal flap and the soft palate are retropositioned resulting in lengthening of the palate. However, extensive areas anteriorly and laterally along the alveolar margin are left nude for secondary healing.

VWK

Fig. 3. The Veau-Wardill-Kilner (VWK) technique: Left: Mucoperiosteal flaps are raised, the hamulus is identified and the tendon of the tensor velopalatini muscle is slipped over the hamulus (not illustrated in the figure), the posterior border of the hard palate is freed from muscle insertions. Right: The nasal mucosa is sutured separately (not shown), the oral mucosa is closed with mattress sutures which within the soft palate also unite the muscle bundles on each side. Raw wound surfaces are left for secondary healing laterally and anteriorly. (Illustration by L. Raud Westberg. Used with kind permission by Karsten et al. (84), The Cleft Palate—Craniofacial Journal, SAGE Publications, Inc.)

1.3.2.2 1987-1996: MI

In order to diminish the amount of scar tissue in the palate, a new technique, the Minimal Incision was performed, influenced mainly by the work of Mendosa (86) (minimal hard palate dissection) (Fig. 4).

MI

Fig. 4. The minimal incision (MI) technique: Left: Within the hard palate the mucoperiosteum is elevated from the nasal and oral sides of the palatal shelves. In wide clefts, the greater palatine vessels are when necessary, carefully dissected free in order to get better mobility of the oral mucoperiosteum. Through the lateral incisions the hamulus is identified and the tendon of the tensor veli palatini muscle is slipped over the hamulus. In medial direction the muscles are released from the posterior border of the hard palate. The levator muscle is elevated. Right: The nasal- the muscle- and the oral- layers are sutured separately. The wound surfaces behind the maxillary tuberosities are only sutured if this is possible without stretching the tissue. (Illustration by L. Raud Westberg. Used with kind permission by Karsten et al. (84), The Cleft Palate—Craniofacial Journal, SAGE Publications, Inc.)

MMI

Fig. 5. The minimal incision with muscle reconstruction (MMI) technique: Left: Incision lines. The first steps are similar to the MI technique. The oral mucosa of the velum is then dissected off the musculature by knife and blunt dissection to the posterior border of the velum and laterally to the pterygoid hamulus. The nasal mucosa is sutured in the midline and then the muscle and the tendon of the tensor are divided from the posterior hard palate by an incision parallel to it. The tendon of the tensor veli palatini muscle is divided on the medial side of the hamulus and the muscle dissected from the nasal mucosa backwards until the levator muscle is visualized laterally. The levator is then dissected, so that the muscle bundles are felt to be freely mobile on each side, and is united with sutures in the midline. Right: The nasal- the muscle- and the oral- layers are sutured separately. The wound surfaces behind the maxillary tuberosities are only sutured if this is possible without stretching the tissue. (Illustration by L. Raud Westberg. Used with kind permission by Nyberg et al. (87), The Cleft Palate—Craniofacial Journal, SAGE Publications, Inc.)

1.3.2.3 1997-2011: MMI

In an effort to improve speech, muscle reconstruction was added to the previous technique, assuming that normalizing of the musculature of the soft palate could assist better speech development. The main influence was from Sommerlad (radical muscle reconstruction) (88, 89) (Fig. 5). The palatoplasties were performed using magnifying loops (x 2.5) and not using a microscope as instructed by Sommerlad.

1.3.2.4 2012- : Two-stage palatoplasty

Since 2012, in an effort to improve speech, a two-stage procedure was preferred: closure of the soft palate around the 5th month of age and closure of the hard palate at the age of 2 years (Gothenburg primary early veloplasty and delayed hard palate closure (90)).

Time period	Surgical Technique	Age at operation
-1986	One stage: VWK	12 months
1987-1996	One stage: MI	12 months
1997-2011	One stage: MMI	12 months
2012-	Two-stage : 1st: Soft palate closure / 2nd: Hard palate closure (Gothenburg)	1st: 4-6 months / 2nd: 2 years

Table 2. Protocol for surgical treatment of Isolated Cleft Palate patients in Stockholm.

1.4 FACIAL GROWTH (MAINLY OF THE MAXILLA AND THE MANDIBLE)

1.4.1 Normal facial growth

Emerging different growth theories described throughout the years, proposing the bone (91), the cartilage (92) or the soft tissue matrix (93) as the primary determinant of growth, as well as the knowledge gained mainly from Bjork's work (94), where consecutive cephalograms of children with metal implants were analyzed, we can briefly summarize how the maxillas and the face grow throughout the years (95, 96). Individual variability when studying growth is present, and it is clinically difficult, but important, to know whether an individual is within the range of the normal variation or not (95).

1.4.1.1 Maxilla

The maxilla develops by intramembranous ossification. Sutural growth, both at the palate itself (median and transverse palatine sutures, Fig. 6) and in its connection with the cranial base, takes place. Surface remodeling, due to apposition and resorption sites, plays a

significant role in maxillary growth, and happens in the opposite direction that the maxilla is being translated: as the maxilla is carried forward and downward, most of its anterior surface tends to be resorbed. Additionally, the maxilla is translated forward from the growth of the cranial base till the age of 7 years. Function, through soft tissue stimulation, plays an important role in the overall growth of the maxilla. Speed varies according to age and different growing curves are available for most ethnic groups.

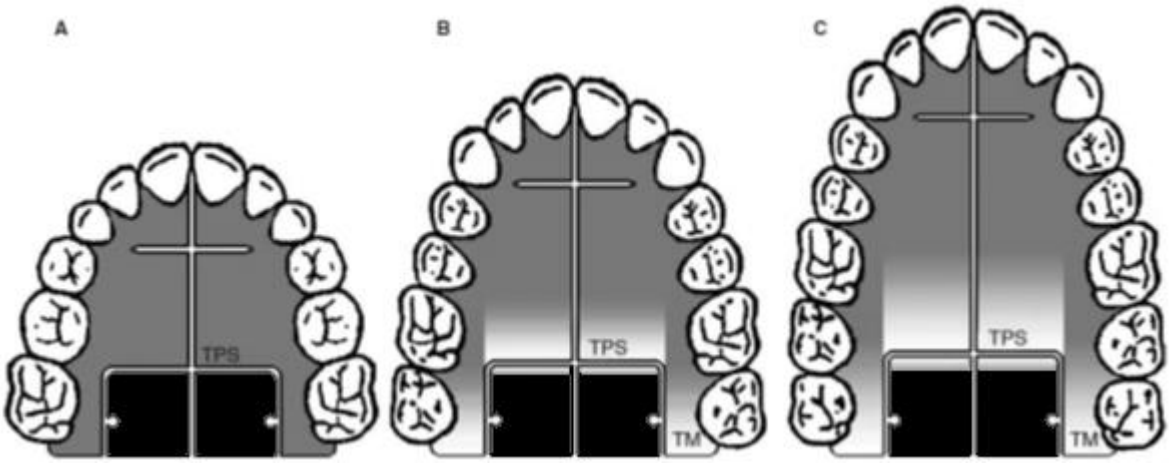

Fig. 6. Schematic drawings at three different ages of the hard palate from three anthropological human skulls. Black: horizontal part of the palatine bone (part of the whole maxilla). Grey: maxilla. Gradually decreasing color: maxillary sagittal growth areas, the weakest coloring occurs in areas with newly formed bone. Transversal growth zones (due to median palatine suture) are not indicated. TPS: transpalatal (transverse palatine) suture. TM: tuber maxillae. (A) The primary dentition has fully erupted and the first molar is in its initial eruption phase. (B) The permanent canines and premolars have fully erupted and so has the second molar. (C) The permanent canines and premolars have fully erupted and so has the third molar. (Reprinted with kind permission from Damgaard et al. (97), Acta Odontologica Scandinavica, Taylor & Francis)

1.4.1.2 Mandible

The mandible grows through endochondral (at the condyle) and intramembranous ossification. The mandibular condyle at the temporomandibular joint is covered by cartilage, which provides endochondral growth, while the rest of the mandible grows through apposition and resorption sites. The displacement from the cranial base is negligible. Function is important, as the mandibular growth follows the pull from the soft tissues.

Relative to the skull the mandible grows forward and downward with time. However, most of the growth changes happen at the posterior part of the bone and at the condyle. Concerning remodeling, there is mainly resorption in the anterior surface of the ramus and apposition at the posterior surface of the ramus, so the mandible itself actually increases in size backward and upward.

1.4.1.3 Facial soft tissues

Growth of the face is mostly influenced by the growth of the underlying skeletal structures but does not perfectly follow their growth. The lips prior to adolescence grow less than the

maxillas, but then, through a growth spurt, catch up and reach also their maximum thickness. The nose, after the age of 10 years, grows from the cartilage of the nose and from the soft tissue traction. At adolescence the growth of the nose and the chin show a spurt, becoming more prominent than the lips. Additionally, there is increase and decrease in thickness of the muscles and mainly of the skin. Function plays a major role in facial growth.

1.4.2 Facial Growth in children with ICP

1.4.2.1 Untreated

Studies on untreated children born with ICP are rare but provide valuable information, as any change in growth should be attributed to the intrinsic growth of the cleft itself, or to the functional particularity of the cleft.

Adults with unoperated CP were found to have a normal size and position of the maxilla (98), while in another study a more posterior position of the maxilla and the mandible in relation to the cranial base was found (99). Maxillary retrusion and a steeper mandible increasing with age (100), bimaxillary retrognathism (60), reduced length of the maxilla in the mixed dentition and maxillary retrusion and reduced maxillary length in adulthood, showing a worsening with age (101) have also been reported.

Investigating unoperated children with submucous ICP a reduced length of the maxilla, a slightly retrognathic maxilla (102), a shorter and slightly more retrusive maxilla, a shorter mandible with a steeper mandibular plane at 7 years (103) have been reported.

At 2 months of age, children with ICP (compared to unilateral incomplete cleft lip) had a short maxilla with reduced posterior maxillary height, an increased posterior maxillary width, and a short mandible with reduced posterior height (104).

1.4.2.2 Surgically treated

Some investigations on surgically corrected ICP showed various results depending on the evaluating period and the surgical technique used. Progressive maxillary underdevelopment with an acceptable facial balance (105)(Fig. 7), a retruded and more inclined maxilla (106), retruded both the maxilla and the mandible (99), a retruded maxilla (107), a shorter and retruded maxilla, a shorter and posteriorly rotated mandible (108), a shorter maxilla and mandible, reduced posterior upper face height (109) were found.

When comparing children with repaired ICP to untreated individuals no significant differences were found (99, 101, 107). When a comparison was made on the use of different surgical techniques, no obvious differences in facial skeletal morphology were reported that could be attributed to the surgical technique itself (99, 106). Palatoplasty with the push-back procedure had no effect on the anteroposterior position of maxilla, but a shorter posterior upper face height and a posterior rotation of the maxilla were found (110)

Fig. 7. A classical study indicating, at treated children with ICP, the direction and extent of growth from 6 to 15 years of some of the facial landmarks. Growth increments were plotted from the base line 6-year-old groups and represented by arrows. Note: as it was known then that children with ICP would probably be on average smaller and that cranial base reflects general body size, the diagrams were enlarged to a fixed cranial base length and the linear measurements were also size-adjusted (Used with kind permission by Shibasaki and Ross (105), The Cleft Palate Journal, SAGE Publications, Inc.)

1.5 SURGERY FOR PATIENTS WITH ICP

1.5.1 Time of intervention: pros and cons

There is an ongoing debate on time for surgical correction of ICP. Theoretically the faster the cleft is corrected the better the speech will develop. Similarly the later the cleft is corrected the least influence surgical intervention will have on growth. In 1954, Jolleys evaluating clinical records from 254 patients with cleft palate, proposed two options: repair of the soft palate at the age of a "few months" and of the hard palate "a few years later", or repair of the entire cleft at 18 months of age "at the risk of some maxillary deformity" (111). Intervention on soft palate closure seems important for speech, while on hard palate closure important for palatal growth. According to a study, 74% of the respondents surgeons in the U.S. perform palatal repairs between the ages of 6 and 12 months and the majority was using an one-stage technique (112).

Concerning speech development, children having surgical correction of the cleft at 8 months or older were in need for increased speech therapy, had moderate to severe hypernasality, and glottal articulation (113). As the age of palatoplasty moves farther from the sensitive period for acquiring speech motor skills (4 to 6 months of age), the greater difficulty the patient will face integrating velopharyngeal movements with the other components of the speech production system (114). Articulation, and not chronological, age of the child was mentioned as a factor to choose the best timing for the palatoplasty (115), while a study concluded that some differences in articulation found at earlier age, were not traceable after the age of 39 months (116). For speech, an optimal treatment regimen is one that includes primary palatal surgery no later than 13 months of age (113).

Concerning growth, late hard palate repair was mainly supported by good maxillary growth results after the Schweckendiek procedure (hard palate closure at 12 to 14 years of age) (117-119), enhanced by more favorable maxillary growth found when the repair of the hard palate was performed at 9 years than at 3 months of age (120). Other studies provided similar and satisfactory maxillary growth when hard palate closure was performed at 6 months or 2.5 years (121), 10 months or 4 years (122), 1.5, 4.5 or 9.5 years (123), 3 or 6 years (124), 5 or 9 years of age (125), while a study found better maxillary growth when the palatoplasty was performed before 12 months than after 20 months (119). According to the systematic review on the timing of the hard palate repair, the need for further studies was highlighted (126).

1.5.2 Surgical techniques

Elevation of mucoperiosteal flaps and denuded areas of bone left for secondary intention healing lead to formation of fibrous scar tissue that is mainly considered responsible for the disturbance of ensuing growth (127). This resulted in the development of many techniques throughout the years, and different techniques are used in various countries, even in different cities of the same country. A main grouping is whether the correction of the cleft is performed in one operation (one-stage) or in two operations (two-stage), one for the correction of the soft palate and another later on for the closure of the hard palate.

1.5.2.1 One-stage

In some cleft centers the cleft in the soft and/or hard palate is surgically corrected by one palatoplasty around 9-18 months. The main idea is to perform the palatoplasty at the ideal time between not being late, affecting speech development, and not being early, disturbing maxillary growth. Most commonly used palatoplasty was the VWK technique (Fig. 3) and nowadays Bardach two flaps, double-opposing Furlow and Sommerlad's techniques are mostly performed (89, 112, 128). At our department the VWK, then the MI, and later MI with the addition of muscle reconstruction (influenced by Sommerlad) were applied (Fig. 3-5).

1.5.2.2 Two-stage

In some other cleft centers the cleft is surgically corrected in two steps: an early operation is performed around the 6 months of age to facilitate speech development, and later, at around 18-30 months, a second palatoplasty is performed to close the hard palate. The first operation will facilitate speech development, while the delay in the closure of the hard palate is supposed to facilitate palatal growth (129).

1.6 EVALUATING GROWTH IN PATIENTS WITH ICP

1.6.1 Cephalometrics

Cephalometry, measurements on a standardized radiograph of a precisely oriented head taken from the side under controlled magnification, was first presented simultaneously in 1931, by Broadbent in U.S. and Hofrath in Germany, introducing a brand new era in orthodontics: exact measurements of the hard and short tissues of the face could be performed for every individual, which could also be repeated later in time. Throughout the years many cephalometric analyses were proposed (130), including different variables measuring the same structures (Fig. 8).

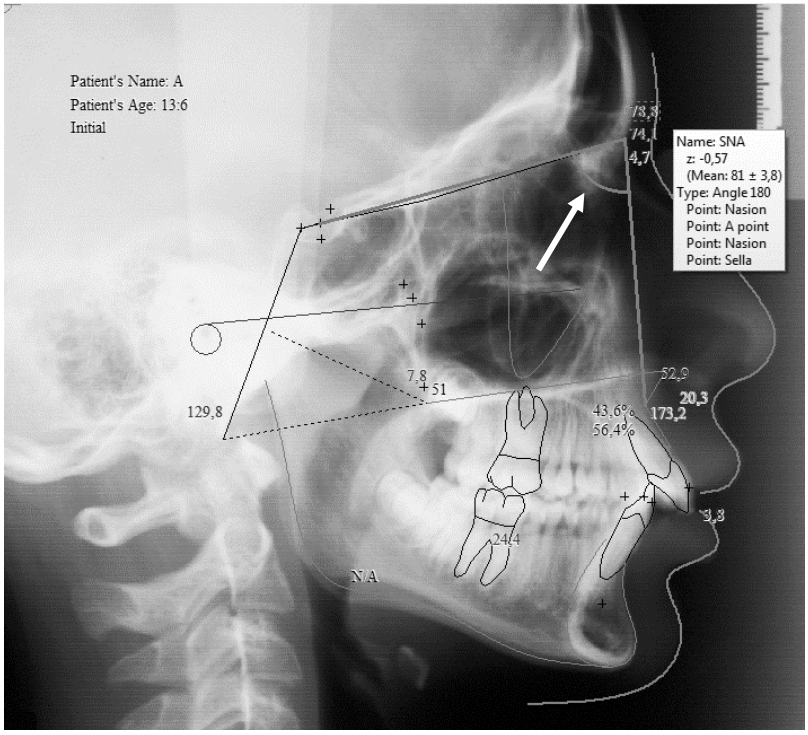

Fig. 8. Tracing and cephalometric measurements on a lateral cephalogram. The variable SNA, which indicates the anteroposterior position of the maxilla in relation to the anterior cranial base, is shown by the grey arc (arrow).

The main limitation is that the lateral cephalogram is a deformed image of the compressed 3D (three-dimensional) skull. Precise positioning of the head is of high importance. Different areas of the film have different magnification and some points used in the analyses are helpful but rather imaginary ones. Limited information is provided concerning the transversal plane.

Shifting to 3D imaging, using CT (Computed Tomography) or CBCT (Cone Beam Computed Tomography) in dentistry, provide complete information of the deformity and growth condition of the individual. Increase in dose of radiation with those techniques raises protection issues for the population, especially in children, and cost-benefit analysis in every individual case is important.

1.6.2 Indices evaluating dental occlusion using casts

An ideal index should be valid, reliable, requiring minimal judgment, be applicable to statistical analysis, acceptable by the profession and administratively simple (131). Many indexes (categorical or numerical) were proposed and are used for the evaluation of dental occlusion mainly for the cleft lip and palate. For example, Huddart and Bodenham (HB) (132) , GOSLON Yardstick (133), GOAL Yardstick, Five-Year-Old (134), Modified Huddart and Bodenham (MHB) (135), Bauru-Bilateral Cleft Lip and Palate Yardstick (136) indices. The HB and the MHB indices can be applied for the ICP.

The MHB index was introduced in 2003 (Fig. 9) (135). As the MHB index is a categorical one, the main limitation could be that the decision of putting a pair of teeth in a specific group may be hard and debatable in borderline cases and subjective to the eye of the beholder. However, the index was evaluated (137) and validated (138) later on, providing excellent intra-examiner and inter-examiner agreement. In a recent study, the MHB index equaled or outperformed the rest of the examined indices (139), while lately 3D automatic calculation of the index was presented and tested as valid, reliable and more objective compared to manual evaluation (140, 141).

In the future, improved indices and applications in a 3D environment are important for further and improved investigations. The use of 3D models may assist to get more objective measurements, provided the possibility to calculate volumes and to superimpose models

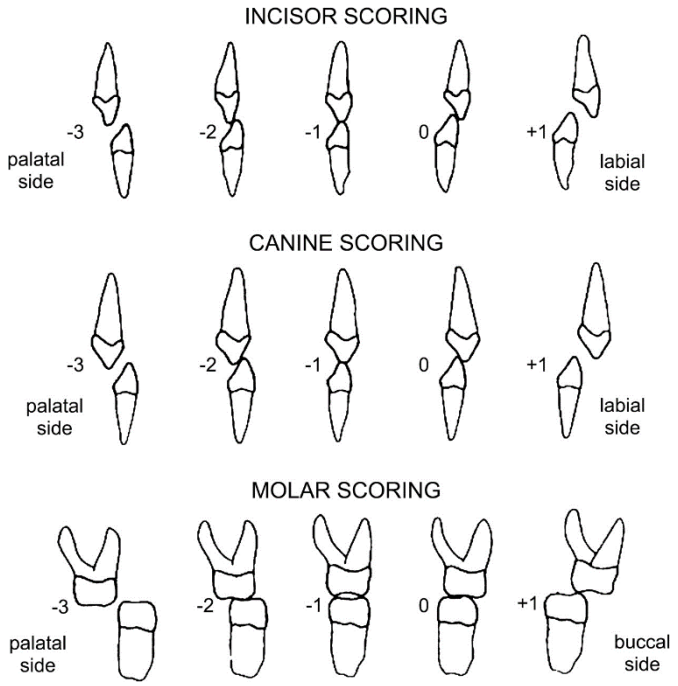

Fig. 9. The Modified Huddart and Bodenham scoring instructions (142).

2 AIM

General:

The aim of this research was to evaluate three different palatoplasties for the correction of ICP mainly concerning growth later in life.

Specific:

The aim of studies I and III was to compare the VWK technique, the MI technique and the MMI technique regarding facial growth at 5 and 10 years of age in patients born with isolated cleft palate.

The aim of study II was to compare the MI technique with the MMI technique repair of isolated clefts regarding surgical complications and dentoalveolar outcome at 5 years of age.

The aim of study IV was to compare the growth of children born with an isolated cleft in the palate and treated with a one-stage palatoplasty with that of a normal population at 10 and 16 years of age.

Secondary:

Does initial anteroposterior length of the cleft influence later growth of the face or occlusion?

Does inclusion of children with PRS influence results of later growth of the face and occlusion?

Is there a gender difference in growth of treated children born with ICP at 10 and 16 years of age?

3 MATERIAL AND METHOD

3.1 TREATED GROUP

The treated group consisted of consecutive, non-syndromic, Caucasian patients born with ICP in the area of Stockholm from 1980 to 2007 and surgically corrected applying the VWK (1980-1986), MI (1987-1996) or MMI (1997-2007) technique at the mean age of 13 months (Table 3). Children with available data and with PRS were included in the studies.

3.1.1 VWK group

The group treated with the VWK palatoplasty consisted of 59 children (21 boys, 38 girls; 7 PRS).

3.1.2 MI group

The group treated with the MI palatoplasty consisted of 86 children (40 boys, 46 girls; 12 PRS).

3.1.3 MMI group

The group treated with the MMI palatoplasty consisted of 102 children (43 boys, 59 girls; 12 PRS).

3.1.4 Treated group compared to untreated control

The treated group, matched for gender and age with a control group of untreated children, consisted of 55 children (25 boys, 30 girls) born with ICP, treated with the MI or MMI technique and providing lateral cephalograms at both 10 and 16 years of age.

3.2 CONTROL GROUP

The control group consisted of 110 Caucasian children born without a cleft (50 boys, 60 girls), 55 children providing lateral cephalograms at the age of 10 years and another 55 children at the age of 16 years. They were normal (molar and canine Angle Class I, overjet and overbite 1–3 mm, normal transverse occlusion, without congenitally missing teeth or crowding, ‘straight’ profile without any obvious asymmetry) without history of orthodontic treatment (143).

Table 3. Material (patients with ICP, their casts and lateral cephalograms, and controls) used per study

	Study I				**Study II**				**Study III**				**Study IV**	
Birth years	1980-1996				1987-2007				1987-2005				1987-2001	
Caucasian non-syndromic ICP	168				202				185				141	
Excluding / Missing	23				22				15				33	
Final Total (casts)	145				180 (128)				170				108	
Surgery	**VWK**		**MI**		**MI**		**MMI**		**MI**		**MMI**		**MI+MMI**	
Patients (casts)	59		86		78 (56)		102 (72)		85		85			
Matched													55	
Cleft length	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**
Children	34	25	30	56	26	52	24	78	30	55	21	64	15	40
♂ / ♀	13/21	8/17	16/14	24/32	14/12	21/31	13/11	30/48	16/14	24/31	12/9	29/35	7/8	18/22
PRS (♂)	2 (1)	5 (1)	1 (1)	11 (4)	1 (1)	11(4)	0	12(2)	1 (1)	11 (4)	0	9 (3)	9(3)	
Xrays 5y.	21+8	19+6	24+4	43+10					24+4	42+10	12+5	46+9		
Xrays 10y.	21+5	19+0	24+2	43+3					24+2	42+3	12+4	46+9	15	40
Xrays 16y.													15	40

3.3 CEPHALOMETRIC EVALUATION

All analogue lateral cephalograms were scanned using the same scanner (Epson Perfection V700 Photo, Seiko Epson corp., Japan) to provide digital cephalograms. These were combined with original digital cephalograms taken in more recent years. All radiographs were adjusted to zero magnification as they were taken using different radiological equipment.

Cephalometric analysis was performed by the same orthodontist, who was not involved in the treatment of the children, with the aid of a specific computer program (Viewbox v.3/v.4, dHAL Software, Kifissia, Greece) to increase accuracy. A computerized tracing technique was used as it is less time consuming and equally reliable to hand-tracing as far as cephalometric measurements are concerned (144). Selection of well tested and frequently used cephalometric variables for evaluation of horizontal and vertical growth of the face was made (Fig. 10).

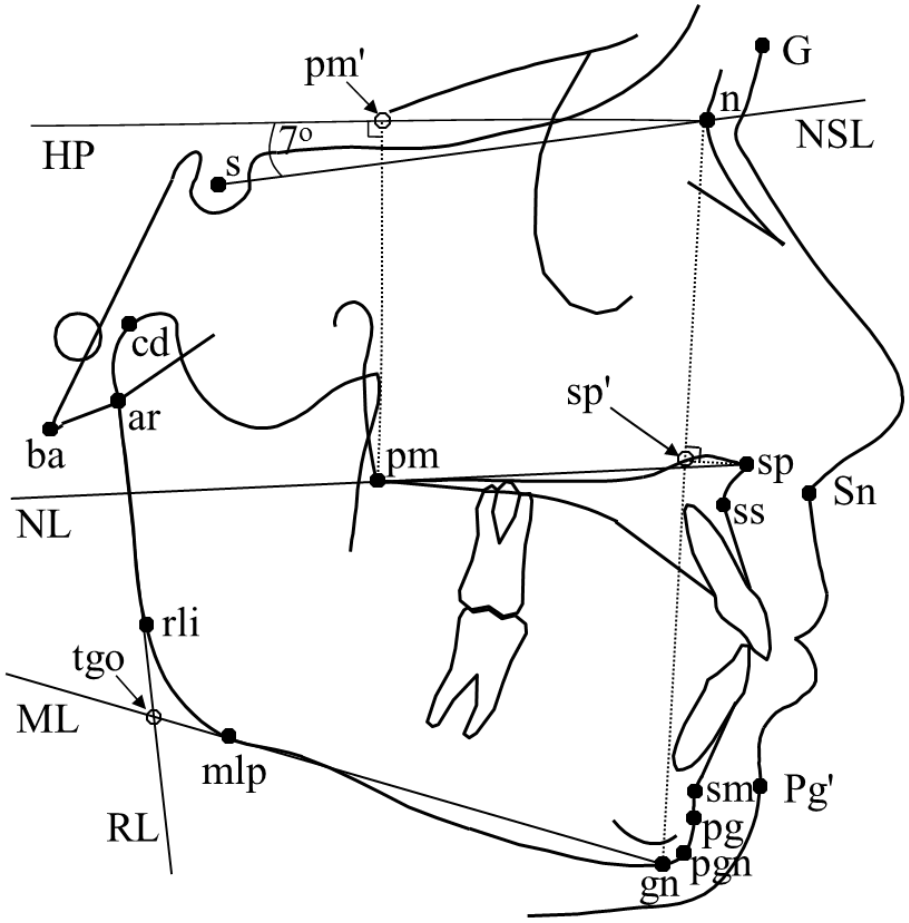

Fig. 10. Reference points and lines used for the cephalometric measurements

- Hard tissue measurements: NSBA (n-s-ba)º, SNA (s-n-ss)º, SNB (s-n-sm)º, ANB (ss-n-sm)º, NSL / NLº, NSL / MLº, NL / MLº, ML / RL º, NAPg (n-ss-pg)º, Palatal plane length (sp-pm), Mandibular length (cd-pgn), n-sp´/n- gn (%), sp´-gn/n- gn (%), Posterior upper Face Height (pm-pm´), Posterior Face Height (s-tgo). Soft tissue measurement: Facial convexity (GSnPg')º

3.4 CAST ANALYSIS

Measurements evaluating the dentition in all three dimensions, using models at 5 years, were performed by two experienced orthodontists working in the cleft team:

- Sagittal: Normal, Postnormal, Prenormal. Overjet in millimetres.
- Vertical: Normal, Open, Deep. Overbite in millimetres.
- Transversal: upper and lower: intercanine & intermolar distances (Fig. 11) in millimetres.
- The validated MHB index (Fig. 9) was used.
- Height of the palatal vault: measured distal of first and second molars (Fig. 12) in millimetres.
- Structure of the palatal mucosa: Normal or minor scar tissue, visible ridge of the vomer in the midline, heavy scar tissue (84).

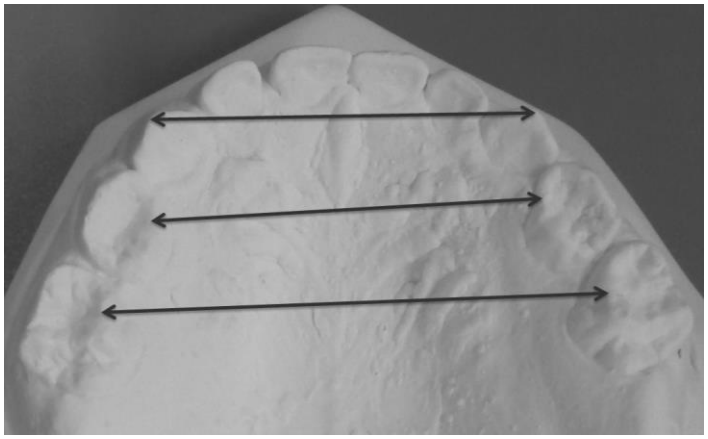

Fig. 11. Intercanine and intermolar distances measured during cast analysis.

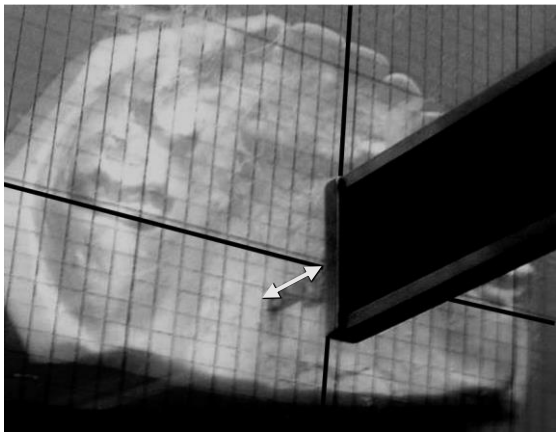

Fig. 12. Height of the palatal vault measured with the aid of a digital caliper.

3.5 MEDICAL RECORDS

Five variables were recorded with the aid of a plastic surgeon, specialized in operating patients with cleft palate, by reading carefully the medical records of every patient:

- Time of surgery for the palatoplasty (minutes)
- Blood loss (millilitres)
- Complications in the immediate postoperative period
- Frequency of fistulas
- Additional pharyngeal flap surgery

3.6 CLEFT CLASSIFICATION

According to the anteroposterior length, the clefts were divided into *small* (short) or *big* (long) clefts. The borderline was a notch up to 3 mm in the posterior border of the hard palate. An experienced plastic surgeon, who treated all surgical groups, categorized the clefts

based on medical records and casts. Diagnose was finally decided when performing the surgery.

3.7 SURGEONS

In total 10 surgeons were involved in the correction of the ICP. The VWK, MI and MMI palatoplasties were performed by 9, 4 and 2 surgeons respectively. Three main surgeons operated most of the children.

3.8 METHOD ERROR

3.8.1 Digitizing the lateral cephalograms

Thirty randomly selected lateral cephalograms were traced twice by the same orthodontist with an interval of 2 weeks.

The Dahlberg's formula was applied for the calculation of the *intra-observer* error.

3.8.2 Measuring dental casts

The measurements were repeated by two experienced orthodontists in ten randomly selected pairs of casts with an interval of 3 weeks.

Intra-observer method error was calculated according to the Dahlberg's formula, and *inter-observer* error was estimated using Intra class correlation coefficient and Cohen's Kappa coefficient.

3.9 STATISTICAL ANALYSIS

The following statistical analyses, according to the investigating comparison, were applied while performing the studies:

- Comparison of lateral cephalograms at 5, 10 or 16 years: 2-way ANOVA (studies I, III, IV)
- Comparison of lateral cephalograms for changes from 5 to 10 years: 3-way ANOVA (study I) and Mixed model analysis (studies I, III)
- Comparison of lateral cephalograms for changes from 10 to 16 years: Mixed model analysis (study IV)
- Comparison of casts & medical records for continuous variables: Student's t-test (study II)
- Comparison of casts & medical records for proportions: Chi-square test (study II)
- Examining co-variables from medical records: Multiple regression and Multiple logistic regression analysis (study II)

Confidence Intervals were also calculated (studies I-IV). Due to multiple testing the level of significance was set to 1%.

3.10 ETHICAL APPROVAL

Medical records, casts and lateral cephalograms were available according to the national care guidelines for patients born with ICP. Ethical approvals were provided for all studies from the Ethical Committee in Stockholm: Study I and III: dossier nr. 2009/1680-31/2, study II: dossier nr. 2011/1303-31/1, study IV: dossier nr. 2016/158-31.

4 RESULTS

Only the *statistically significant results* at the level of 1% will be presented below.

4.1 CEPHALOMETRIC ANALYSIS

4.1.1 At FIVE years of age (studies I, III)

Comparing the groups VWK big (2) and MI big (2) *at 5 years of age* a statistically significant difference was found for the mandibular length ($p<0.01$) which was shorter in group MI2 (study I). An increased inclination of the palatal plane (NSL/NL) in the MMI2 cleft group compared to the MI2 cleft group ($p<0.01$) was seen (Table4) (study III).

At 5 years of age a statistically significant longer mandibular length ($p<0.001$) and an increased posterior upper face height ($p<0.01$) in the MI small (1) cleft group compared to the MI big (2) cleft group was found (Table 4) (studies I and III).

4.1.2 At TEN years of age (studies I, III)

No statistically significant differences were found between the VWK and MI groups *at the age of 10 years* (study I). A statistically significant increased inclination of the palatal plane (NSL/NL), a decreased posterior upper face height and a longer palatal length in the MMI big cleft group compared to the MI big cleft group ($p<0.001$, $p<0.001$ and $p<0.01$ respectively) was seen at 10 years of age (Table5) (study III).

4.1.3 Changes from FIVE to TEN years of age (studies I, III)

From 5 to 10 years the main significant finding was the growth changes with time. In all techniques, the variables NAPg, palatal plane length, mandibular length, n-sp´/n-gn were increased, while ANB, NSL/ML and the gonial angle were decreased significantly ($p<0.001$) from 5 to 10 years (studies I and III). Comparing VWK to MI, an increase was also found in the variable facial convexity (Study I). Comparing MI to MMI a significant increase at variables NSL/NL and both posterior face heights, while a significant decrease in variable SNA were observed ($p<0.001$) (Tables 4, 5) (study III).

Concerning type of surgery, statistically significant differences in results were found comparing MI to MMI, showing a higher increase in the NSL/NL angle ($p<0.001$) and in the n-sp´/n-gn ratio ($P<0.01$) from 5 to 10 years in the MMI group (Tables 4, 5) (study III).

Table 4. Cephalometric measurements at 5 years for treated children with ICP.

5 years	VWK1 (n=29)		VWK2 (n=25)		MI1 (n=28)		MI2 (n=52)		MMI1 (n=17)		MMI2 (n=55)	
Variable	Mean	S.D.	Mean	S.D.	Mean	S.E.	Mean	S.E.	Mean	S.E.	Mean	S.E.
NSBa (n-s-ba)°	127.6	5.6	127.1	5.1	127.6	1.1	126.6	0.6	127.4	0.9	128.1	0.7
SNA (s-n-ss)°	81.0	3.8	79.7	3.4	80.7	0.7	80.8	0.5	82.8	0.8	80.1	0.5
ANB (ss-n-sm)°	4.7	2.6	3.5	2.3	3.8	0.6	4.8	0.4	4.9	0.7	3.5	0.5
NSL/NL°	9.1	4.8	7.6	4.4	6.8	0.7	8.3[a]	0.5	7.9	1.0	10.3[a]	0.5
NSL/ML°	36.5	5.7	35.1	5.1	35.7	1.1	35.6	0.8	33.7	1.4	35.4	0.7
ML/RL°	132.5	5.5	131.8	5.5	132.4	1.1	132.2	0.8	130.7	1.3	130.7	0.8
NAPg (n-ss-pg)°	170.6	5.3	173.2	4.3	172.2	1.3	170.8	0.7	170.8	1.4	173.2	1.0
Palatal plane length (sp-pm) mm	42.8	2.5	41.8	2.5	42.6	0.5	42.1	0.3	42.4	0.5	41.9	0.4
Mandibular length (cd-pgn) mm	89.1	6.0	88.9[b]	4.6	89.1[c]	0.6	85.5[b,c]	0.7	87.2	0.6	86.5	0.6
n-sp´/n-gn (%)	40.6	1.9	41.2	2.6	41.0	0.5	41.4	0.3	41.2	0.5	42.1	0.3
Posterior upper FH (pm-pm´) mm					38.8[d]	0.5	37.2[d]	0.4	37	0.5	36.6	0.4
Posterior FH (s-tgo) mm					58.2	0.7	56.6	0.6	58	0.9	57.2	0.5
Facial convexity (G-Sn-Pg')°	10.6	5.2	11.1	3.2	11.0	1.1	12.1	0.8	12.7	1.5	12.1	0.9

[a] p=0.004 ** [b] p = 0.004 ** [c] p < 0.001 *** [d] p=0.007 ** (** p<0.01 ; *** p<0.001)

Table 5. Cephalometric measurements at 10 years for treated children with ICP.

10 years	VWK1 (n=26)		VWK2 (n=19)		MI1 (n=26)		MI2 (n=45)		MMI1 (n=16)		MMI2 (n=55)	
Variable	Mean	S.D.	Mean	S.D.	Mean	S.E.	Mean	S.E.	Mean	S.E.	Mean	S.E.
NSBa (n-s-ba)°	127.4	4.7	126.4	5.6	127.2	1.2	126.3	0.8	128.9	1.5	127.7	0.7
SNA (s-n-ss)°	80.1	3.6	79.9	3.7	80.2	0.7	80.3	0.6	80.1	0.8	80.1	0.5
ANB (ss-n-sm)°	3.9	2.4	2.5	2.4	2.9	0.6	3.2	0.4	3.3	0.6	2.3	0.4
NSL/NL°	9.6	4.4	7.6	4.7	8.3	0.6	8.2[a]	0.5	11.0	1.1	11.8[a]	0.4
NSL/ML°	35.9	6.5	34.1	5.1	35.0	1.2	34.1	0.9	33.7	2.0	33.1	0.8
ML/RL°	127.9	5.8	127.3	5.4	128.7	1.1	126.8	0.9	125.6	1.9	125.9	1.0
NAPg (n-ss-pg)°	173.3	5.6	176.0	5.1	175.3	1.3	175.6	1.0	175.3	1.5	177.3	0.9
Palatal plane length (sp-pm) mm	46.0	3.1	44.0	3.4	44.9	0.5	45.2[b]	0.4	46.7	0.6	47.8[b]	1.0
Mandibular length (cd-pgn) mm	98.5	5.7	98.3	4.6	99.2	1.1	97.2	0.9	98.9	1.0	100.1	1.9
n-sp´/n-gn (%)	42.5	1.9	42.6	2.5	42.8	0.4	43.4	0.4	44.5	0.7	44.4	0.2
Posterior upper FH (pm-pm´) mm					43.6	0.5	43.5[c]	0.4	43	0.8	41[c]	0.4
Posterior FH (s-tgo) mm					65.9	0.9	64.7	0.7	66.3	1.4	64.6	0.8
Facial convexity (G-Sn-Pg')°	14.3	6.0	13.5	5.0	10.8	1.3	13.8	0.9	13.0	1.8	11.8	0.9

[a] $p < 0.001$ *** [b] $p = 0.009$ ** [c] $p < 0.001$ *** (** p<0.01; *** p<0.001)

4.1.4 Changes from TEN to SIXTEEN years of age (study IV)

From 10 to 16 years of age in the T group statistically significant changes with time were seen. The variables SNB, NAPg, Palatal plane length, Mandibular length, Posterior upper and total face heights were increased ($p<0.001$), while the variables ANB, NSL/ML, ML/RL ($p<0.001$), NSL/NL and NL/ML ($p<0.01$) decreased with time (Tables 6, 7).

4.2 MEDICAL RECORDS (STUDY II)

4.2.1 Time of surgery

As a mean, more time was spent for the operation applying the MMI (mean=103, range=30-180, SD=27 min) than the MI technique (mean=61, range=33-110, SD=18 min) ($p<0.001$). Additionally a statistically significant difference was found ($p<0.01$) between big clefts (mean=89, range=30-180, SD=31 min) and small clefts (mean=74, range=33-139, SD=29 min).

4.2.2 Blood loss, complications in the immediate postoperative period and frequency of fistulas

Regarding blood loss, complications in the immediate postoperative period and frequency of fistulas no statistically significant differences were found between the different surgical techniques or the length of the cleft.

4.2.3 Additional pharyngeal flap surgery

It was found that pharyngeal flap surgery was performed from the age of three until the age of nine years. Between small and big cleft groups, the big group exhibited increased need for pharyngeal flap operation (25.4% versus 4%; $p<0.001$). Concerning the surgical techniques, the addition of muscle reconstruction decreased the need for pharyngeal flaps (12.7% versus 28.2%; $p<0.01$).

4.2.4 Regression analysis

For the co-variable surgeon the only difference found was the additional flap surgery where one surgeon, who operated only the MI group, showed increased percentage ($p<0.05$).

4.3 CAST ANALYSIS (STUDY II)

4.3.1 Dental occlusion

4.3.1.1 Sagittal, vertical and transversal relations

Regarding sagittal, vertical and transversal relations no statistically significant differences were found.

4.3.1.2 MHB index

Regarding MHB scores no statistically significant differences were found.

4.3.2 Height of the palatal vault

At the statistical evaluation of the measurements of the height of the palatal vault, the MI cleft groups showed higher values (13.1+/-2 mm) than the MMI cleft groups (11.8+/-1.6 mm) only at first primary molars ($p<0.001$), showing a higher palate at the area distal of the first deciduous molars.

4.3.3 Structure of the palatal mucosa

Regarding structure of the palatal mucosa no statistically significant differences were found.

4.4 COMPARING CHILDREN WITH ICP TO CHILDREN WITHOUT A CLEFT (STUDY IV)

4.4.1 At TEN years of age

In the T group at 10 years of age the maxilla and the mandible expressed pronounced retrognathic values (SNA, SNB). The Palatal plane and Mandibular lengths were shorter. The inclination of the maxilla was increased (NSL/NL) and the posterior upper face height was shorter ($p<0.001$) (Table 6).

In males, an increased mandibular inclination (NSL/ML) ($p<0.001$) and shorter posterior face height was found ($p<0.01$). Comparing males to females, a more retrognathic maxilla (SNA) was discovered in the male population ($p<0.01$) (Table 6).

4.4.2 At SIXTEEN years of age

In the T group at 16 years of age the maxilla and the mandible expressed pronounced retrognathic values (SNA, SNB). The Palatal plane length was shorter and the inclination of the maxilla (NSL/NL) was increased ($p<0.001$) (Table 7).

In males, an increased mandibular inclination (NSL/ML) ($p<0.001$) and in females, a shorter posterior upper face height ($p<0.01$) was found. Comparing males to females, a longer Mandibular length was found in boys in the cleft group. In both the T and C groups an increased posterior upper and total posterior height was observed in the male population ($p<0.01$) (Table 7).

Table 6. Cephalometric variables at 10 years for T and C group

10 years	Group T m (n=25)		Group C m (n=25)		Group T f (n=30)		Group C f (n=30)	
Variable	Mean	S.E.	Mean	S.E.	Mean	S.E.	Mean	S.E.
SNA (s-n-ss)°	77.6[a,c]	0.6	83.5[a]	0.8	80.3[b,c]	0.7	84[b]	0.6
SNB (s-n-sm)°	75.3[d]	0.6	79.4[d]	0.6	77.3[e]	0.7	80[e]	0.6
NSL/NL°	10[f]	0.6	5.7[f]	0.4	9[g]	0.5	5.9[g]	0.5
NSL/ML°	36.6[h]	1.3	30.1[h]	1.1	32.9	1	29.8	0.8
Palatal plane length (sp-pm) mm	44.9[i]	0.5	49.6[i]	0.5	45.1[j]	0.5	48.7[j]	0.4
Mandibular length (cd-pgn) mm	98.2[k]	1	103[k]	0.8	96.9[l]	0.9	101.1[l]	0.7
Posterior upper FH (pm-pm') mm	43.4[m]	0.6	46.6[m]	0.5	42.1[n]	0.6	46[n]	0.4
Posterior FH (s-tgo) mm	65.4[o]	1.1	69.5[o]	0.9	64.6	0.8	67.5	0.7

[a] p<0.001 *** [b] p<0.001 *** [c] p=0.006 ** [d] p<0.001 ***
[e] p=0.003 ** [f] p<0.001 *** [g] p<0.001 *** [h] p<0.001 ***
[i] p<0.001 *** [j] p<0.001 *** [k] p<0.001 *** [l] p<0.001 ***
[m] p<0.001 *** [n] p<0.001 *** [o] p=0.002 ** (** p<0.01; *** p<0.001)

Table 7. Cephalometric variables at 16 years for T and C group

16 years	Group T m (n=25)		Group C m (n=25)		Group T f (n=30)		Group C f (n=30)	
Variable	Mean	S.E.	Mean	S.E.	Mean	S.E.	Mean	S.E.
SNA (s-n-ss)°	79.6[a]	0.6	84[a]	0.7	80.5[b]	0.9	84.7[b]	0.7
SNB (s-n-sm)°	78.4[c]	0.9	81.8[c]	0.6	78.7[d]	0.7	82.1[d]	0.6
NSL/NL°	8.7[e]	0.8	4.6[e]	0.6	8.7[f]	0.6	4.9[f]	0.5
NSL/ML°	33.4[g]	1.5	27.1[g]	1	30.1	1.2	27.3	1
Palatal plane length (sp-pm) mm	49.6[h]	0.5	52.2[h]	0.6	47.4[i]	0.8	50.7[i]	0.5
Mandibular length (cd-pgn) mm	113.5[j]	1.2	115.2	1.4	107.8[j]	1.5	111.2	0.6
Posterior upper FH (pm-pm') mm	50.4[k]	0.9	52.1[l]	0.5	46.2[k m]	0.7	49[l m]	0.4
Posterior FH (s-tgo) mm	78.5[n]	1.3	79.8[o]	0.9	74.2[n]	1	75.4[o]	0.7

[a] p<0.001 *** [b] p<0.001 *** [c] p=0.001 ** [d] p<0.001 ***
[e] p<0.001 *** [f] p<0.001 *** [g] p<0.001 *** [h] p=0.004 **
[i] p<0.001 *** [j] p=0.001 ** [k] p<0.001 *** [l] p=0.001 **
[m] p=0.002 ** [n] p=0.002 ** [o] p=0.002 ** (** p<0.01; *** p<0.001)

4.5 DIFFERENCES IN LENGTH OF THE CLEFT (STUDIES I-III)

At 5 years of age a statistically significant longer mandibular length (p<0.001) and an increased posterior upper face height (p<0.01) in the MI small (1) cleft group compared to the MI big (2) cleft group was found (studies I and III).

As a mean, more time was spent for the operation in the big clefts (mean=89, range=30-180, SD=31 min) than in the small clefts (mean=74, range=33-139, SD=29 min; $p<0.01$) (study II).

Between small and big cleft groups, the big group exhibited increased need for pharyngeal flap operation (25.4% versus 4%; $p<0.001$) (study II).

4.6 EXCLUDING PATIENTS WITH PRS (STUDIES I, II, III)

When excluding the patients with PRS, the statistical evaluations provided the same statistically significant results as when including them in the material. At 5 years of age, the longer mandibular length ($p<0.01$) in the MI small cleft group compared to the MI big cleft group was less significant when excluding children with PRS (study III).

4.7 DIFFERENCES IN GENDER FROM TEN TO SIXTEEN YEARS (STUDY IV)

Regarding differences in gender from 10 to 16 years, an accentuated increase was found in males compared to females regarding Posterior upper face height ($p<0.001$) and Posterior face height ($p<0.01$).

5 DISCUSSION

Ideally, care for children born with an ICP should be performed by a multidisciplinary team (145). By tradition the team would consist of a plastic surgeon, who reconstructs the palate, a speech and language pathologist, who attends to the development of speech, and an orthodontist (82, 145). A psychologist is commonly included in the team today to better help the patients with their self-esteem. It is the responsibility of the orthodontist, as part of this multidisciplinary team, to supervise growth and development of the jaws, provide conventional orthodontic treatment and dentofacial orthopedics, collect standardized records, and perform follow-up studies on growth and development (146). Evaluation of results of a palatoplasty, requiring collection of a rare material, may have to be extended to a period of at least 20 years. To evaluate the total result of a palatoplasty, best midfacial growth, optimal speech development, hearing and quality of life (147) should be examined.

Various surgical techniques, in many modifications, are applied for the correction of the deformity of a child born with an ICP (89, 128, 129, 148). Investigation of palatoplasties, based on high quality standardized records, is important for providing best cost-effective treatment. Consequently, with limited knowledge on the effect of only palatoplasty on children with ICP, evaluation of growth after the surgical techniques applied in the Stockholm area was the main purpose of this project.

The results from the medical records and the cast analyses revealed that 70% additional time was needed for the surgical procedure of the muscle reconstruction and 20% more time in the patients with a big cleft. Additional pharyngeal flap surgery was performed 6 times less in the small group, and 2.2 times less when the muscle reconstruction was performed. Finally, the height of the palatal vault was decreased by 1.3 mm, as a mean, only distal of the first deciduous molars when the muscle reconstruction was applied. (study II)

The results from the cephalometric investigation (Tables 4, 5) revealed a similarity in growth between the VWK and the MI technique concerning growth at 5 and 10 years of age. Only the mandibular length was found to be shorter in the MI2 group at 5 years of age, which was not valid later on at the age of 10 years. Applying the muscle reconstruction (MMI technique), an increased inclination of the palatal plane was found in the MMI2 group. This remained at the age of 10 years. At the last age, a decreased posterior upper face height and longer maxilla were also revealed. Additionally, big clefts, compared to small ones, showed a smaller mandible and decreased posterior upper face height at 5 years, when the MI technique was used. Here, one should note that posterior face heights were not calculated for the VWK technique in study I. (studies I, III)

Children with ICP, compared to children without a cleft (Tables 6, 7), were found at 10 years of age to have shorter and retrognathic upper and lower jaws, with the maxilla posteriorly

inclined and the posterior upper face height reduced. In males, a posterior inclination of the mandible and shorter posterior face height was found. At 16 years of age, the differences at mandibular length and posterior upper face height were not statistically significant any more, while in males the posterior face height was normalized. (study IV)

As expected, the duration of the surgery was almost doubled when the muscle reconstruction was applied, as an additional radical muscle reconstruction must be performed. Time was also increased for the big compared to the small cleft group, as the corrected defect was larger. Postoperative complications didn't seem to differ.

The percentage of fistulas after the MI and MMI techniques seems low and in agreement with another study presenting fistulas in 5% of the cases after Sommerlad palatoplasty in a Swedish population (149). A decreased need for pharyngeal flap surgery in the MMI as well as in the small cleft groups was found. This is in agreement with a previous study of the same techniques at a similar population concerning speech outcome (87) and a recent investigation of two-stage palatoplasties, where decreased need for pharyngeal flap surgery was found in the small cleft group (150).

Comparing casts from the MI and the MMI techniques, no differences were found concerning sagittal, transversal or vertical relations on dental occlusion at 5 years of age. This means that the need for orthodontic treatment was the same for both groups at 5 years. In another study comparing the VWK to the MI technique regarding dental occlusion, differences were reported in the transversal dimension, as the VWK technique seemed to result in restricted transversal growth mainly in the area of the premolars (84).

A statistically significant higher palatal vault distal to the first deciduous molars was found in the MI group. This could be explained by the omission of muscle reconstruction and consequently the less repositioning of the muscles of the soft palate and the less stress of the soft tissue. In a normal Swedish material at the age of 5 years measuring the palatal height at the area distal to the deciduous second molars provided similar values, which were especially close to those of the MI group (151). This implies that the findings from the MMI technique is slightly shallower than those expected with normal growth.

The structure of the palatal mucosa was the same between the MI and the MMI techniques. In a previous study, comparing the VWK with the MI technique, the MI method guided to less scar tissue and pits (84).

The cephalometric measurements of children with ICP in this project were similar to those of another study on Swedish patients with ICP at 5-6 and 9-11 years treated with a two-stage technique (152). The main difference is the smaller NSL/ML angle in this material at both 5

and 10 years of age. According to other studied materials on ICP at six years of age treated with a one-stage procedure (153, 154) the cephalometric values that differ were the smaller NSBa angle, the bigger SNA angle, and the smaller NSL/ML angle.

The smaller mandible found in the groups with big clefts supports a previous study, where patients with total clefts had shorter mandibular lengths (155). The restriction of the posteriorly vertical growth of the palate, showed by the posterior inclination of the maxilla and the reduced posterior upper face height at the age of 10 years after the use of the muscle reconstruction, seems similar to the findings at 9 and 14 years of treated Japanese children with submucous ICP (110). Interestingly, a longer palatal length was found in the MMI group when comparing the groups with big clefts at the age of 10 years, but, as the value for SNA was similar among the groups, no difference in the anteroposterior position of the maxilla was found. So, earlier studies (105, 107, 108) presenting a restricted growth mostly in the maxilla in the anteroposterior direction could be not confirmed.

Most of the changes in treated patients with ICP from 5 to 10 and 16 years followed the changes according to normal development (143). The observed increased inclination of the maxilla from 5 to 10 years seemed to be normalized later, as it decreased from 10 to 16 years. The findings in treated, compared to untreated, children agree with previous studies where reduced anteroposterior maxillary length (99, 101, 105, 108), maxillary retrognathism (99-101, 107, 108) has been reported. These patients have also been found to have a posterior inclination of the mandible (99-101, 105, 108) and at a less extent mandibular hypoplasia (101, 108) as well as a retrognathic mandible (99, 105), resulting in an almost harmonious bimaxillary relationship. An increased inclination of the palatal plane (108) and a reduction of the posterior maxillary height (110) was also found. On the contrary, in a Chinese sample, a protrusive mandible in the permanent dentition was reported (101). Similar results were also found when treated children with submucous palatal clefts were compared to non-cleft groups (103, 110). The maxilla was found smaller and retruded with a steeper palatal plane which increased with age, a smaller mandible and a reduced posterior upper face height. Consequently, it seems that the increased inclination of the palatal plane and the reduced upper face height, showing the disturbance of the vertical growth of the maxilla influenced by the surgical procedure in the posterior part of the palate, could be due to the intrinsic growth pattern of the cleft palate. The palatal plane angle does not increase with time. This indicates that any disturbance in the vertical growth of the posterior part of the maxilla stops or does not worsen further maxillary growth.

As no statistically significant differences among groups at both ages regarding ANB, NL/ML, NAPg, Facial convexity angles and the ratio n-sp’/n-gn were found, patients with an ICP have an harmonious middle and lower facial profile despite their retrognathic jaws.

The differences found at 10 years in mandibular length and posterior face height were not significant anymore at the age of 16 years. This indicates a normalization of the lower jaw with time. In contrast, posterior upper face height remained different in the female group, as less increase of posterior face height in females than in males was found to be statistically significant from 10 to 16 years. Sexual dimorphism found during growth from 10 to 16 years mainly in linear variables (mandibular length, posterior heights), indicating more growth in males than in females, could be expected by the different degree of maturation among the two genders during the investigated period (143).

A strength of this project was the complete collection of children born with ICP in the area, treated by the same specialized team, following the same protocols according to the national guidelines for cleft care. Strict criteria were applied to exclude syndromic cases and non-Caucasian population, diminishing an already small population. Only Caucasian children were selected, as it is known that there are different growth patterns and growth increments according to various ethnic groups (143). As syndromes consist of another group of complex interaction of various problems and genetic background, they were not included in the investigation. However, as no genetic screening was performed, children with syndromes might have wrongly been included in this investigation. Children used as controls were of the same ethnicity. They were matched with the treated group for age and sex. In the future, due to increased moving of the population, it will be even more difficult to collect homogeneous samples based on the ethnicity world-wide.

The same criteria for subgrouping in small or big clefts were applied throughout the examined period by the same surgeon, who additionally confirmed the operation applied and the grouping of the structure of the palatal mucosa at the casts. Subgrouping was confirmed and finalized during the surgery. The same high volume surgeon decided the selection of cases with PRS.

The limitation of this project is, apart from its retrospectivity, that few children met the inclusion criteria lead to subgroups composed of rather small number of patients, decreasing the power of the analysis. Expansion of the period if investigation throughout 3 decades was needed to collect enough material. Patients in the control group were born around 30-40 years earlier and possible secular changes may have affected our results (156). The stature of patients with ICP, compared to the remaining population, was found in general smaller, their muscular strength reduced, and the lengths of the cranial base and visceral skull reduced (107, 157-160). This should be considered when evaluating linear variables.

Due to a variety of clinical criteria and interest in whether children with PRS consist of a different entity, this group was included in the material of this project. Compared to patients with ICP, children with PRS seem to have a wider and U- or V- shaped cleft (161). At the age

of 4-7 years they have similar mandibular lengths, but at the age of 10-13 years they have a shorter mandible and a slightly shorter maxilla (162). Additional analyses were performed to examine whether their inclusion would influence the results. The distribution of the 31 children with PRS was uneven among the groups, yet this did not seem to influence the validity of the findings. A limitation in the study was the application of clinical criteria as a base for the selection of children with PRS.

Lateral cephalograms and casts were collected following the national guidelines in a standardized way and at specific chronological ages. Cephalograms differ in quality, magnification and format (analogue or digital). Some cephalograms and more casts were not found. Drop-outs existed due to moving from the area, refusal of registering, not-found material and delayed surgery.

As the present project consisted of retrospective studies, registration material at all ages for all children was not possible to collect. It was decided, in order to increase the statistical power of the comparisons, to include all the material (longitudinal and cross-sectional) in the project. Although, statistical evaluation including only longitudinal data was also performed. This provided similar results, of reduced significance in some variables, but may still be considered as indicative. At 5 and 10 years of ages, due to a limited material and the fact that children had not reached adolescence yet, it was decided to include both genders in the same group. However, in the cephalometric investigation of the C group at 10 and 16 years males and females were tested separately.

The same observer, who did not treat the children, performed all the cephalometric measurements for studies I, II and IV. Two experienced orthodontists of the team performed the measurements on casts for study II. Method error was calculated in the cast evaluation study and both the intra and inter-observer errors were found in agreement with similar studies. The method error of the cephalometric measurements was checked three times and in the first study it was found higher. The main explanation could be the quality and aging of the films used for study I, especially the soft tissue profile that was hard to recognize in some cephalograms. Only points definitely identified on the cephalograms were used. Consequently, mainly measurements on facial convexity were influenced, leading to a small subgroup (VWK2) where just 15 cephalograms were used.

To measure the height of the palatal vault on dental casts was found to be difficult, due to an uneven surface of the palatal mucosa in the midline in some of the casts. Furthermore, a big range was found in our material especially for the big cleft groups. Consequently, the found difference of 1.3 mm as a mean should be validated in a larger study.

Ideally, the effect of palatoplasty should be evaluated on a material of patients treated by the same operator, as the surgeon is an important factor (160). In study I, 10 surgeons were involved in the project. When applying the regression analysis a difference was revealed for the need of velopharyngeal flap surgery on the found results from one of the main surgeons. Additionally, when material from only one main surgeon was analysed, similar results were found but in decreased significance and power. One child that was included in study I was excluded from study III in an effort to improve the factor surgeon. The excluded patient was the only child treated by a different surgeon, and, even if both cephalograms of this patient were available, it was decided to be excluded in study III where the total number of surgeons was 4 instead of 10. A proposal, made more than 30 years ago, was that also the surgeon, plays an important role in the final result after surgical correction of a cleft (160). This still seems to be valid.

All surgical methods for correction of cleft palate, VWK, MI and MMI, as well as both cleft lengths, extension in only soft or both soft and hard palate, seems to produce equal sagittal and vertical results at 5 years and permit similar further growth from 5 to 10 years. Concerning speech quality, it showed no apparent differences between the VWK and the MI technique at 5 years of age (163). Comparing the MI to the MMI technique no significant differences in speech evaluation were found, apart from decreased need (less than 50%) for further surgical correction of velopharyngeal insufficiency when applying the MMI technique (87).

In patients with CLP it was proposed that treatment by a multidisciplinary team working only on children born with a cleft provides better results than treatment by non-specialized individual doctors (164). These multidisciplinary teams need to follow strict protocols to collect data and thereafter continuously evaluate their work and compare it to other centers. Continuous evaluation of outcome after surgical correction of a cleft is of importance, as it will refine our protocols in the clinical care of the future children born with ICP, providing the best available treatment.

At cease of growth, patients with cases of skeletal discrepancies of both class II and class III were treated, exhibiting a wide range of possible malocclusions in adulthood. When the patients in our center have reached adulthood an investigation may be performed on final growth and on the need of orthognathic surgery.

Longitudinal and cross-sectional materials were combined in the cephalometric studies in an effort to increase the number of cephalograms and increase the power of the analyses. On the other hand the combined method decreased the advantage of analyzing only longitudinal data, even if most of the data was longitudinal. In the last study the rare control material was

cross-sectional, but, in order to increase the validity of the results, the material was compared to a longitudinal material of children with ICP.

The results from the present investigation revealed a similarity in growth at 5 and 10 years in patients with ICP treated with the VWK or the MI technique. Taking into consideration previous findings from dental occlusion at 5 years, where transversal constriction and scar tissue was found after the VWK palatoplasty (84), shifting to the MI technique was justified and proposed, as transversal constriction of the arch, mainly in the premolar area, was found when the VWK technique was applied.

Concerning the idea of radical muscle reconstruction, comparison of growth, dental occlusion and speech (87) did not confirm superiority of MMI versus the original MI technique. In long clefts, muscle reconstruction may restrict vertical growth of the maxilla posteriorly, but to a small magnitude. Medical records showed an expected increased operation time for MMI, but less need for velopharyngeal flap surgery later in childhood. So, from the present data, the increased surgical time implied by the radical muscle reconstruction, apart from improved velopharyngeal function, where secondary surgery could be avoided in some patients, puts its application in children with ICP in doubt. Further investigation on the need for muscle reconstruction is needed through prospective well-designed multicenter studies, in order to verify the present results. Thorough investigations of speech are also needed, as contradictory results were found: similar speech but increased need for secondary surgery with MI than with MMI (87).

When deciding on which surgical technique to use, one suggestion would be to base the decision on the individual patient. More factors, as e.g. the specific anatomy and the severity of the cleft, could influence the final choice of technique. It seems, from clinical observation, that for most cases closure of the palate can be performed in one-stage without extreme tension and risk for fistula formation, and perhaps in long, wide and extreme cases a two-stage approach could be more beneficial, reducing risks for future operations.

As the factor surgeon is confirmed as a very important confounder, it is of outmost importance that the plastic surgeon masters the technique he uses and treats patients with clefts on a regular basis (165, 166). Treatment of patients with clefts in specialized centers also helps to increase the load of the involved surgeon. It is still unclear if one technique is superior to another in all aspects. But, as children with clefts treated at special centers constitute just a percentage of the total operations performed by the surgeon of the cleft team, and mastering of a palatoplasty is of vital importance, perhaps deep knowledge and excellent performance of 1-2 different surgical techniques may be proposed (167).

In the Stockholm Craniofacial Team, cephalometric registrations are performed at 5, 10, 16 and 19 years of age in children born with ICP. This is of importance if the team is to evaluate its own work regarding growth outcome. Prospective controlled high quality multicentre studies are needed to definitely answer the question of how to provide the best evidence-based care in children born with clefts in terms of an ideal surgical correction leading to maximum growth, normal function of oral and nasal cavities, facial aesthetics, optimal speech development, ideal self-esteem and well-being of the child (166, 168).

6 CONCLUSION

The general conclusions of this project were: the Veau-Wardill-Kilner palatoplasty provides the same horizontal and vertical growth as the Minimal Incision technique, and the Minimal Incision with muscle reconstruction palatoplasty similar growth and dental outcome as the MI technique at 5 and 10 years of age. Muscle reconstruction needs more surgical time but decreases the need for secondary surgery due to velopharyngeal insufficiency. Treated children have retrognathic but harmonious jaws at 10 and 16 years of age.

There was a minor difference in craniofacial morphology between patients treated with the VWK technique, the original MI and the modified MI with muscle reconstruction technique (MMI). At the age of 5 years, comparing the VWK to the MI technique, a statistically significant shorter mandibular length ($p<0.01$) was found in cleft group 2 for the surgical technique group MI. At the age of 5 years, comparing the MI to the MMI technique an increase in the inclination of the palatal plane to the anterior cranial base, a decreased posterior upper face height and a shorter mandibular length was found in the big cleft group. At 10 years of age an increased inclination of the palatal plane, a decreased posterior upper face height and a longer palatal length was found in the MMI group when compared to the MI group.

Concerning surgical complications and dentoalveolar outcome at 5 years of age, the muscle reconstruction has been shown to result in a demand for an almost doubled operation time, a slightly decreased height of the palatal vault, but to less need for pharyngeal flaps.

The craniofacial cephalometric morphology at 10 and 16 years of age in treated patients born with an isolated cleft in the palate differs in both jaws compared to the morphology of a normal control group in both genders. At both 10 and 16 years of age the maxilla and the mandible were retrognathic, the maxilla was shorter and with increased inclination in the treated group. Additionally at 10 years the mandible and the posterior upper face height were shorter in the treated group.

Minor differences according to the extent of the cleft were found. In patients treated with the MI technique, a longer mandibular length and an increased posterior upper face height were found in the small compared to the big cleft group at 5 years of age. An increase in time needed for the surgical procedure and need of pharyngeal flap operation was noted in the group of big clefts.

Almost identical results were provided including or excluding patients with PRS during the statistical evaluation.

Small gender differences were found at 10 and 16 years in the treated patients born with ICP. Males, compared to control group, showed an increased mandibular inclination in both ages and a shorter posterior face height at 10 years, while females showed a shorter posterior upper face height only at 16 years of age. Comparing males to females, a more retrognathic

maxilla was discovered in males at 10 years. In males a longer mandibular length and an increased posterior upper and total height were found at 16 years of age.

7 FUTURE

The outcome after the three investigated palatoplasties (VWK, MI, MMI) will be measured at the age of 16 and 19 years in order to investigate morphology at cease of growth and whether the found changes will remain in adulthood. As orthodontic intervention may influence facial growth, the choice of orthodontic treatment provided to the patients, the period of orthodontic treatment, as well as its possible alteration on the growth of the individual will be further investigated. Speech outcome after various palatoplasties and influence of surgical intervention on further growth in children born with cleft lip and palate is presently studied by members of the Stockholm Craniofacial Team.

As effort is taken to isolate the non-syndromic patients, genetic tests could be applied to trace all syndromes that are difficult to identify only by the phenotype. This will be helped by our increasing knowledge of the genetic contribution in the formation of the cleft, as gene expression can be traced and its influence on all types of clefts clarified.

With the fast advance in imaging methods, possible evaluation using a suitable three dimensional diagnostic tool would provide an improved and more accurate view of altered growth in children born with a cleft.

Well-designed prospective multicenter studies are needed to verify and expand the results of this research. They should also include studies on quality of life for patients living with an isolated cleft.

8 ACKNOWLEDGEMENTS

Many people throughout the years significantly contributed and made possible this research and I would like to express my sincere gratitude to:

First of all, my main supervisor, Agneta Karsten, for endless support, guidance, ideas, instructions, creative discussions, friendship, solving any problem on the spot, and for always devoting time, taken from other crucial everyday tasks, whenever needed.

My co-supervisor, Ola Larson, for continuous support, simplified but in deep explanations, ideas, fruitful discussions, friendship and for always coming happily to last minute meetings despite any difficulties.

My mentor at KI, Mona Dahlström, for availability and support.

My precious previous clinical supervisor, Johan Karsten, for his continuous warm hospitality, support, friendship, corrections in English and for "refreshing" my mind at every meeting.

The head of the orthodontic department during most of my studies, Jan Huggare, for endless help from the very beginning of specialty, to working with patients and giving me the opportunity to start and continue this research journey, for excellently combining real friendship with professional work of high standards.

TUSEN TACK!

The director of my postgraduate studies, Carl-Magnus Forsberg, for continuous support, valuable guidance, ideas and friendship from the first moment of my arrival at Stockholm's airport till today, almost 20 years later.

The supervisor of my master, Eva Hellsing, for precious step by step guidance, ideas, friendship and support during my first attempt in orthodontic research.

The clinical supervisor and co-author of my master's article, Svante Moberg, for excellency in clinical and research guidance and his sincere friendship and concern.

My not previously mentioned clinical supervisors and teachers during my postgraduate studies (Anders Lindner, Henrik Håkansson) for increasing my love to orthodontics and my knowledge and skills as a specialist.

My precious colleagues-friends that shared the experience of getting the orthodontic specialization at KI: Oded Zilberman, for contributing to knowledge and making staying in Sweden easier, even for that small extra project which finally helped many others. Jiotta Tsarapatsani, for great help in getting used to Swedish life fast, valuable support, sincere friendship and continuous sharing of experiences and ideas. Fariba Banaie, for helping during studies, ideas, nice time and the research journey.

All following postgraduate students at the orthodontic department at KI, and most of the old ones that I had the chance and joy to meet, for real friendship, support, criticism, information and making hard everyday issues easy to solve.

My precious everyday colleagues and dear friends, Idil Alatli Burt, Marie Pegelow, Mathias Lamberger, Malin Vasterbacka and Simon Sundell for fresh ideas, deep scientific discussions, warm company and making real fun the work on orthodontic subjects.

All professors, teachers and clinicians, orthodontic assistants, nurses, receptionists, secretaries and technicians at the Orthodontic department at KI throughout all those years for support, friendship, providing valuable comments in science and in life, making every day worthy spending with them. It would be long and…"risky" to mention everyone one by one here, as there are too many happy faces coming immediately to my mind and I may forget someone who worked here just for a short period, but you all know what you all mean to me! I hoped I had more free time to share with, but you are always more than welcome to my home island, to be able to pay back for your unforgotten immediate, precious assistance and warn hospitality, and spend nice time there also.

All members and staff of Stockholm Craniofacial Team for warm welcome, continuous support, being always available, for helping in collecting the material, explaining records, answering questions and providing up-to-date knowledge, ideas and proposals.

All staff at Pedodontic department for sharing rooms, experiences, knowledge and happy time, when our departments were/are merged or not!

The staff at KI throughout the years, for trying and finding fast the best solution in whatever was needed.

The committee at my half time seminar Catharina Hagberg, Valdemar Skog and Monica Barr Agholme for critical and useful comments and guidance.

Special thanks to statistician Elisabeth Berg for valuable help and advices on the statistical evaluation of all papers, and to speech and language pathologist Liisi Raud Westberg, apart from others, for the nice illustrations of the three different surgical techniques.

The colleagues and staff at Eastman Institute in Stockholm, mainly during the three years of my postgraduates studies, for acquiring knowledge, sharing nice moments and creating strong friendships.

The American Dental Society of Sweden (ADSS) for supporting the presentation of the results from paper 4 at the 94th European Orthodontic Society congress in Edinburgh.

I can't forget to mention here the staff and colleagues at the orthodontic department at Bordeaux during CECSMO program, for increasing my knowledge and skills, especially in cephalometrics, basic science (anatomy, histology) and wire bending, and mainly for providing guidance on how to search at the sources of our present knowledge.

The military personnel and colleagues during my Greek army service, especially at the dental clinics in Chios and Athens, and at the maxillofacial surgery department of the military

MERCI!

ΕΥΧΑΡΙΣΤΩ!

hospital in Athens, for gladly providing precious knowledge and increasing and perfecting my skills as a dental surgeon.

The staff of the Greek section of MSF, since 1999 also winners of the Nobel prize, for assistance and friendship throughout my first steps in the dental profession.

My precious colleague and sincere friend, Costas Korompelis, and his family, especially for making happy, easy and successful my stay in Athens, a nice break throughout trips.

My professors and colleagues at the Dental school of Athens, for making love for dentistry flourish, providing sound bases, clinical excellence and scientific evidence to our work.

My teachers at the island of Chios for introducing me to happiness of knowledge and being self-standing.

My close friends for help and participation in creative and happy breaks from everyday life.

Everyone that I may have not mentioned here, due to the stressful limited time to write the thesis, but not forgotten!!!

My parents-in-law, Vassilis and Despina, and my "sister" Anna, for support, real love and for being wherever needed anytime!

My parents, Anastasis and Maro, my brother's family and my uncle's family for endless and unintentional love and support in every aspect! Without them I wouldn't even have the opportunity to make this amazing research "journey".

And last, but not least, my present family, Christina and Anastasios, especially for believing in dreams, sacrificing precious family time, providing endless support and giving special and true meaning to life.

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