Diploma Thesis

Mind the Gap: Retrospective Analysis of the Incidence of Oronasal Fistulas Following Primary Cleft Palate Repair – a Single-Center Experience

Submitted by

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Graz, 08.08.2023

Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, 08.08.2023 *Jan Gässler m.p.*

Preface

Since my study deals with the surgical outcomes of on average 9–12-month-old infants, I cannot base my references to the respective gender of the children on self-identification. References such as female/male or girls/boys refer solely to the infants' gender recorded at birth. These are by no means intended to disregard the diversity of gender expressions and identities.

I would like to express my endorsement for all gender expressions and gender identities.

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First and foremost, I would like to thank my supervisor, *Mr. Michael Schwaiger, MD, DMD, PhD*, for his support throughout the process of writing this curricular thesis paper. Even more importantly, he gave me the opportunity to participate in already existing research projects, helped me to initiate studies on my own, and encouraged me to present our results at both national and international congresses. During the last two and a half years, I thoroughly enjoyed to have him as my mentor.

Next, I want to express my gratitude to my secondary supervisor, *Prof. Wolfgang Zemann, MD, DMD, PhD*, who also provided insightful comments on this thesis and significantly contributed to my scholarly enterprises at his department.

I am also grateful to my parents who always instructed me to never settle for mediocrity and taught me that it requires hard work, ambition, perseverance, and dedication to achieve one's goals, even if all odds are against you. Without these valuable life lesion and their constant support, I would not have come this far.

On a related note, my sister deserves an honorable mention as well. As my role model, I continue to look up to her until this present day. She has taught me so many things that I cannot possibly list all of them in this short paragraph.

I am also indebted to my American fathers. They greatly contributed to shaping me into the person I am today and I will forever be grateful to be part of their family.

Last but by no means least, I would like to thank all my dear colleagues who had their fair stake in making the last three and a half years as enjoyable as possible.

"Now, if you'll excuse me, watch me drop some knowledge."

- *Christopher D. Turk, M.D.*

(*Scrubs*. Created by Bill Lawrence. Beverly Hills, CA: Doozer Productions; 2001-2010.)

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Index of Abbreviations

ACOG	American College of Obstetricians and Gynecologists
ANOVA	Analysis of variance
ASA	American Society of Anesthesiologists
BFPF	Buccal fat pad flap
CL	Isolated cleft lip
CLP	Cleft lip with cleft palate
CL/P	Cleft lip with or without cleft palate
CP	Isolated cleft palate
DOS	Duration of surgery
e.g.	*exempli gratia* (Latin for “for example”)
i.e.	*id est* (Latin for “that is”)
IQR	Interquartile range
IVVP	Intravelar veloplasty
LLR	Langenbeck lateral release
LOS	Length of in-hospital stay
MRI	Magnetic resonance imaging
NAM	Nasoalveolar molding
NTD	Neural tube defect
OFC	Orofacial cleft
PRS	Pierre Robin sequence
QOL	Quality of life
SD	Standard deviation
SR-IVVP	Sommerlad radical intravelar veloplasty
TCS	Treacher Collins syndrome
THF	Tetrahydrofolate
TXA	Tranexamic acid
US	Ultrasonography
U.S.	United States
VPD	Velopharyngeal dysfunction
VWS	Van der Woude syndrome

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Zusammenfassung

Einleitung: Orofaziale Spaltbildungen stellen die häufigsten angeborenen kraniofazialen Fehlbildungen dar und umfassen kombinierte Lippen-Kiefer-Gaumen-Spalten sowie isolierte Gaumenspalten. Spaltbildungen unter Beteiligung des Gaumens können weitreichende funktionelle Störungen zur Folge haben und sollten im Idealfall noch vor Vollendung des ersten Lebensjahres chirurgisch geschlossen werden. Als Qualitätsmerkmale bezüglich der chirurgischen Behandlung von Gaumenspalten werden die sprachliche Entwicklung, das knöcherne Mittelgesichtswachstum sowie die Restlückenrate herangezogen. Ziel dieser Forschungsarbeit war die Untersuchung der gegenwärtigen Restlückenrate in Graz.

Material und Methoden: Sämtliche Patient*innen, die seit Einführung der radikalen intravelaren Velumplastik nach Sommerlad (SR-IVVP) an der Grazer *Abteilung für Mund-, Kiefer- und Gesichtschirurgie* einen primären Gaumenverschluss erhalten haben, wurden retrospektiv bezüglich der Restlückenrate sowie weiterer sekundärer Parameter (u.a. OP-Dauer, Krankenhausaufenthaltsdauer etc.) ausgewertet.

Ergebnisse: Insgesamt haben bis dato 42 Kinder (25 Mädchen, 17 Jungen) mit einem medianen Lebensalter von 10,9 Monaten einen primären Gaumenverschluss unter Verwendung der SR-IVVP in Graz erhalten. Bei insgesamt vier Patient*innen kam es zur Entstehung einer oronasalen Fistel (9,5%). Deren Lokalisation verteilte sich auf den Übergang zwischen primären und sekundären Gaumen (n = 2), den harten Gaumen (n = 1) und den labialen Anteil des Alveolus (n = 1).

Fazit: Bei der radikalen intravelaren Velumplastik nach Sommerlad handelt es sich um eine effektive Technik zur chirurgischen Behandlung von Gaumenspalten. Die in Graz im Rahmen dieser OP-Technik beobachtete Restlückenrate entspricht dem internationalen Durchschnitt.

Abstract

Introduction: Orofacial clefts represent the most common congenital craniofacial anomaly and include cleft lip with or without cleft palate (CL/P) and isolated cleft palate (CP). Palatal clefts can cause extensive functional problems and should therefore be ideally corrected prior to completion of the first year of life. Quality indicators of primary palatoplasty include speech development, midface growth, and oronasal fistula incidence. It was this study's purpose to examine the current incidence of oronasal fistulas in Graz.

Materials and methods: All patients who underwent Sommerlad radical intravelar veloplasty (SR-IVVP) for primary CP repair at the local *Division of Oral and Maxillofacial Surgery* were retrospectively examined. In addition to the assessment of the oronasal fistula incidence, secondary outcome measures such as duration of surgery or length of in-hospital stay were studied as well.

Results: In total, 42 children (25 females, 17 males) underwent SR-IVVP for primary CP repair. Their median age at the time of surgery amounted to 10.9 months. Post-operative development of oronasal fistulas was observed in four children. Regarding their location, two fistulas formed at the junction between primary and secondary palate, one fistula was associated with the hard palate, and the last one was classified as labial-alveolar.

Conclusion: SR-IVVP represents an effective technique for the surgical repair of CP. The oronasal fistula incidence which was observed in Graz corresponds to the published international standard.

Publication Disclaimer

The results of this curricular thesis paper have not been published and are currently not under consideration for publication, too.

Excerpts of preliminary results, however, have been publicly shared within the framework of an oral presentation at the *63rd Annual Meeting of the Austrian Society of Surgery* (Graz, Austria; June 15th–17th, 2022).

1 Introduction

Orofacial clefts (OFCs) represent a spectrum of common congenital anomalies that are limited to the upper lip and/or the palate (see Figure 1.1).[1,2] A cleft can be understood as “an abnormal opening or fissure in an anatomical structure that is normally closed” and results from disrupted fusing or merging along suture lines during embryonic development.[3] The common practice of subdividing OFCs into clefts of the upper lip either with or without involvement of the palate (i.e., cleft lip with or without cleft palate, CL/P) and those clefts that solely affect the palate (i.e., isolated cleft palate, CP) is based on distinct differences in terms of etiopathogenesis.[2] Nonetheless, the two entities are closely related to each other and have similar clinical implications as both require complex multidisciplinary treatment including maxillofacial surgery, plastic surgery, otolaryngology, orthodontics, dental care, speech therapy, and psychological counseling that extends from birth to adulthood.[4,5] Despite the greatest efforts to accomplish definite rehabilitation by means of high-quality care, OFCs can burden the individual since they may have an unfavorable lifelong impact on long-term health, socioeconomic and psychosocial wellbeing, and overall quality of life (QOL).[4,6] Skyrocketing costs through increased need of various healthcare services is yet another challenge associated with OFCs.[6,7]

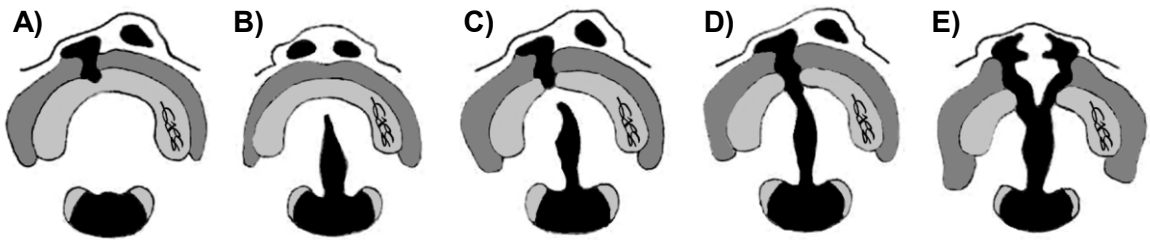

Figure 1.1 – Spectrum of Orofacial Clefts. A) Cleft lip. B) Cleft palate. C) Incomplete unilateral cleft lip and palate. D) Complete unilateral cleft lip and palate. E) Complete bilateral cleft lip and palate.

1.1 Classification of Orofacial Clefts

Due to their morphological and anatomical heterogeneity on the basis of extent of tissue involvement and laterality, the various subtypes of CL/P and CP are conveniently categorized into incomplete or complete (see Table 1.1, page 2) and

unilateral (i.e., a cleft of the lip and/or premaxilla that is restricted to a single side of the face) or bilateral (i.e., a cleft that involves both sides of the lip and premaxilla), respectively.[2] Based on their occurrence either with or without "concurrent physical or developmental defects", OFCs can additionally be classified as syndromic or nonsyndromic.[2] In this regard, it should be noted that this broad distinction does not fully capture the complexity of the presence or absence of other major malformations in conjunction with OFCs (see Chapter 1.3.2.1, page 9). Nonetheless, the practice of differentiating between syndromic and nonsyndromic OFCs for the sake of simplicity remains widely popular.

Type of cleft	Description
Incomplete cleft lip	Partial labial cleft without extension across the nasal sill
Complete cleft lip	Confluent labial cleft extending into the nasal floor
Incomplete cleft palate	Palatal cleft restricted to the secondary palate
Complete cleft palate	Palatal cleft extending along the entire length of the primary and secondary palate

Table 1.1 – Distinctive Features Between Complete and Complete Clefts. The categorization of orofacial clefts into either complete or incomplete is attributable to the different extents of tissue involvement.[2]

Regardless of the aforementioned options to categorize OFCs, more sophisticated classification systems allowing for standardized description of the cleft phenotype are not only needed to make an exact diagnosis but also for the assessment of the patient's respective prognosis (e.g., facial growth, speech development).[8] A multitude of different classification systems has been described over the years. Each one of them comes along with its own benefits and drawbacks.[2] According to Allori et al., a scheme for the universal, simple, and practical classification of OFCs should provide an accurate description of the involved anatomic structures as well as the cleft's side (i.e., right or left), laterality (i.e., unilateral or bilateral), and severity (i.e., complete or incomplete). Its routine application would enable clinicians to unambiguously diagnose OFC patients and to anticipate the appropriate treatment protocol from the respective diagnosis.[9] The LAHSHAL classification (see Figure 1.2) serves as an excellent example of a satisfactory classification system as it ticks all those boxes.[10] This particular scheme is a right-to-left palindromic system in which each letter represents one of the anatomic

structures that can theoretically be involved in an OFC. Capital letters (L, A, H, S) identify clefts as complete, whereas incomplete clefts are indicated by lowercase letters (l, a, h, s). Moreover, periods (.) and asterisks (*) are used to denote normal anatomy and microform or submucous clefts, respectively. In spite of its limitation of having a steep learning curve, utilization of the LAHSHAL classification system to categorize OFCs is recommended because of its comprehensiveness, comparably high implementation rate worldwide, and convenience of usage.[11] Furthermore, its complementarity with the 10th revision of the *International Statistical Classification of Diseases and Related Health Problems* (i.e., the ICD-10 system) is another advantage of the LAHSHAL scheme.[11,12]

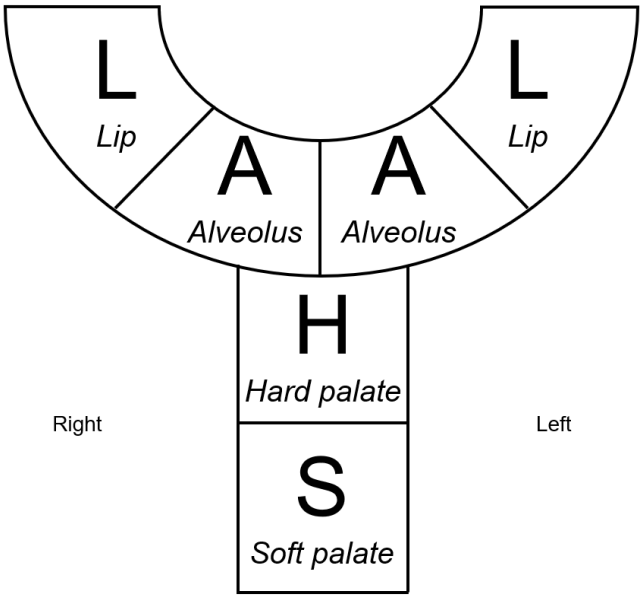

Figure 1.2 – The LAHSHAL Classification System. Kriens defined simplicity, conciseness, flexibility, exactitude, morphological descriptiveness, and graphic presentability as the premises of an ideal recording and classification system for orofacial clefts.[10]

1.2 Epidemiology of Orofacial Clefts

1.2.1 Demographic profile of Cleft Lip with or without Cleft Palate

CL/P represents the most common congenital craniofacial anomaly. Across all major birth defects (excluding overall congenital heart defects), it ranks third after clubfoot and Down syndrome.[13] The pan-European prevalence of CL/P amounts to 7.7/10,000. Throughout Europe, considerable variation relative to the geographical location is present (e.g., 3.5/10,000 in Southern Portugal, 11/10,000

in the Northern Netherlands).[14] In fact, a positive correlation between degree of latitude and prevalence has been noted within Europe.[15] Globally, the prevalence of CL/P is 9.92/10,000.[15] North American data points out that variable prevalence rates also exist in the context of ethnicity. Population-based estimates by the *National Birth Defects Prevention Network* show that CL/P is most common among Americans of non-Hispanic American-Indian/Alaska Native descent (15.21/10,000), followed by non-Hispanic Whites (10.68/10,000), Hispanics (10.59/10,000), non-Hispanic Asians/Pacific islanders (9.35/10,000), and non-Hispanic Blacks (6.55/10,000). The overall United States (U.S.) national prevalence (10.25/10,000) is equivalent to the international average.[13] As opposed to these statistics from the U.S., it is universally believed that the prevalence in Asian populations is about two times higher than in Caucasians. However, Cooper et al. were able to show that this figure is considerably too high. The actual prevalence of CL/P in Asians much more likely corresponds to 11.9/10,000 which still is significantly greater than in Caucasians but also nowhere near the much-cited prevalence of approximately 20/10,000. This discrepancy might be explained by the fact that numerous authors included stillbirths as well as they did not differentiate between syndromic and nonsyndromic clefts, or CL/P and CP.[16]

As its name implies, CL/P may either present as cleft lip with cleft palate (CLP) or isolated cleft lip (CL). On average, CLP is roughly twice as common as CL.[13,15] Unilateral clefts are about twice more prevalent than bilateral clefts in CLP, and almost nine times more prevalent in CL.[7] In unilateral clefts, a tendency toward the left side can be observed (58.9% in CLP, 63.1% in CL).[15] It has been speculated that this phenomenon may trace back to the fact that following the embryological development, the left palatine process attains its horizontal position somewhat later compared to the right palatine process.[2] Gender variation is also present with a 3:2 male-to-female predominance for CLP and CL alike.[17] According to the *International Perinatal Database of Typical Oral Clefts*, almost four out of five cases of CL/P (76.8%) were not associated with further congenital anomalies.[15] The most frequent malformations associated with CL/P include anencephaly, encephalocele, anophthalmia/microphthalmia, and polydactyly.[18]

1.2.2 Demographic profile of Isolated Cleft Palate

CP is less prevalent than CL/P (e.g., 5.1/10,000 in Europe, 5.93/10,000 in the U.S.), shows significant geographical (e.g., 3.1/10,000 in the Valencia Region, 10/10,000 in Malta) as well as ethnic (e.g., 4.06/10,000 in non-Hispanic Blacks, 6.73/10,000 in non-Hispanic American Indians/Alaska natives) variability, and is slightly more common in girls than boys (5:4 female-to-male predominance).[14,15,17] It has been proposed that increased susceptibility to teratogens resulting from delayed fusion (i.e., by a time frame of approximately one week) of the palatal shelves in girls could account for this marginal female predominance.[3,19] By comparison with CL/P, associated congenital anomalies occur more frequently with CP (roughly 50%). Common representatives of these malformations include different neck anomalies as well as congenital heart defects, hydrocephaly, urinary tract defects, and polydactyly.[18]

1.3 Etiopathogenesis of Orofacial Clefts

1.3.1 Embryological Development of Craniofacial Structures

Basic understanding regarding the embryology of the nose, lip, and palate is necessary to fully comprehend the pathogenesis of OFCs. Thus, this chapter will start with a brief review of the relevant information on this topic.

Embryonic development of the head region in vertebrates is closely linked to neural crest cells.[20,21] The neural crest is a unique mesenchymal cell population that is primarily associated with the formation of an extensive variety of neural derivatives throughout the entire body.[21,22] Also, it “provides an extensive non-neuronal mesenchymal population in the head”.[22] As opposed to its counterpart in the trunk, migration of head neural crest cells from the edges of the cranial neural folds occurs prior to the closure of the neural tube.[21,22] Through dorsolateral migration around the neural tube’s sides, the crest populations reach the pharyngeal arches and facial region on the ventral side of the head where they will eventually give rise to the entirety of the viscerocranium (i.e., the face) as well as parts of the membranous and cartilaginous components of the neurocranium (i.e., the skull).[22,23]

At the end of the fourth week of fetal life, the stomodeum marks the topographic center of facial development.[23,24] Through further proliferation and migration of neural crest cells within the region, five facial structures or primordia surrounding the stomodeum form.[24,25] Subsequently, these structures become recognizable as the frontonasal prominence as well as the bilateral maxillary prominences and the bilateral mandibular prominences (see Figure 1.3A).[25] The latter two structures are derivatives of the first pharyngeal arch. It possesses both a dorsal and ventral process which form the maxillary and mandibular prominence, respectively.[21] The frontonasal prominence, on the other hand, is the result of proliferation of mesenchymal cells ventral to the brain vesicles.[23] On either side of the frontonasal prominence, nasal placodes emerge as thickenings of the local ectoderm (see Figure 1.3B).[23,26] During the fifth week of embryonic development, rapid tissue growth within their margins creates a horseshoe-shaped ridge that causes gradual deepening of the nasal placodes.[23,25,26] Ultimately, continued invagination leads to the formation of the nasal pits.[23] The surrounding ridges turn into the nasal prominences. The prominences that are located on the outer edge of the nasal pits are referred to as lateral nasal prominences whereas those on the inner edge go under the name of medial nasal prominences.[23]

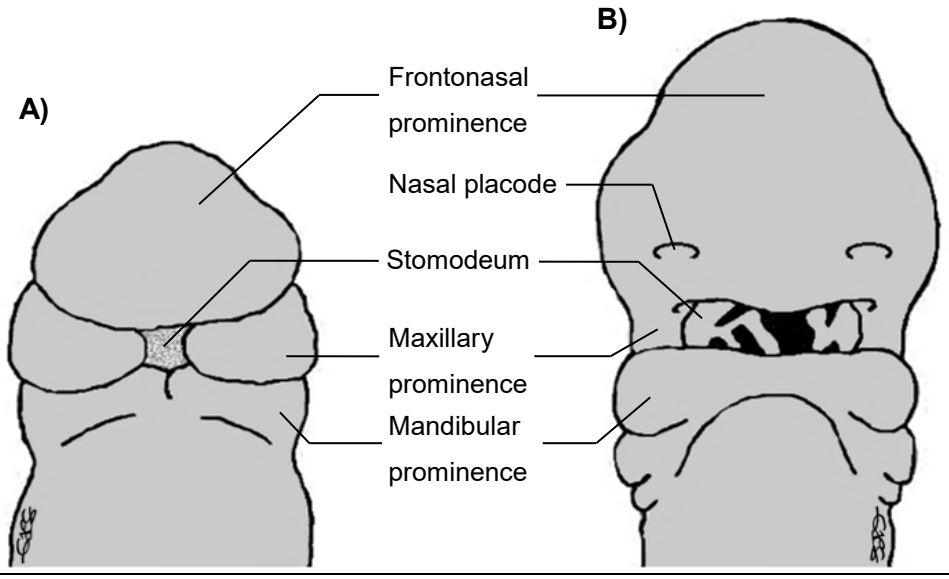

Figure 1.3 – The Five Facial Prominences. A) At approximately 24 days, five mesenchymal prominences surround the stomodeum. B) At approximately 30 days, further differentiation has led to the formation of the nasal placodes.

During the following two weeks, the maxillary prominences grow steadily larger while also expanding medially which results in compression of the medial nasal prominences toward the midline.[23] Eventually, the maxillary prominences merge with the medial nasal prominences and both medial nasal prominences fuse with each other.[26] This process leads to the development of the intermaxillary segment. Simultaneous merging of the mandibular prominences across the midline results in genesis of the lower lip and mandible.[23] The maxillary prominence and the lateral nasal prominence are initially separated from each other through the nasolacrimal groove. Following the development of a solid epithelial cord within the groove, canalization of said cord gives rise to the nasolacrimal duct. Subsequent detachment of the cord allows for merging between the maxillary prominence and the lateral nasal prominence.[26] Successional enlargement of the maxillary prominences causes formation of the cheeks and maxillae.[23] The abovementioned fusion of the medial nasal prominences does not only occur at the surface but also at a deeper level. As a consequence, the intermaxillary segment is made up of a labial component that forms the upper lip's philtrum, an upper jaw component containing the four maxillary incisor teeth, and a palatal component that gives rise to the triangle-shaped primary palate.[23,26] The main part of the definitive palate, however, is not derived from the intermaxillary segment. Instead, two shelflike outgrowths from the maxillary prominences, namely the palatine shelves, are associated with the formation of the secondary palate. The palatine shelves first appear during the sixth week of fetal life.[23] Initially, they lie in an obliquely downward direction under the tongue.[23,25] Throughout the seventh week, concomitant growth of the mandible enables the tongue to attain an inferior placement within the oral cavity which in turn allow the palatine shelves to grow toward each other and ascend to a horizontal position.[25] Fusion of the shelves with each other resulting in the emergence of the secondary palate as well as their merging with the triangular primary palate of the intermaxillary segment continues through the ninth to twelfth week (see Figure 1.4, page 8).[25,26] After the completion of fusion, the hard palate is formed by continuous bone extending from the maxillae and palatine bones into the shelves. Both the soft palate and the uvula develop from the posterior part of the secondary palate that does not ossify.[25]

The embryonic development of craniofacial structures that involves formation of the lip and palate is an intricate process which is accurately controlled by several key signaling pathways and their underlying cellular mechanisms as precise timing and positioning of the facial prominences is of crucial importance.[20,26,27] Thus, any alteration may cause an OFC.[25] Labial clefts, on the one hand, occur with failure of one or both medial nasal prominences to merge with the corresponding maxillary prominence(s). Palatal clefts, on the other hand, are most likely associated with growth defects in the palatine shelves, delayed shelf elevation, and/or failed fusion of the adjoining shelves.[21]

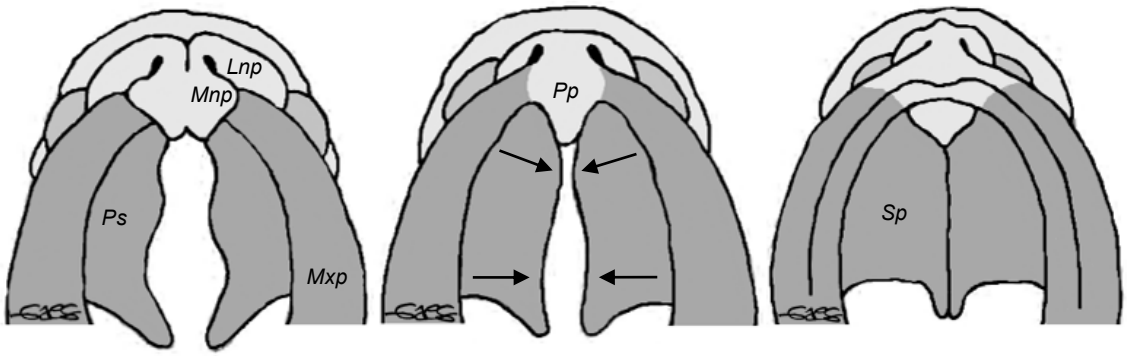

Figure 1.4 – Progress of Palatal Development. The primary palate results from fusion of the medial nasal prominences across the midline whereas the secondary palate forms through fusion of the palatal shelves. *[Abbreviations: Lnp = Lateral nasal prominence; Mnp = Medial nasal prominence; Mxp = Maxillary prominence; Pp = Primary palate; Ps = Palatal shelf; Sp = Secondary palate]*

1.3.2 Causes

The question of what exactly triggers the interferences with normal embryonic craniofacial development that subsequently result in the formation of OFCs has been and still is subject to laboratory science and clinical research. Historically, the majority of studies on the etiology of OFCs has focused on the examination of either genetic or environmental factors in isolation. Over the course of the past two decades, however, multiple works were published that insinuate that the genesis of OFCs may actually result from a complex gene-environment interplay.[28] This concept became popular under the designation “multifactorial threshold model” which implies that either a single major gene or multiple so-called polygenes provoke a continuous “genetic liability” regarding the risk for OFCs. This risk can

then again be influenced by further unspecified non-genetic factors, too.[29] The complexity in view of the possible causes of OFCs has also been described by Leslie who wrote that their multifactorial etiology involves “the cumulative action of multiple risk factors and environmental exposures, also modified by other gene, epigenetic, and environmental factors”.[30]

1.3.2.1 Genetic Factors

Epidemiological data from population-based cohort studies shows strong familial aggregation of OFCs, thus suggesting genetics as a significant contributing factor to their etiology. For instance, Sivertsen et al. demonstrated that first-degree relatives’ overall risk of recurrence of CL/P and CP is increased by a factor of 32 and 56, respectively.[31] Moreover, a twin study from Denmark found out that the concordance rate for OFCs is roughly 5-times higher in monozygotic twins than in dizygotic twins (47% versus 7.8%).[32] Evidence of consanguinity as a risk factor for OFCs is yet another argument in favor of the genetic background of clefts.[33] Since 1970, several advances in statistical genetic approaches and molecular biology methods have led to the discovery of multiple genes and loci associated with OFCs.[30] The list of genetic factors in question of contributing to the development of clefts can be separated into syndromic and nonsyndromic.[34] Syndromic OFCs are defined as those clefts that present with additional physical or cognitive abnormalities whereas nonsyndromic OFCs lack any additional features.[35] It is worthy of mention that even though they are conventionally referred to as syndromic, not every OFC that is accompanied by associated congenital malformations does in actuality fall within the specific definition of a “syndrome”. However, for reasons of simplification, the adjectives “syndromic” and “nonsyndromic” as well as the term “clefting syndrome” will be used throughout this thesis paper.

It is agreed upon that syndromic clefts are more tractable to genetic analysis which has resulted in the identification of the causal genetic mutation in a number of different clefting syndromes.[36] As a matter of fact, approximately three out of four of the described syndromes have a known genetic cause (see Table 1.2, page 10).[35] The spectrum of syndromic OFCs includes more than 500 Mendelian

syndromes as well as a range of syndromes arising secondary to chromosomal abnormalities or teratogenic effects.[36] Thus, not every case of a syndromic cleft has a genetic background.

Syndrome	Gene	Associated cleft type
Apert	FGFR2	Isolated cleft palate
CHARGE	CHD7	Isolated cleft palate
Pierre Robin *	SOX9	Isolated cleft palate
Stickler type 1	COL2A1	Isolated cleft palate
Stickler type 2	COL11A1, COL11A2	Isolated cleft palate
Treacher Collins	TCOF1	Isolated cleft palate
Van der Woude	IRF6	Cleft lip with or without cleft palate
Velocardiofacial	TBX1	Isolated cleft palate

Table 1.2 – Selected Clefting Syndromes with Identified Genetic Cause. This table represents a selection of a list published by Leslie and Marazita[35] featuring a choice of syndromic OFCs in which the exact mutated gene had previously been described. Note that the majority of syndromes are rather associated with isolated cleft palate than cleft lip with or without cleft palate (** Pierre Robin is strictly speaking not a syndrome, but instead it is a sequence*). *[Abbreviations: CHARGE = coloboma, heart defects, atresia choanae, retardation of growth and development, genitourinary problems, ear abnormalities; CHD7 = chromodomain helicase DNA binding protein 7; COL2A1 = collagen type II alpha 1 chain; COL11A1 = collagen type XI alpha 1 chain; COL11A2 = collagen type XI alpha 2 chain; FGFR2 = fibroblast growth factor receptor 2; IRF6 = interferon regulatory factor 6; SOX9 = SRY (sex determining region Y)-box 9; TBX1 = T-box; TCOF1 = Treacher Collins-Franceschetti syndrome 1]*

The multifactorial model of inheritance which is grounded on the interaction between genetic risk factors and environmental covariates makes genetic analysis of nonsyndromic OFCs especially challenging.[36] Nonetheless, application of genetic approaches such as linkage analysis, chromosome rearrangements, candidate gene-based association studies, and genome-wide association studies as well as the advent of genomic sequencing technologies allowed for the discovery of a number of genes involved with nonsyndromic clefts.[30,35,37-42] These genes are scattered around the human genome as multiple genetic loci (e.g., 8q24, 10q25, or 17q22) have been identified as possible risk factors.[35,40] Gene variants responsible for predisposition to nonsyndromic OFCs include growth factors, transcription factors as well as genes associated with the metabolism of

xenobiotics, nutritional metabolism, and immune response.[38] Interestingly enough, these genetic variants of susceptibility are often not present in the affected children themselves, but rather their biological mothers.[38] Furthermore, significant genetic overlap between syndromic and nonsyndromic OFCs in evident as genes related to syndromic clefts (e.g., interferon regulatory factor 6) may contribute to up to 10 percent of nonsyndromic cases.[43]

In the foreseeable future, the ever-growing knowledge on the genetic background of OFCs may open the way to personalized medicine for targeted prevention strategies and better clinical care.[38,41]

1.3.2.2 Environmental Factors

Generally speaking, environmental risk factors show greater potential for modifiability when compared with genetic risk factors, thus making them an important target in disease prevention.[36,44] Their identification is pivotal in establishing effective primary prevention measures.[4,36,44] In the context of OFCs, "such preventive efforts might entail manipulation of maternal lifestyle, improved diet, use of multivitamin and mineral supplements, avoidance of certain drugs and medicines, and general awareness of social, occupational, and residential risk factors".[4] Given the high incidence of OFCs, even minor reductions in environmental risk factors by means of primary prevention have the potential to significantly favor public health.[45]

Micronutrients

The role of folate (or vitamin B9) deficiency as a risk factor for failure of neural tube closure (e.g., spina bifida, myelomeningocele or anencephaly) and the consequential success of periconceptional folate supplementation as a primary prevention strategy to forestall the development of these neural tube defects (NTDs) has long been established.[46] Accordingly, the *American College of Obstetricians and Gynecologists* (ACOG) recommends periconceptional intake of folic acid for "all women planning a pregnancy or capable of becoming pregnant" (see Table 1.3, page 13).[47] Prepregnancy counseling visits should be seen as an opportunity to encourage women to take folic acid-containing supplements.[48] The

ideal timeframe for supplementation extends from at least one month before conception until completion of the first 2-3 months of pregnancy.[49] Over the course of the last three decades, multiple studies have suggested a relationship between folate and OFCs that is similar to the one seen with NTDs.[50-56] Folate is an umbrella term which stands for a family of water-soluble compounds including folic acid as well as tetrahydrofolate (THF) and its many derivatives (e.g., 5-methyl-tetrahydrofolate).[57,58] Folic acid represents the synthetic, parent compound of this family and does not possess any active coenzyme properties. Its conversion into the metabolically active THF requires a two-step enzymatic reduction involving dihydrofolate reductase. THF functions as a coenzyme which facilitates the transfer of one-carbon units.[58] Folic acid shows greater stability when compared with the active form and is therefore the go-to option for preventive administration. In certain conditions (e.g., hyperhomocysteinemia, methylenetetrahydrofolate reductase gene mutations), supplementation with bioactive 5-methyl-tetrahydrofolate is preferred because it is immediately bioavailable to both the mother and fetus as it does not require metabolic activation.[59] Fetal development heavily relies on sufficient supplies of THF as it plays a key role in cell growth and division through catalysis of nucleic acid synthesis. In order to meet the increased demand resulting from embryonic development and fetal growth as well as maternal changes (e.g., increased erythropoiesis), adequate levels of dietary folate intake both before and during pregnancy are necessary.[60] Exceptionally high expression of folate receptors in embryonic neural crest cells serves as an indicator of high folate demand in this particular cell population.[61] Since neural crest cells are extensively involved in the development of craniofacial structures, folate insufficiency may potentially cause OFCs through this mechanism. Another explanation for the hypothesized relationship between folate and clefts suggests deficient function of dihydrofolate reductase as the root of decreased cell proliferation and increased apoptosis resulting in the depletion of cellular populations of the face that express crucial genes associated with differentiation of the jaw.[62] In accordance with these theories, multiple reviews and meta-analyses came to the conclusion that folic acid administration during pregnancy protects against OFCs.[63-65] Jayarajan et al. differentiated between the two main subtypes of OFCs and observed that the protective effect of folic acid only holds true for CL/P, but not CP.[66] On the other

hand, a *Cochrane* review from 2015 denied evidence of any preventive effects of periconceptional oral folate supplementation on OFCs.[67] According to Wehby and Murray, mixed results regarding the estimated effects of folic acid can be partially traced back to "differences in the studied dose and definition of folic acid supplements (multivitamins, folic acid supplements, or both), measurement and sample selection biases, and statistical models including adjustment for confounders".[68]

Target group	Folic acid supplementation regimen
All women of reproductive age (i.e., 15-45 years)	*Daily dose:* 400 micrograms *Period:* 1 month prior to conception until completion of the twelfth week of pregnancy
Women at high risk of neural tube defects (NTDs)	*Daily dose:* 4,000 micrograms *Period:* 3 months prior to conception until completion of the twelfth week of pregnancy

Table 1.3 – Periconceptional Folic Acid Supplementation. The *American College of Obstetricians and Gynecologists'* current recommendations' understanding of women at high risk of NTDs includes females "with histories of previous pregnancies affected with NTDs, women who are affected with an NTD themselves, those who have a partner who is affected, or those with a partner with a previous affected child".[47]

A connection between OFCs and micronutrients other than folates has been established by a number of independent studies. For one thing, it was observed that periconceptional intake of vitamin A resulted in reduced risk of OFCs, thus suggesting a potential protective effect.[69,70] For another thing, deficiency of certain representatives of the vitamin B complex as well as selected trace elements have been found to be associated with increased OFC risk. An animal study conducted by Scheller et al. came to the conclusion that lower concentrations of thiamine (vitamin B1) and pantothenic acid (vitamin B5) in the amniotic fluid correlates with increased OFC appearance in mice, thereby confirming the importance of the vitamin B complex in the context of early fetal development.[71] Wallenstein et al. found out that low intake of riboflavin (vitamin B2), cobalamin (vitamin B12), magnesium, calcium, and zinc led to an at least twofold elevated risk for CP. At the same time, a commensurable risk increase for CL/P was linked with low intake of riboflavin, niacin (vitamin B3), cobalamin, and

calcium.[72] Low maternal zinc concentrations as a risk factor for OFCs were described by other authors as well.[73-75] Last but not least, a high level of selenium in the umbilical cord was brought up as a potential protective factor whereas in utero exposure to higher levels of molybdenum was associated with an increased risk of CL/P.[75]

Prescription drugs

Regarding environmental risk factors for OFCs, a number of different prescription drugs have been brought up for discussion. Most notably, maternal intake of antiepileptic drugs (e.g., phenytoin, carbamazepine, lamotrigine, valproate, topiramate, phenobarbital, primidone, ethosuximide, or trimethadione) during pregnancy was found to increase the risk of having a child with an OFC.[5,76-79] Other drug classes associated with OFCs include antibiotics (e.g., amoxicillin, oxytetracycline), β-blockers (e.g., oxprenolol), antiemetics (e.g., thiethylperazine), and antimetabolites (e.g., methotrexate).[5,76,80,81] Compared to the peri-conceptional use of acetaminophen, Interrante et al. reported a significant association between the intake of aspirin and OFCs.[82] The overall evidence regarding the relationship between maternal use of corticosteroids during pregnancy and OFCs in the offspring is mixed. On the one hand, two studies failed to detect such an association.[83,84] Moreover, a *Cochrane* review by Chi et al. concluded that there was no association between OFCs and maternal exposure to topical corticosteroids during the first 12 weeks of gestation.[85] On the other hand, a meta-analysis by Xiao et al. found an elevated CL/P risk with maternal use of corticosteroids during the first trimester. They admitted, however, that the absolute risk is extremely small.[86]

Recreational drugs

Maternal cigarette smoking has been repeatedly described as an environmental risk factor which increases the likelihood of OFCs in the offspring.[87-93] Multiple studies classified the association between smoking during pregnancy and clefting as either minor or moderate.[87,88,92,93] Owing to the large of number of women who continue to smoke during pregnancy, the overall effect of maternal cigarette smoking on OFC risk is still considerable.[87,88] Moreover, maternal passive smoking exposure can also influence the overall risk of having a child with CL/P or

CP.[91,94,95] The potentially detrimental effects of alcohol on fetal development are believed to be the result of multiple mechanisms. Alcohol can either directly affect the fetus through its teratogenic activities (e.g., disruption of neuronal cell-cell adhesion, apoptosis of cranial neural crest cells) or indirectly by its metabolites and its effects on maternal physiology (e.g., inhibition of biotin and pyridoxine transport and decreased oxygen delivery across the placenta).[96] In fact, even low levels of alcohol consumption during the first trimester can substantially impact fetal craniofacial development.[97] However, multiple authors were unable to detect an association between moderate maternal alcohol consumption during pregnancy and OFCs in their infants.[98-100] Only women who reported binge-drinking at least three or more times during the first trimester had a significantly increased risk of having a child with CL.[99] Against the backdrop of the raging opioid epidemic in the U.S., recent studies concentrated on the possible correlation between maternal opioid use during pregnancy and OFCs. They came to the conclusion that prenatal exposure to opioids does actually increase the risk of developing a cleft.[101-103]

Miscellaneous environmental factors

Other environmental factors associated with the development of OFCs include maternal obesity, fever during pregnancy, and age of less than 25 years.[104-109] On the contrary, paternal age, does not influence the occurrence of OFCs.[109] Periconceptional stress (i.e., physical and/or emotional) has been identified as another risk factor for clefts.[110,111] However, Mahapure and Powar were unable to reproduce these findings since their observation of an association between high maternal stress scores and OFC frequency did not reach statistical significance.[112] Moreover, increased incidence of OFCs was seen with several indicators of lower socioeconomic status (e.g., lower education attainment or maternal enrollment with the *Special Supplemental Nutrition Program for Women, Infants, and Children*).[113] It is possible that the observed relationship between CL/P and prematurity can also be traced back to the role of lower socioeconomic status as a risk factor.[114] Last but not least, multiple pathogens including viruses (e.g., Epstein-Barr virus, herpesvirus, cytomegalovirus, influenza virus), bacteria (e.g., *Mycoplasma pneumoniae, Chlamydia trachomatis, Treponema pallidum*)

and protozoa (e.g., *Toxoplasma gondii*) have also been considered as potential risk factors for OFCs.[44]

1.3.3 Selection of Syndromic Orofacial Clefts

Less common than their nonsyndromic counterparts, syndromic OFCs contribute to approximately 30 percent of CL/P and approximately 50 percent of CP cases.[115] It is paramount to grasp the significance of syndromic clefts since the presence of their associated abnormalities can substantially affect the designated treatment protocol. For example, it may be necessary to postpone reconstruction of the lip and/or palate if the surgical management of grave symptoms such as airway issues or feeding problems has been given priority.[116] Aside from that, anomalies associated with syndromic OFCs may also "affect anesthesia management, behavior and compliance, wound healing, […] and long-term predictability of the surgical procedures".[117] The spectrum of syndromic OFCs is vast and heterogenous as it is composed of over 500 Mendelian syndromes together with a multitude of other syndromes that are reducible to either chromosomal or teratogenic effects.[36] Common representatives of this heterogenous cluster of conditions include Van der Woude syndrome (VWS), velocardiofacial syndrome, Pierre Robin sequence (PRS), Apert syndrome, CHARGE syndrome, Stickler syndrome, and Treacher Collins syndrome (TCS).[117-120]

1.3.3.1 Van der Woude syndrome

VWS represents the most common form of syndromic OFCs, being responsible for roughly 2 percent of all CL/P cases.[35,38] The incidence of VWS amounts to approximately 1:35,000 live births.[115] VWS is inherited in an autosomal dominant fashion and has a comparably high penetrance of about 80-99 percent.[38,121] The causal mutation affects the interferon regulatory factor 6 gene which is heavily involved in oral and maxillofacial development, thus explaining the high risk of OFCs that is associated with this disease.[122] The phenotypic expression of VWS is highly variable.[38] The clinical presentation of infants born with VWS is primarily characterized by facial anomalies such as paramedian pits of the lower lip as well as clefts of the lip, palate, or both.[121] Dental and craniofacial features that may

become present throughout the further development of affected individuals include hypodontia, vertical facial growth pattern, skeletal class II due to mandibular retrognathism, and dental biretrusion.[117,122] Apart from the obvious surgical interventions that are intended to address the issues resulting from the presence of a cleft (e.g., cleft palate closure), children born with VWS are also recommended to undergo surgical removal of the lower lip pits. Simple excision of these pits is considered inferior to more sophisticated surgical techniques like the vertical wedge excision or inverted-T lip reduction due to the higher likelihood of pit recurrence or mucocele formation with the first-mentioned approach.[123] Capon-Degardin et al. have argued in favor of early surgical repair of lower lip pits (i.e., at 10-12 months of age) in order to facilitate normal socialization of affected children.[124] In comparison with nonsyndromic OFCs, cleft patients with VWS require secondary surgery for the correction of velopharyngeal dysfunction (VPD) twice as often. They also show a significantly higher rate of participating in speech therapy at ten years of age.[121]

1.3.3.2 Velocardiofacial syndrome

Velocardiofacial syndrome (also known as 22q11.2 deletion syndrome or DiGeorge syndrome) is caused by a hemizygous microdeletion in chromosome 22, or, to be more precise, on the long arm of chromosome 22 at the 11.2 locus (i.e., 22q11.2).[125] This locus contains the TBX1 gene which belongs to the gene family of T-box transcription factors.[126] Since TBX1 mutations have been observed in affected patients, this particular gene is considered a candidate gene for velocardiofacial syndrome.[127] Among other functions, the gene is involved in the development of the skeletal structures of the face and neck.[125] The majority of the chromosomal deletions of the 22q11.2 locus occur de novo, but autosomal dominant inheritance has also been observed in 6-28 percent of patients.[127] The incidence of velocardiofacial syndrome is approximately 1:4,000 live births.[125,127] Its phenotypical features typically include cardiovascular defects, hypoplasia of the thymus and parathyroid glands, and craniofacial malformations such as overt or submucous CP.[127] As a matter of fact, overt CP has been found in roughly every tenth patient suffering from velocardiofacial syndrome.[126] During childhood,

developmental delay may present in the form of learning deficits, impaired language acquisition, or behavioral abnormalities.[125]

1.3.3.3 Pierre Robin sequence

The clinical presentation of PRS is characterized by a triad of microretrognathia, glossoptosis, and airway obstruction with variable inclusion of a palatal cleft.[128] PRS serves as an example for a sequence which describes “a recognizable pattern of multiple anomalies that occurs when a single problem in morphogenesis cascades, resulting in secondary and tertiary errors in morphogenesis and a corresponding series of structural alterations”.[129] In PRS, microretrognathia represents the initial spark which hereinafter leads to the retropositioning of the tongue (i.e., glossoptosis) and glottic airway obstruction.[128] During fetal development, the glossoptotic tongue may interfere with fusion of the palatal shelves and thereby cause CP.[130] PRS occurs with an incidence of 1:8,000-14,000 live births.[128] The pathogenesis of PRS is believed to heavily rely on participation of the SOX9 gene which plays a decisive role in modulating chondrogenesis in the mandibular cartilage (i.e., Meckel’s cartilage).[131] Thus, it can be assumed that mutations in the SOX9 gene result in microretrognathia, subsequently triggering the sequential cascade of anomalies associated with PRS. Compared with nonsyndromic CP, enteral nutrition, respiratory problems, and pregnancy complications are more likely to be observed in children with PRS.[132] Higher rates of VPD resulting in an increased need for secondary corrective surgery as well as less favorable speech outcomes are also associated with PRS.[132-134] Moreover, PRS significantly differs from nonsyndromic CP with regard to the morphology of the cleft (e.g., increased width of the cleft at both the level of the soft palate and the posterior end of the hard palate, increased total length of the cleft).[135] Also, due to the glossoptotic tongue acting as an obstacle regarding the fusion of the palatal shelves during fetal development, PRS typically results in U-shaped palatal clefts, rather than the V shape that is linked to nonsyndromic CP.[129,130] Despite these significantly different cleft characteristics, patients with PRS do not show a higher likelihood of developing post-operative palatal fistulas.[132,133] Isolated PRS (i.e., PRS without any additional organ system abnormalities) is not associated with a higher risk of mortality.[136]

1.3.3.4 Apert syndrome

Craniosynostosis syndromes represent a heterogenous group of congenital malformation syndromes that share premature fusion of multiple cranial sutures (i.e., craniosynostosis) as mutual features.[137] Restricted growth perpendicular to the fused sutures results in distorted head shapes, the hallmark of craniosynostosis.[138] The majority of cases of craniosynostosis is isolated or nonsyndromic, but the proportion of syndromic forms ranges between 9 and 40 percent.[138] Additional key characteristics comprise limb anomalies, facial dysmorphology, and neurocognitive deficiencies.[139] The four most common craniosynostosis syndromes include Crouzon syndrome, Muenke syndrome, Apert syndrome, and Pfeiffer syndrome.[138] Occurrence of CP in infants born with either Muenke or Pfeiffer syndrome has been reported in very few instances.[140,141] With Crouzon syndrome, associated palatal clefts can rarely be found, too.[137,142] In Apert syndrome cases, however, CP has been described as a common phenotypical finding.[143] Apert syndrome is a congenital disorder that can be traced back to mutations in the fibroblast growth factor receptor 2 gene.[130,137] Most cases are sporadic, but autosomal dominant inheritance may also be possible.[137] Its incidence amounts to about 1:80,000-160,000 live births.[143] Prominent morphological characteristics include multisuture craniosynostosis, midface retrusion, and syndactyly of the hands and feet.[143] The treatment of Apert syndrome is complex as it involves a multitude of extensive reconstructive procedures (e.g., fronto-orbital advancement, posterior vault correction, monobloc advancement, facial bipartition distraction) geared towards enhancement of self-confidence and social integration through harmonization of facial appearance.[144]

1.3.3.5 CHARGE syndrome

CHARGE syndrome is a genetic condition whose estimated incidence is at roughly 0.1 per 10,000 live births.[145] Various alterations (e.g., heterozygous mutations, deletions, translocations, or chromosomal rearrangements) within the chromo-domain helicase DNA binding protein 7 gene have been linked to the etiology of CHARGE syndrome.[146] Despite reports of familial CHARGE syndrome by means of autosomal dominant inheritance, the vast majority of cases (i.e., 97%) occur spontaneously.[146] The term “CHARGE” is an acronym that describes the

spectrum of phenotypic features associated with this disorder (i.e., coloboma, heart defects, atresia choanae, retardation of growth and development, genitourinary problems, ear abnormalities).[120] The presence of OFCs has been witnessed in 15-20 percent of patients born with CHARGE syndrome.[147] Compared to nonsyndromic children, clefts associated with CHARGE syndrome are typically more severe and the time of their surgical correction is often delayed due to recurrent chest infections and other urgent operations such as cardiac surgery or tracheoesophageal fistula repair.[147] Subpar speech development is a common feature in CHARGE patients.[148] Although VPD following palatal closure was reported to occur more frequently in clefts related to CHARGE syndrome than in nonsyndromic OFCs, speech issues can also result from sensorineural hearing loss secondary to the high prevalence of middle and inner ear malformations as well as tracheostomy, learning disabilities, developmental retardation, and rhombencephalic anomalies.[145,148]

1.3.3.6 Stickler syndrome

Stickler syndrome is an autosomal dominant collagenopathy that shows variable expressivity.[120] Mutations in the genes coding for type II (i.e., collagen type II alpha chain 1 gene) and type XI collagen (i.e., collagen type XI alpha 1 chain gene) represent the most prevalent causes of Stickler syndrome.[149] The incidence is estimated to be at about 1 per 7,500 live births.[150] Its chief characteristics include CP, hearing loss, arthropathy, joint hypermobility, reduced height, and different ophthalmic features (e.g., retinal detachment).[120] Another hallmark of children with Stickler syndrome is the typical facial morphology comprising midface deficiency, depressed nasal bridge, long philtrum, and micrognathia.[151] Furthermore, Stickler syndrome is regarded as the most common syndromic cause of PRS which manifests with microretrognathia, glossoptosis, and airway obstruction.[118,120] Thus, in contradistinction to nonsyndromic cleft patients, children with Stickler syndrome are at an increased risk of suffering from early airway compromise requiring surgical airway management (e.g., tracheostomy).[151] VPD following repair of a palatal cleft has been observed as a frequent issue in Stickler syndrome.[149] Despite this finding,

speech outcomes in patients with Stickler syndrome are not different or only slightly poorer than in nonsyndromic patients.[150,151]

1.3.3.7 Treacher Collins syndrome

TCS (also known as mandibulofacial dysostosis or Franceschetti-Klein syndrome) is a genetic disorder that primarily affects structures of the mandibulomaxillary complex and has an estimated incidence of approximately 0.2 in 10,000 live births.[118,130,152] In the majority of cases, TCS can be traced back to mutations in the Treacher Collins-Franceschetti syndrome 1 locus which encodes for the Treacle protein.[152] Forty percent of patients with TCS demonstrate autosomal dominant inheritance whereas the remaining 60 percent of cases are attributable to de novo mutations.[118,152] Faulty Treacle function is associated with deficient ribosome biogenesis and subsequent neural crest insufficiency, thereby interfering with the development of the first and second branchial arch.[130,152] Consequently, mandibular and midface hypoplasia are the most common features of TCS, followed by orbital and ophthalmic deformities such as downward-slating palpebral fissures or notching of the lower eyelids.[153] CP is another frequent finding which affects roughly every third TCS patient and is usually associated with more severe manifestations of the syndrome.[152-154] According to Plomp et al., there is no specific evidence suggesting deviations from the default timing of surgical cleft repair in TCS.[155] By comparison with other CP patients, closure of palatal clefts associated with TCS may be more challenging because of complicating factors like a high-arched palate, smaller oropharynx, limited mouth opening as well as thin, atrophic soft tissues.[154] As a matter of fact, TCS patients presenting with CP have significantly higher palatal fistula risk following surgery than other children with CP.[156] Both hypernasality and hyponasality, but also mixed resonance patterns testify the frequent impairment of speech development with TCS.[155] Since this particular patient population is associated with a much higher incidence of articulatory-based VPD than structural VPD, secondary surgery to achieve speech and language rehabilitation is discouraged as it would provide no benefit. Instead, comprehensive speech therapy to ensure optimization of functional results is critically needed in children with TCS.[157]

1.4 Presentation of Orofacial Clefts

1.4.1 Prenatal Imaging

Obstetric ultrasonography (US) screening represents one of the cornerstones of prenatal care since it is noninvasive, and readily available. The *ACOG* advises that standard prenatal US screening should include “an evaluation of fetal presentation and number, amniotic fluid volume, cardiac activity, placental position, fetal biometry, and an anatomic survey” as well as the facultative examination of the maternal cervix and adnexa.[158] Due to the perfunctory offering of prenatal US to pregnant women, congenital malformations in general and OFCs in particular are increasingly diagnosed well before birth. As a matter of fact, Ensing et al. have shown that introduction of the routine 20-week fetal anatomy scan in the Netherlands in 2007 has led to a significant increase in the percentage of CL/P diagnosed prenatally while also reducing the median gestational age at time of diagnosis.[159] The *International Society of Ultrasound in Obstetrics and Gynecology* stresses prenatal diagnosis of OFCs by specifically recommending visualization of the upper lip for the evaluation of potential cleft lip anomaly as part of the anatomical survey during routine mid-trimester fetal US screening.[160] Prenatal US diagnosis of clefts allows for a sense of preparedness for the majority of affected families.[161] Because of improved image resolution owing to the continuous progress in US technology, assessment of the facial anatomy of the fetus as early as during the first trimester became increasingly popular in recent times.[162]

Conventional (i.e., two-dimensional) US screening for the exemplary signs of OFCs (see Table 1.4) typically utilizes the three standard orthogonal views. Display of the nares as well as the upper lip can best be accomplished by use of the coronal view. The midsagittal view on the other hand is primarily intended for visualization of the hard and soft palate. Lastly, the axial view is especially helpful in the context of assessing the maxillary alveolar ridge.[163] It has been reported that standard US is able to indentify CL/P with a sensitivity of 82-88 percent.[159,164] The overall sensitivity for all OFCs combined, however, is much lower (64.5%) since two-dimensional US fails to reliably detect cases of CP.[164] According to Campbell, “severe shadowing by the maxillary bone [makes] visualization of the

secondary palate virtually impossible".[165] It has been proposed that oblique views may help with the indirect assessment of the fetal palate. However, CP remains to be rarely diagnosed with prenatal US.[166]

Defect	Ultrasonographic characteristics
Cleft lip	Hypoechoic region in the upper lip
Cleft alveolus	Linear hypoechoic region within the highly echogenic dental arch
Cleft palate	Absent *"equals sign"* – failure to visualize the uvula as a linear echogenic structure surrounded by parallel anechoic spaces

Table 1.4 – Ultrasonographic Morphology of Orofacial Clefts. Prenatal display of the ultrasonographic signs of orofacial clefts involves the coronal, midsagittal, and axial view.[163]

As a consequence, three-dimensional US has been proposed as a means to overcome this intricacy. It is considered advantageous over conventional US because of its capacity to easily and rapidly acquire a multitude of different planes. It also allows for the display of planes that, if using two-dimensional US, would otherwise be mostly inaccessible.[158,165] In actuality, Martínez-Ten et al. have shown that the utilization of three-dimensional US during the first trimester resulted in the detection of all clefts of the primary palate and 86 percent of the clefts affecting the secondary palate.[167] Other published data regarding the diagnostic accuracy of three-dimensional US in prenatal visualization of CP range from 0 to 89 percent.[168] James and Schlieder suggest that the "lack of uniform terminology in [US] literature" of what differentiates the various subtypes of OFCs from each other may be the reason for such dispersion.[169] Despite its theoretical advantages over two-dimensional US, three-dimensional US has not fully found its way into the practice of prenatal standard care. In point of fact, it has been acknowledged rather as an adjunct than a replacement to conventional US.[158] The "lack of time needed to train clinicians during busy clinical schedules, […] lack of applications specialist's support from vendors, costs of implementation and maintenance of new hardware and software, [as well as] clinician's attitudes toward adapting and learning new technology" have been listed by Ramos et al. as possible reasons for the inadequate acceptance of three-dimensional US as a screening tool for the prenatal diagnosis of OFCs amongst physicians.[170]

Regardless of whether two-dimensional or three-dimensional imaging techniques are used, US is subject to limitation through fetal factors (e.g., position, overlying limbs), maternal factors (e.g., obesity, oligohydramnios) or iatrogenic factors (e.g., examiner's skills).[171] Against this backdrop, magnetic resonance imaging (MRI) has been repeatedly proposed as an auxiliary method for the prenatal screening of OFCs on the ground that it has been proven superior (e.g., better accuracy, greater reliability) to US in diagnosing them.[171-175] Moreover, MRI provides additional information such as the extent of possible palatal involvement.[171-173] This increase in knowledge about the cleft's morphology is deemed helpful regarding the planning of corrective surgery as well as parental counseling.[173,174] Prenatal MRI can also help with the detection of associated malformations (e.g., micrognathia or glossoptosis in PRS).[176] Concerning the safety of MRI in fetuses, Strizek et al. have shown that the exposure to routine MRI at 1.5 T between 16 weeks of gestation and term has no deleterious effects on neonatal hearing or intrauterine growth.[177] The intensity of MRI-induced tissue-heating is known to reach its maximum at the body surface and gradually decreases towards the body center, thus minimizing the likelihood of teratogenesis resulting from thermal damage in exposed fetuses.[178] Accordingly, the *ACOG* labeled MRI as an imaging technique of choice for pregnant women.[179] In their latest "Manual on MR Safety", the *American College of Radiology* classified field strengths of up to 3 T as not harmful and, therefore, safe in case of pregnancy.[180]

In summary, both US and MRI allows for the prenatal diagnosis of OFCs. According to Sreejith et al., earlier identification is not merely of academic interest but also comes along with concrete benefits for the care of the child. For one thing, it buys the becoming parents precious time to come to terms with the reality of the child's condition. In general, parents experience high levels of psychological distress after having received the diagnosis of an OFC. With that said, prenatal diagnosis renders appropriate and timely psychological counseling for the parents possible which in turn prepares them to adequately meet the needs of their affected child. For another thing, OFC identification at an early stage also ensures that there is enough time to educate the parents about the malformation and, especially, the available therapy options. Both psychological counseling and

education positively influence the quality of the treatment which ultimately benefits the QOL of the affected child.[181]

1.4.2 Newborn Examination

Following the prenatal detection of an OFC, definitive confirmation of the diagnosis ensues via visual and physical assessment of the newborn immediately after birth. Besides documentation of the infant's gestational age plus relative growth and development as well as evaluation of the child's overall health and condition, routine newborn examination also serves the purpose of "[uncovering] signs of birth-related trauma or congenital anomalies".[182]

The wide spectrum of labial involvement in OFCs usually becomes immediately apparent with inspection of the neonate's face. Identification of shallow pits located along the lip except for the labial commissure may point towards a subepithelial cleft. Alternatively, this finding could also be understood as a sign of a sinus tract. It needs to be noted that sinus tracts of the lower lip are often associated with syndromic OFCs (e.g., VWS).[183]

Visualization of the palate during the initial newborn examination is specifically recommended by the *American Academy of Pediatrics* to make sure that palatal clefts are not inadvertently missed.[184] In healthy newborns, the uvula normally appears as a cone-like projection in the back of the mouth.[183] A bifid uvula, on the other hand, is commonly associated with a submucosal cleft.[183,185] Furthermore, palpation of the hard and soft palate permits the examiner to check for both submucosal and mucosal clefts.[183,185] Another important aspect of the physical newborn assessment refers to the identification of cleft-related conditions such as the clinical triad seen with PRS (i.e., microretrognathia, glossoptosis, and airway obstruction).[184]

1.4.3 Anatomy of Orofacial Clefts

1.4.3.1 Labial clefts

Clefts of the upper lip result from failure of one or both of the medial nasal prominences to with the corresponding maxillary prominence(s) during embryonic development of the face.[21] In healthy individuals, the appearance of the upper lip's vermilion zone (i.e., the exposed red-lip surface) is considerably formed by its junction with the external, hair-bearing skin of the upper lip. This junction almost always has the shape of a double-curved Cupid's bow (see Figure 1.5A). Below the surface, skeletal muscle fibers of the orbicularis oris form the core of lip.[186] Depending on their severity, labial clefts may substantially alter the appearance of the upper lip (see Table 1.5). They are usually divided into complete (i.e., involvement of the lip's full vertical height) or incomplete, and unilateral or bilateral clefts, respectively.[187] Interruption of the Cupid's bow is the mutual hallmark of all types of labial clefts.[186] Microform CL epitomizes the least severe variant of labial clefting and presents with vermillion deficiency, mild notching at the vermillion border, indentation of mucosa, and an elevation of the affected side's Cupid's bow.[2]

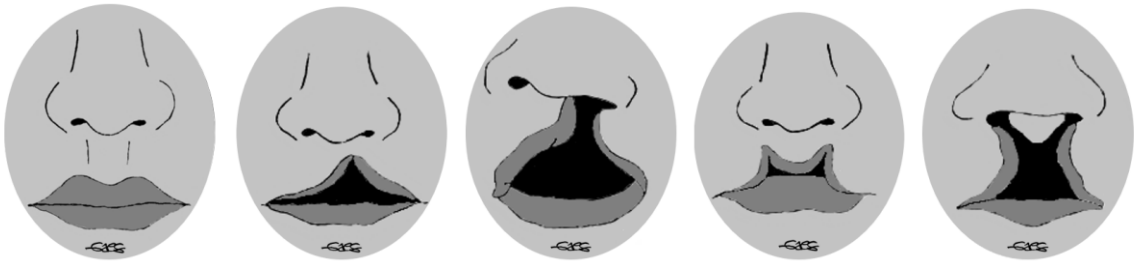

Figure 1.5 – Cleft Lip Variations. A) Nasolabial region in healthy individuals. B) Unilateral incomplete cleft lip. C) Unilateral complete cleft lip. D) Bilateral incomplete cleft lip. E) Bilateral complete cleft lip.

The morphology of unilateral CL (see Figure 1.5B-C) is characterized by ipsilateral rotation and distortion of the vermillion concomitant with loss of both the Cupid's bow and philtral landmarks.[187] The nasal septum shows a deviation to the contralateral side.[21] This disfigurement of the nasolabial region (see Table 1.6, page 28) is caused by abnormal muscular forces resulting from disruption of the orbicularis oris muscle whose fibers run parallel to the margin of the cleft and

insert on the alar base on the cleft's lateral side, the columellar base as well as the septum on cleft's medial side.[188]

	Normal	Unilateral cleft lip	Bilateral cleft lip
Skin	Intact across lip	Fully (*i.e., complete*) or partially (*i.e., incomplete*) deficient across vertical height of upper lip	Fully (*i.e., complete*) or partially (*i.e., incomplete*) deficient across vertical height of upper lip
Muscle (*Orbicularis oris*)	Intact across lip, circumferentially orientated	Usually deficient and/or disoriented across cleft	Usually deficient and/or disoriented across cleft
Lip	Cupid's bow and philtrum present and symmetrical	Cupid's bow less noticeable and upwardly rotated toward the cleft side; shortened philtral column on the cleft side	Bilateral loss of Cupid's bow and philtral structures
Bone (*Premaxilla*)	Intact	Ranges from intact to a wide alveolar cleft	May be significantly protruded

Table 1.5 – Upper Lip Anatomy in Healthy Individuals and Cleft Patients. Substantial alterations of the anatomy of the upper lip can be seen with unilateral and bilateral labial clefts when compared with healthy individuals.[187]

Bilateral clefts (see Figure 1.5D-E) are comparably symmetrical in appearance and feature considerable protrusion of the premaxilla which is detached from the two labial-alveolus-palatine elements of the maxillae on either side.[2,187] The prolabium is completely devoid of muscle fibers since the orbicularis oris inserts on the alar margins of both sides.[187,188] The prolabial skin lacks Cupid's bow and philtral structures.[188] Severe shortening or absence of the columella and lateral displacement of the lateral crura causes a broad, flat nasal tip that is typically associated with bilateral labial clefts (see Table 1.6, page 28).[187]

	Normal	Unilateral cleft lip	Bilateral cleft lip
Nasal tip	Symmetric	Flat and deflected to non-cleft side	Flat and broad (in complete cases only)
Columella	Symmetric	Shortened on cleft side	Short
Nasal base	Symmetric	Displaced laterally, posteriorly, and inferiorly on cleft side	Displaced laterally, posteriorly, and inferiorly on both sides
Nostril	Oriented vertically	Oriented horizontally on cleft side	Oriented horizontally on both sides
Caudal septum	Symmetric	Displaced to non-cleft side	-

Table 1.6 – Anatomy of the Nose in Healthy Individuals and Cleft Patients. Labial clefts, both unilateral and bilateral, can also cause significant disruption of the nose's normal anatomy.[187]

1.4.3.2 Palatal clefts

The palate forms the roof of the oral cavity and is usually divided into two parts (i.e., the hard palate and the soft palate). The palatine processes of the maxillae and the horizontal plates of the palatine bones form the basic framework of the hard palate.[189] The soft palate is a mobile musculoaponeurotic flap that is attached to the hard palate's posterior border.[190] Palatal clefts exhibit disorientation of palatal muscles as their mutual hallmark.[187] For one thing, the insertion of the tensor veli palatini muscle is displaced from the hard palate's posterior edge to the osseous margins of the cleft. For another thing, the levator veli palatini sling is disrupted due to the muscle's abnormal insertion onto the posterior border of the hard palate.[188] Submucosal CP represents the mildest variant of palatal clefting and is characterized by a "classic triad of findings including a bifid uvula, notching of the posterior hard palate, and midline mucosal attenuation known as the zona pellucida".[2] In spite of the absence of an overt cleft, submucosal CP may still cause functional problems.[2,21] Overt clefts of the palate result in an open communication between the oral and nasal cavity.[2] Incomplete palatal clefs are restricted to the secondary palate whereas complete clefts extend across the entire length of both the primary and secondary palate.[2]

1.4.4 Functional Sequelae of Orofacial Clefts

1.4.4.1 Early feeding problems

The degree of feeding problems of infants born with an OFC shows considerable variability as it depends on the cleft's respective type (i.e., lip or palate), laterality (i.e., unilateral or bilateral), and severity (i.e., incomplete or complete). On the one hand, CL, especially if it is restricted to only one side, is typically not associated with significant feeding problems. Initially, these infants may find it troublesome to achieve a sufficient lip seal on the nipple in order to generate the effective negative pressure needed for sucking. However, breastfeeding helps to overcome this hurdle because of the breast tissue's tendency to conform to and fill in the cleft area. Alternatively, specialized nursing bottles using soft, wide-based nipples produce a similar effect. Upon intraoral placement of the nipple, the tongue and jaw movements of the infant are usually enough to produce adequate compression of the nipple to make effective sucking possible.[3] On the other hand, feeding difficulties may be more severe in infants being born with CP.[191] Despite normal sucking and swallowing reflexes, they have problems to produce the necessary intraoral negative pressure to allow sucking breast or bottle milk. This is due to the disoriented musculature and the continuity between nasal and oral cavity.[1,3] The lack of a hard palatal surface for compression of the nipple as well as nasal regurgitation because of the open palate can impede the feeding process as well.[3] The challenges of breastfeeding among infants with clefts involving the palate have been confirmed by a recent review and meta-analysis.[191] In most cases, infants with complete palatal clefts are unable to breastfeed and require supplemental nursing systems.[3]

1.4.4.2 Velopharyngeal dysfunction and speech difficulties

Velopharyngeal competence, which refers to the ability to completely close the velopharyngeal sphincter, is required for the regular production of all sounds in the English language except for the nasal consonants (i.e., /m/, /n/, and /ng/).[192,193] Velopharyngeal closure during speech is achieved through the action of various muscles. For one thing, the levator veli palatine muscle acts as a sling which pulls the velum in a posterior-superior direction. For another thing, the tensor veli palatini muscle tenses and stabilizes the soft palate. Other muscles responsible for

velopharyngeal competence include the musculus uvulae, the palatoglossus and palatopharyngeus muscles as well as the superior pharyngeal constrictor muscle.[193] In palatal clefting, both the levator veli palatini and the tensor veli palatini muscles are subject to displacement.[188] VPD describes the consequential inability to adequately close the velopharynx during speech.[192] Non-cleft causes of VPD include deep pharynx, adenoid atrophy, adenoidectomy, irregular adenoids, hypertrophic tonsils, tonsillectomy, maxillary advancement, and surgical resection of oral, nasal, and pharyngeal cavity tumors.[3] Overt clefts of the palate, however, are considered as the most common etiology.[194] It may also occur in roughly 20-30 percent of patients who previously underwent palatal cleft repair.[195,196] The main symptoms of VPD are nasal air escape and hypernasality. Articulatory speech errors (i.e., distortions, substitutions, or omissions) may occur subsequently.[192] In OFC patients, screening for VPD should ideally start at approximately 18 months of age and continue into early adulthood.[196] The definitive diagnosis of VPD can be made by means of perceptual (i.e., a formal speech evaluation by an experienced speech-language pathologist) and instrumental (e.g., nasometry, speech aerodynamics, speech videoflouroscopy, nasopharyngoscopy) speech analysis as well as radiologic imaging techniques (e.g., MRI).[193-195,197,198] The management of VPD involves secondary speech surgery which comprises a number of different techniques including pharyngeal flaps, soft palate lengthening, or sphincter pharyngoplasty.[198]

1.4.4.3 Ear problems

The tensor veli palatini muscle, whose normal anatomy is disrupted in the context of palatal clefting, is not only responsible for stabilization of the soft palate but also opening and closure of the Eustachian tube.[193] Eustachian tube dysfunction leads to poor middle ear ventilation which in turn creates a negative pressure within the middle ear space, thus causing impairment of the tube's mucociliary clearance function and stasis of middle ear secretions.[199,200] Eventually, otitis media with effusion may develop if pathogens ascend from the nasopharynx into the middle ear.[1,200] Chronification of middle ear inflammation bears the risk of causing a 25-40 decibel conductive hearing loss.[1,199] Early onset hearing loss can negatively impact the development of speech, language, social behavior, and cognitive

abilities in affected children.[199,200] To prevent this unfavorable outcome, infants with palatal clefts need to have their middle ear drained via insertion of a small plastic tube in a previously created hole through the tympanic membrane (i.e., myringotomy).[1]

1.4.5 Dental Problems of Orofacial Clefts

Individuals with OFCs have been observed to have a higher prevalence of tooth abnormalities than those without OFCs.[201] For instance, clefts of the alveolus typically extend between the maxillary lateral incisor and the maxillary canine area, thus causing absence and ectopic or delayed eruption of these particular teeth, respectively.[1] Further abnormal dental conditions associated with CL/P and CP comprise the presence of natal and neonatal teeth, microdontia, taurodontism, enamel hypoplasia, and delayed tooth maturation.[202] Malocclusion is another issue that is related to the presence of OFCs. Mandibular pseudoprognathism (i.e., relative prognathism of the mandible due to maxillary retrusion) results in class III malocclusion. Retardation of maxillary growth is reducible to the operative trauma of cleft repair and the consequential fibrosis (i.e., scar contracture). Absent and supernumerary teeth may also marginally contribute to the observed malocclusion.[1]

1.5 Treatment of Orofacial Clefts

The treatment of OFCs involves multiple disciplines and extends from birth to adulthood.[4,5] The *American Cleft Palate-Craniofacial Association* states that the management of cleft patients is preferentially provided by an interdisciplinary team of specialists. This team may include experts in anesthesiology, audiology, radiology, genetic counseling, neurology, neurosurgery, nursing, ophthalmology, oral and maxillofacial surgery, orthodontics, otolaryngology, pediatrics, pediatric dentistry, plastic surgery, prosthodontics, psychiatry, psychology, social work, and speech-language pathology.[203] This plethora of involved specialist disciplines underlines the versatility of symptoms associated with OFCs and the resultant challenge of their management. The following subchapters will focus on primary cleft repair, whereas secondary surgical procedures and nonsurgical treatment

modalities (e.g., speech therapy or orthodontic treatment) will not be described in detail.

1.5.1 Presurgical Treatment

Presurgical treatment of infants with OFCs serves the purpose of reducing the defect's severity in order to improve the outcome of primary surgical repair.[204] This is particularly useful in wide or bilateral complete clefts.[3] Available options of presurgical molding include passive methods such as lip taping, nasoalveolar molding (NAM), and lip adhesion as well as active methods (i.e., presurgical orthopedics).[2]

Active appliances (e.g., Latham-Millard Pinned Appliance) create the desired effect of correcting the cleft deformity through exertion of a progressive and turnable force across tissues.[2] The practice of presurgical orthopedics has recently been put into question since significant long-term benefits on speech, nutritional status, nasolabial esthetics, occlusion, and parents' satisfaction could not be observed.[204,205]

The intended ramifications of passive methods depend on the application of a static tension or compressive force on tissues.[2] Lip taping is a simple and inexpensive method that involves the application of surgical tape across the lip.[2,206] It permits "preliminary approximation of the greater and lesser lip elements with medialization of the cleft side alar base".[2] Taping is a safe method to successfully decrease the cleft defect prior to primary cleft lip surgery.[206] Lip adhesion is more invasive as it describes a surgical procedure to reapproximate the lip elements without disturbance of tissue or key landmarks needed for definitive lip closure.[2,207] Reduction of alveolar and palatal cleft width can be achieved with lip adhesion. However, its effect on nasolabial esthetics remains unclear.[208] Wound dehiscence as a potential drawback of lip adhesion occurs in 5 to 19.1 percent.[208,209] In summary, lip adhesion should ideally be reserved for excessively wide labial clefts.[209] The practice of NAM relies on the use of a custom appliance which consists of an intraoral molding plate and intranasal stents.[210] Its goals comprise alignment of the alveolar segments as well as

correction of the preoperative nasal deformity.[2,210] The success of NAM heavily relies on parental compliance as it necessitates time commitment, regular clinic visits, adjustments, and awareness of problems.[211] Reduction of the initial defect's severity through NAM has been associated with more favorable nasal outcomes following primary repair.[212] Specifically, increased nasal tip projection, improved symmetry of the lower alar cartilages, and elongation of the columella count among the expected benefits to the appearance of the nose.[210] In addition to the advantageous esthetic impact, positive surgical, functional, and socio-economic effects have been linked to NAM as well.[213] NAM does not negatively affect long-term facial growth.[214] By comparison with lip adhesion, NAM may be less expensive. On the downside, it may place a higher burden of care on the affected children's families.[215]

1.5.2 Surgical Treatment

1.5.2.1 Cleft lip repair

Documentation of the first surgical repair of CL (i.e., cheiloplasty) comes from China and dates back to 317 AD.[216] Straight-line closure, geometric repair, and rotation-advancement techniques represent the contemporary schools of cleft lip repair design.[209] Continuity of skin, muscle (i.e., orbicularis oris), and mucous membranes, symmetry of the nostrils and Cupid's bow, natural appearance of the vermillion border, and minimization of visible scarring are the goals of surgical CL repair.[3] Primary labial cleft surgery is usually performed when the infant is approximately three months old.[2] In the recent past, the much cited "rule of 10s", which recommends the delay of surgery until the infant weighs more than 10 lb., has a hemoglobin concentration greater than 10 g/dl, and a leukocyte count of less than 10,000 cells/µl, has been brought into question.[217] In fact, Wlodarczyk et al. recently published encouraging results that demonstrate the efficacy of primary CL repair in patients younger than three months.[218] In premature infants, however, postponement of the procedure for the sake of avoiding possible adverse events is recommended.[219]

In unilateral CL repair, several surgical techniques are available.[2] Millard's rotation-advancement repair and its modifications (e.g., Mohler) count among the

most widely used techniques both in the U.S. and worldwide.[209,220] The advantaged of rotation-advancement flaps over other surgical approaches (e.g., Rose-Thompson, LeMesurier, Randall-Tennison) include maximal preservation of tissues and less conspicuous scarring as well as the fact that individual adaptations in relation to the cleft's severity are possible.[2,220] Inadequate rotation and/or scar contracture resulting in a short and notched upper lip is possible limitation of rotation-advancement flaps.[221] In recent years, Fisher's Anatomical Subunit Approximation technique has gained popularity due to its favorable post-operative results. In their comparison between modified Millard's rotation-advancement repair and Fisher's technique, Patel and Patel observed that the outcomes of the latter approach were seemingly less dependent on cleft lip severity.[222] Currently, Fisher's Anatomical Subunit Approximation represents the technique of choice for primary repair of unilateral CL at the *Division of Oral and Maxillofacial Surgery* in Graz, Austria.

Surgical repair of bilateral CL is particularly challenging due to the defect's unique configuration. The hallmark of bilateral labial clefts is non-attachment between the premaxilla and both the palatal shelves and maxillae which subsequently results in unrestrained advancement of the premaxilla.[223] If the distance between the central premaxilla and lateral maxillary segments exceeds a width of 1 cm, clefts are considered "wide" which typically require presurgical preparatory treatment (e.g., lip taping or NAM).[224] Surgical techniques have evolved from multistage to single-stage repairs.[225] Historically, staged repair of bilateral CL has been the option of choice since it was feared that the projecting premaxilla "would put the labial repair under too much tension".[226] However, multiple revisions are suspected to cause increased scarring and contracture of affected tissues. Thus, single-stage surgery is preferred in contemporary practice as it is believed to yield better esthetic and functional results.[227] Tension-free closure with single-stage bilateral CL repair has been facilitated through presurgical preparation of the premaxilla.[225] The most widely used repair techniques include Millard repair, Mulliken repair, and modified Broadbent-Manchester repair.[3,225]

1.5.2.2 Cleft palate repair

Surgical repair of CP (i.e., palatoplasty) intends to restore the functional impairments (e.g., feeding difficulties, speech dysfunction) associated with the underlying defect.[2] In addition to speech and feeding, palatoplasty can also determine the outcome of the infant's Eustachian tube function.[228] The primary goal of CP surgery is separation of the oral and nasal cavities and creation of a competent velopharyngeal sphincter. Secondary goals comprise the prevention of oronasal fistulas as well as minimization of maxillary growth disturbances and dentoalveolar deformities.[2,229] Tension-free closure, repositioning of the velar muscles, and multilayer closure represent the core principles of palatoplasty.[230] An age of 10-12 months is widely regarded as the ideal time for surgical repair of palatal clefts.[231] Single-stage CP repair is much more popular among cleft surgeons than staged reconstruction. Advocates of the latter option justify their respective preference with concerns over possible limitations in midface growth secondary to single-stage repair. However, the evidence regarding this issue is inconsistent. At the same time, speech and language development is significantly limited with two-stage palatoplasty in comparison to single-stage surgery.[232] Various surgical techniques for the repair of CP are available. Cleft type and width are factors that determine which particular type of palatoplasty and associated adjustments will be performed.[228] Reconstruction of the hard and soft palate are typically "amalgamated together to encompass a single repair technique".[2] For the sake of a better understanding, however, hard and soft palate repair techniques will be separately described.

Popular surgical approaches for hard palate closure include the von Langenbeck technique, Veau-Wardill-Kilner technique (i.e., V-Y pushback), and Bardach two-flap palatoplasty.[2] All techniques for hard palate repair involve axial muco-periosteal flaps that are based on the greater palatine vessels.[2,196] Relaxing incisions (i.e., Langenbeck lateral releases or lateral relaxing incisions) at the hard palate's lateral aspects are employed to guarantee for sufficient mobility of the flaps.[196] Langenbeck lateral releases (LLRs) leave denuded areas of palatine bone behind that are allowed to heal by secondary intention.[1,2] In some cases (e.g., bilateral complete palatal clefts), adjuvant utilization of vomerine flaps (i.e., mucoperiosteal flaps elevated from the vomer) can help to provide additional

tissue for nasal closure.[1,2,230] Short-term and long-term outcomes of vomerine flap closure of the hard palate were not associated with a higher incidence of maxillary growth restriction when compared with nonvomerine repair.[233,234]

The soft palate is composed of three distinct tissue layers, namely the oral mucosa, muscle layer, and nasal mucosa.[2] It is paramount that surgical repair of clefts of the soft palate includes all these layers to secure the closure's integrity under function.[1,235] Simple midline reapproximation of the layers, as it was practiced with early forms of soft palate repair, fails to address the underlying issue of aberrant insertion of the levator veli palatini muscle.[2,3] Intravelar veloplasty (IVVP) was the first surgical technique which dealt with this abnormality. It involves delamination of all three layers of the soft palate, release of the levators' anterior insertion from the posterior border of the hard palate and cleft margins, transposition of the muscles across the midline, and, conclusively, their reapproximation at the posterior aspect of the soft palate. In summary, IVVP results in reconstitution of the velopharyngeal sling.[2] Restoration of normal anatomy results in optimized elevation of the palate against the pharynx which substantially benefits both velar and pharyngeal function.[34] Even greater mobility of the levator muscles can be achieved through modifications (e.g., Sommerlad radical intravelar veloplasty, SR-IVVP) such as transection of the tendon of tensor veli palatini or extensive dissection of the velar muscles from the oral and nasal mucosa.[2,236] The main disadvantage of IVVP is insignificant increase in palatal length.[2] Alternatively, Furlow double opposing Z-palatoplasty can be employed for surgical soft palate repair.[2,34] It lengthens the soft palate while also reconstructing the levators' muscular sling.[34] However, transverse tension across the palatal closure complicates feasibility of Furlow's technique in wider clefts.[2] A recently published study introduced the combination of both Furlow's technique and SR-IVVP into one hybrid technique which may be regarded as a treatment of choice in wider clefts.[237] Buccal fat pad flaps (BFPFs) can be used as a supplement to primary cleft closure.[2]

Sommerlad radical intravelar velopasty

SR-IVVP represents the contemporary technique of choice for primary repair of soft palate clefts at the *Division of Oral and Maxillofacial Surgery* in Graz, Austria.

Since it also plays a key role in this thesis paper's objective, the various steps of SR-IVVP will be described in more detail (see Figure 1.6).

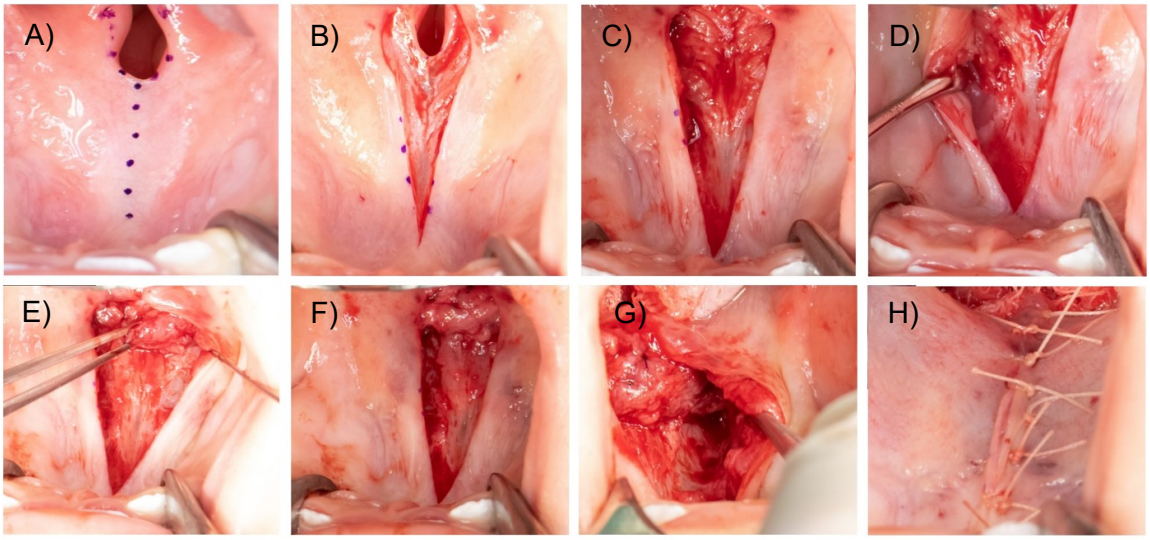

Figure 1.6 – Sommerlad Radical Intravelar Veloplasty. A) Surgical markings delineate the extent of the cleft. B) Incision along the margins of the cleft. C) Exposure of the posterior border of the hard palate. D) Bilateral extension of intravelar dissection. E) Release of the left levator's aberrant insertion. F) Reapproximation of the levators at the soft palate's posterior aspect. G) Reconstitution of the velopharyngeal sling. H) Sutures of the nasal layer and oral layer. *[Courtesy of Michael Schwaiger, MD, DMD, PhD; Medical University of Graz, Graz, Austria]*

Brian C. Sommerlad described repair of the entire palate at six months as the objective of SR-IVVP. Standardized use of a microscope for salient magnification and illumination of the structures of interest is specifically recommended. Incisions along the cleft margins at the junction between oral and nasal layer represent the initial step in SR-IVVP. Even in clefts that are restricted to the soft palate, extension of the incision onto the hard palate is advocated in order to thoroughly expose the hard palate's posterior border. Next, lateral dissection serves the purpose of visualization of the tensor tendon's oral component. Its incision facilitates closure of the oral layer, thus helping to avoid LLRs. The oral layer is then dissected off the velar muscles. Division of the tensors' posterior fibers results in noticeable retropositioning of the muscles and thereby permits exposure of the levator veli palatini. Mobilization of the levators ensues through sharp and blunt dissection under concomitant preservation of as many neurovascular structures as possible. Union of the two levators via sutures forms the

velopharyngeal sling. Additional stitches keep it in its posterior position. Closure of the nasal and oral layer terminate the surgical procedure.[236]

Complementary surgical procedures

The senior cleft surgeon at the *Division of Oral and Maxillofacial Surgery* in Graz, Austria frequently supplements SR-IVVP with complementary surgical procedures such as LLRs, BFPF, or A-stitches in order to further minimize tension, prevent fistula formation, and secure the retropositioned velar muscles in their newly adopted location. LLRs allow for sufficient mobilization of the flaps during CP closure.[196] Utilization of BFPFs as a middle lamella in the void immediately posterior to the transposed velopharyngeal musculature has potential to prevent the palatal muscles' secondary contracture and repositioning.[2] A-stitches describe simple interrupted sutures between oral and nasal layer directly anterior to the levator veli palatini muscle to keep it in its retropositioned spot.

1.5.2.3 Secondary surgical procedures

Secondary surgical procedures in patients with OFCs include rhinoplasty, operative insertion of myringotomy tubes, speech surgery, alveolar cleft bone grafting, orthognathic surgery (e.g., *Le Fort* I advancement with or without mandibular osteotomy) as well as revisional surgery in case of persisting deformities (e.g., oronasal fistula).[2]

1.6 Objective

From March 2019 onwards, SR-IVVP was adopted as the standardized technique for primary repair of the soft palate in children with OFCs at the *Division of Oral and Maxillofacial Surgery* in Graz, Austria. As mentioned above, the goals of CP repair include closure of the defect to separate oral and nasal cavity from each other, creation of a competent velopharyngeal sphincter to ensure development and production of normal speech as well as prevention of oronasal fistulas and maxillary growth restrictions.[2,229] VPD (i.e., inadequate closure of the velopharynx during speech), midface hypoplasia, and oronasal fistula formation represent the three major complications of CP repair.[238,239] Thus, many regard them as metrics and quality indicators of palatoplasty.[238] However, Naidu et al. pointed out that

the former two outcomes cannot be easily measured as “evaluation of speech is often subjective and lacks standardized reporting mechanisms” and assessment of the repair’s effects on facial growth typically require at least 15-20 years of follow-up.[240] Oronasal fistula occurrence, on the other hand, is an invaluable metric of surgical CP repair success.[241] Thus, this thesis paper will evaluate the quality of primary CP repair at the *Division of Oral and Maxillofacial Surgery* in Graz, Austria on the basis of oronasal fistula incidence. The results will be compared to another surgical concept which was practiced in Graz between October 2014 and December 2016. It employed conventional IVVP for the surgical repair of CP and also involved simultaneous repair of both labial and palatal clefts in children presenting with CLP (i.e., all-in-one approach).

2 Materials and Methods

This retrospective study was carried out in accordance with the spirit of the Declaration of Helsinki (1975) at the *Division of Oral and Maxillofacial Surgery,* which is part of the *Department of Dental Medicine and Oral Health* at the *Medical University of Graz* (Graz, Austria).

2.1 Data Acquisition

Patient records were obtained using the at the university hospital Graz employed hospital information system openMEDOCS (*KAGes m.b.H.*, Graz, Austria). Beginning with March 2019, all children who underwent SR-IVVP for primary CP repair were included in this study and consequentially referred to as the Sommerlad group. Those children who received conventional IVVP to have their palatal clefts repaired between October 2014 and December 2016 formed the control group.

Secondary surgery, deviant surgical techniques, inadequate documentation, and incomplete follow-up (i.e., less than six months) led to the exclusion of patients.

2.2 Sommerlad Group – Surgery and Perioperative Management

The various steps of SR-IVVP have already been described elsewhere (see page 35). All operations were performed by the current senior cleft surgeon of the *Division of Oral and Maxillofacial Surgery* in Graz, Austria. Either bupivacaine or articaine with epinephrine (1:200,000) was used for local anesthesia infiltration of the palate. Surgical antibiotic prophylaxis (amoxicillin/clavulanate) was initiated prior to incision. A surgical microscope (*Leica Microsystems GmbH*, Wetzlar, Germany) has been used in every single operation. Tranexamic acid (TXA) was given when profuse bleeding hampered the overall visibility of the surgical field. Transposition and reconstitution of the velar muscles was achieved through Ethicon® PDS™ II 4.0 sutures (*Ethicon Inc.*, Bridgewater, NJ). Surgical closure of all other layers involves Ethicon® VICRYL™ 5.0 sutures (*Ethicon Inc.*, Bridgewater, NJ).

Regarding post-operative pain management, ibuprofen and metamizole were routinely administered throughout the period of the children's hospitalization. Pro re nata (i.e., as required) administration of opioids was reserved for patients with persistent pain. During their inpatient stay, daily examinations of the children by one of the division's attending physicians served the purpose of ensuring adequate wound management as well as instructing the parents or legal guardians on how to assure appropriate oral hygiene.

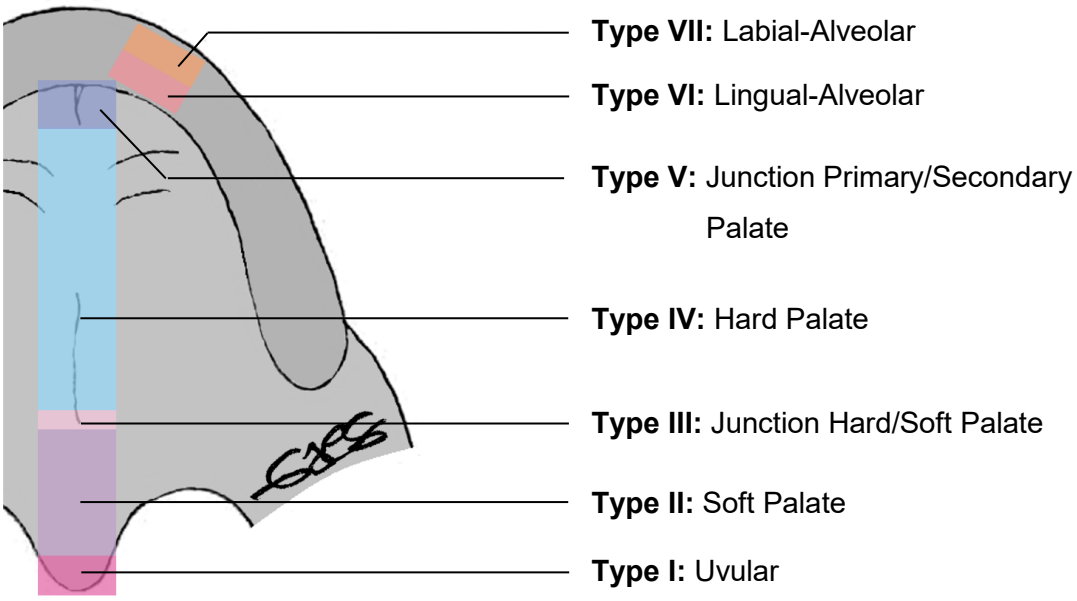

Figure 2.1 – Pittsburgh Fistula Classification System. The *Pittsburgh Fistula Classification System* is a simple, anatomical, numerical classification system that does differentiate between seven oronasal fistula types.[242]

2.3 Primary Outcome

The incidence of oronasal fistulas was defined as this study's primary outcome measure. As mentioned above, oronasal fistula occurrence is considered an important indicator of palatoplasty success.[241] Fistulation prevents the achievement of a competent velopharyngeal sphincter, thus jeopardizing the development of normal speech in affected children.[242] Oronasal fistulas are defined as "a failure of healing or a breakdown in the primary surgical repair of the palate, resulting in a patency between the oral and nasal cavities".[243] The *Pittsburgh Fistula Classification System* was used to categorize the observed

oronasal fistulas dependent on their respective palatal location (see Figure 2.1, page 41).[242]

2.4 Secondary Outcomes

Secondary outcome measures included patient demographics such as gender recorded at birth, age at the time of surgery, and the assigned *American Society of Anesthesiologists' (ASA) Physical Status Classification System* score (see Table 2.1), cleft characteristics (e.g., type, laterality, severity, presence/absence of associated congenital abnormalities), and surgery-related measures (e.g., complementary surgical procedures, duration of surgery (DOS) in minutes, length of in-hospital stay (LOS) in days, post-operative adverse events).

Classification	Definition	Selected pediatric examples
ASA I	Normal, healthy patient	Healthy child, normal BMI percentile for age
ASA II	Patient with mild systemic disease	Asymptomatic congenital cardiac disease, abnormal BMI percentile for age, mild/moderate OSA
ASA III	Patient with severe systemic disease	Uncorrected stable congenital cardiac abnormality, malnutrition, severe OSA
ASA IV	Patient with severe systemic disease that is a constant threat to life	Symptomatic congenital cardiac abnormality, active sequelae of prematurity, severe respiratory distress
ASA V	A moribund patient who is not expected to survive without the operation	Respiratory failure or arrest, decompensated congestive heart failure

Table 2.1 – ASA Physical Status Classification System. Assessment and communication of a patient's pre-anesthesia medical comorbidities to aid with prediction of perioperative risks is the main purpose of this classification which was invented by the American Society of Anesthesiologists[244] more than sixty years ago. *[Abbreviations: ASA = American Society of Anesthesiologists; BMI = body mass index; OSA = obstructive sleep apnea]*

2.5 Statistical Analysis

The collected data was anonymized and stored in a password-protected Microsoft® Excel® Professional Plus 2019 spreadsheet (*Microsoft Corp.*, Redmond, WA).

The subsequent statistical analysis of the data was carried out using IBM® SPSS® Statistics 26.0 (*IBM Corp.*, Armond, NY). In order to test whether data are normally distributed or not, Kolmogorov-Smirnov test was used. Explorative data analysis involved calculation of Student's *t*-test, analysis of variance (ANOVA), Mann-Whitney *U*-test, Fisher's exact test, chi-square test, Kruskal-Wallis test, and Kendall's tau-b correlation coefficient. Results were deemed statistically significant if the respective *p*-value was less than 0.05.

3 Results

3.1 Patient Demographics

The Sommerlad group consisted of 42 patients (25 female, 17 male) in total. Their median age amounted to 10.9 (interquartile range, IQR 2.6) months. Regarding presurgical assessment of the patients' health, 26 children were classified as ASA I, 15 children as ASA II, and 1 child as ASA III.

The control group was made up of 36 (17 female, 19 male) patients whose median age was 5.8 (IQR 4.1) months. 19 children joined the ranks of ASA I, 16 children of ASA II, and 1 child of ASA III. With regard to these parameters, only age demonstrated a statistically significant difference between the two groups (see Table 3.1).

	Sommerlad group	**Control group**	
Gender			$p = 0.363$ *
Female	25 (59.5%)	17 (47.2%)	
Male	17 (40.5%)	19 (52.8%)	
Age (*months*)			$p < 0.001$ †
Median (IQR)	10.9 (2.6)	5.8 (4.1)	
Range	7.8–43.0	3.4–56.3	
ASA classification			$p = 0.718$ ‡
ASA I	26 (61.9%)	19 (52.8%)	
ASA II	15 (35.7%)	16 (44.4%)	
ASA III	1 (2.4%)	1 (2.8%)	

Table 3.1 – Patient Demographics and ASA Score. *[Abbreviations: ASA = American Society of Anesthesiologists; IQR = interquartile range; * Fisher's exact test; † Mann-Whitney U-test; ‡ Chi-square test]*

3.2 Cleft Characteristics

The Sommerlad group was made up of 14 cases of CL/P and 28 cases of CP. Associated congenital anomalies (i.e., syndromic clefts) were observed in approximately every fifth patient ($n = 9$). The most common associated anomaly was PRS ($n = 6$), followed by *Cri du chat* syndrome, fetal alcohol syndrome, and

trisomy 21 which were each observed once. Regarding the severity of clefts, 17 children suffered from incomplete clefts whereas 25 children were diagnosed with complete clefts. Among the OFCs that included the upper lip (*n* = 14), the ratio between unilateral and bilateral clefts was about 4:1.

By comparison, 13 children of the control group were diagnosed with CL/P and 23 children with CP. Syndromic clefts were present in 11 children. Once again, PRS was the most frequent associated anomaly (*n* = 7), followed by congenital heart defects (*n* = 3; including patent foramen ovale and atrial septum defect), and velo-cardiofacial syndrome (*n* = 1). Incomplete clefts (*n* = 16) were outweighed by complete clefts (*n* = 20). Among the children who presented with labial involvement (*n* = 13), unilateral clefts occurred in approximately 70 percent versus bilateral clefts in roughly 30 percent. Each of these cleft characteristics did not show significant differences between the two groups (see Table 3.2).

	Sommerlad group	**Control group**	
Cleft type			*p* = 0.816 *
CL/P	14 (33.3%)	13 (36.1%)	
Isolated Cleft Palate	28 (66.7%)	23 (63.9%)	
Syndromic cleft?			*p* = 0.439 *
Yes	9 (21.4%)	11 (30.6%)	
No	33 (78.6%)	25 (69.4%)	
Severity			*p* = 0.819 *
Incomplete	17 (40.5%)	16 (44.4%)	
Complete	25 (59.5%)	20 (55.6%)	
Laterality			*p* = 0.678 *
Unilateral	11 (78.6%)	9 (69.2%)	
Bilateral	3 (21.4%)	4 (30.8%)	

Table 3.2 – Cleft characteristics. Note how laterality was only assessed in cleft patients with labial involvement. *[Abbreviations: CL/P = Cleft lip with or without cleft palate; * Fisher's exact test]*

In both groups combined, considerably more males (17/27; 63.0%) were born with CL/P than females (10/27; 37.0%). On the contrary, CP occurred more frequently in girls (32/51; 62.7%) than boys (19/51; 37.3%). Regarding laterality, unilateral CL/P affected the left side 1.5 times more often than the right side (i.e., 60%

versus 40%). Moreover, syndromic OFCs (i.e., the presence of further congenital abnormalities) were associated with significantly higher ASA scores in comparison with nonsyndromic clefts (see Table 3.3).

	ASA I	ASA II	ASA III	
Syndromic cleft?				$p < 0.001$ *
Yes	4	14	2	
No	41	17	0	

Table 3.3 – Relationship Between ASA Score and Associated Anomalies. *[Abbreviations: ASA = American Society of Anesthesiologists; * Chi-square test]*

Overall, syndromic OFCs were less prevalent in children presenting with CL/P than CP (14.8% versus 31.4%). Among patients of the Sommerlad group, associated congenital anomalies affected 7.1 percent of CL/P patients and 28.6 percent of CP patients, respectively. In the control group, syndromic clefts contributed to 23.1 percent of CL/P cases and 34.8 percent of CP cases (see Figure 3.1).

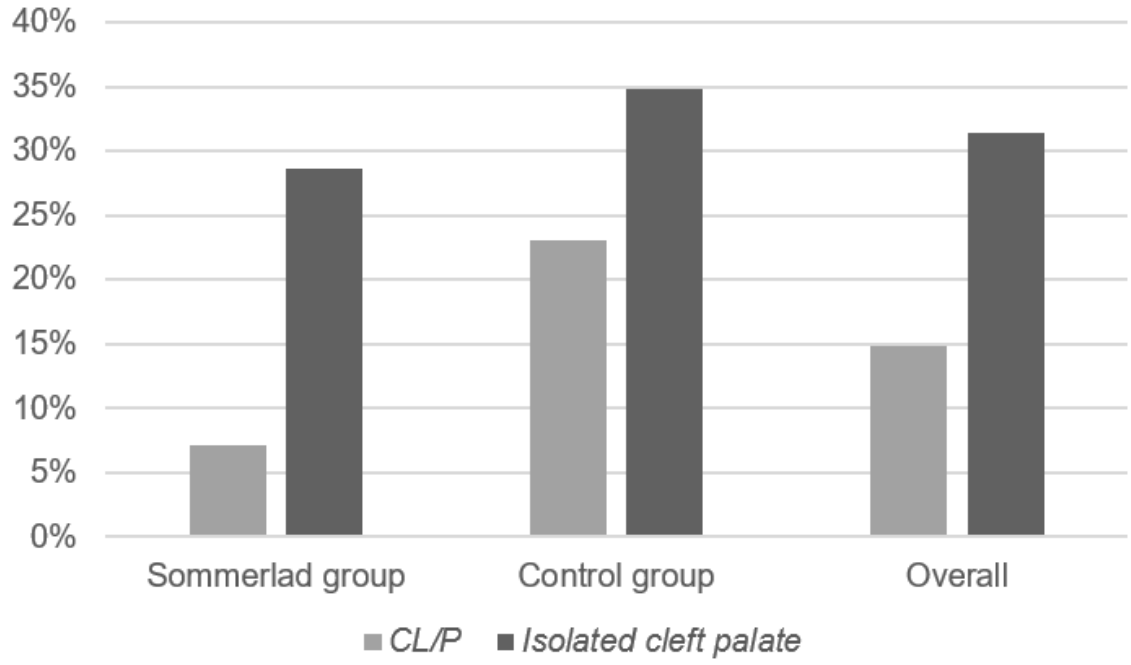

Figure 3.1 – Proportion of Syndromic Clefts to All Clefts. *[Abbreviations: CL/P = cleft lip with or without cleft palate]*

3.3 Primary Outcome – Oronasal Fistula Rate

Following primary CP repair, four children of the Sommerlad group (9.5%) developed an oronasal fistula. Regarding their categorization according to the *Pittsburgh Fistula Classification System*, half of the observed fistulas (*n* = 2) emerged at the junction of the primary and secondary palate (i.e., type V). The other two remaining oronasal fistulas were classified as type IV and type VII, respectively (see Figure 3.2).

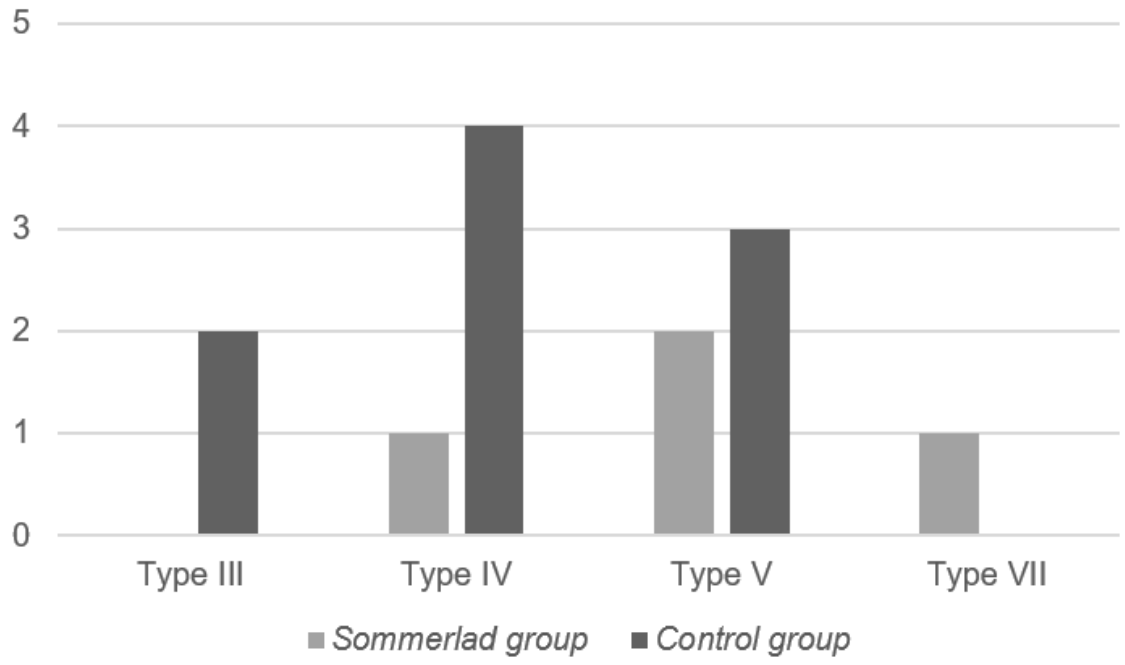

Figure 3.2 – Categorization of Oronasal Fistulas Dependent on Location. The *Pittsburgh Fistula Classification System*[242] was employed to categorize the observed fistulas.

Among children of the control group, oronasal fistulas following primary surgical repair of palatal clefts occurred in every fourth patient (9/36, 25%). Four fistulas were located at the hard palate (i.e., type IV), three fistulas at the junction between primary and secondary palate (i.e., type V), and two fistulas at the junction between hard and soft palate (i.e., type III).

The different incidences of oronasal fistulas between the two groups did not reach the level of statistical significance ($p = 0.125$; *Fisher's exact test*).

3.3.1 Risk Factor Assessment

After combination of the data of the two groups (except for age since that particular variable showed statistically significant differences), the role of the respective patient demographics and cleft characteristics as possible risk factors for oronasal fistulas was examined.

Out of the 42 female patients in total, six developed an oronasal fistula (14.3%). By comparison, fistulas were observed in seven out of 36 male patients (19.4%). Gender had no significant impact on the incidence of oronasal fistulas after primary CP repair ($p = 0.560$; *Fisher's exact test*).

In both groups, age at the time of surgical repair was not significantly associated with the occurrence of oronasal fistulas (see Table 3.4)

	Sommerlad group	**Control group**
Age (*months*)	$p = 0.466$ *	$p = 0.201$ *
No Fistula	10.6 (IQR 2.3)	6.0 (IQR 5.7)
Fistula	11.7 (IQR 4.0)	5.3 (IQR 1.8)

Table 3.4 – Relationship Between Age and Oronasal Fistula Risk. *[Abbreviation: IQR = interquartile range; * Mann-Whitney U-test]*

Slightly more than every third case of CL/P (10/27; 37.0%) resulted in the formation of an oronasal fistula. Children presenting with CP, on the other hand, developed fistulas in three out of 51 cases in total (5.9%). This difference was statistically significant ($p < 0.001$; *Fisher's exact test*).

Oronasal fistulas were also significantly more often seen with increased cleft severity ($p = 0.036$; *Fisher's exact test*). In fact, the relative risk in complete OFCs (11/45; 24.4%) was roughly four times than the one in incomplete OFCs (2/33; 6.1%).

On the contrary, laterality had no significant influence on the occurrence risk of oronasal fistulas ($p = 0.065$; *Fisher's exact test*). Every fourth child with unilateral

clefting developed fistulas (5/20; 25.0%) whereas bilateral clefts resulted in the formation of a fistula in approximately 70 percent of all cases (5/7; 71.4%).

Associated congenital anomalies (i.e., syndromic OFCs) also did not lead to a statistically significant (p = 0.496; *Fisher's exact test*) alteration of the oronasal fistula incidence (2/20; 10.0%) when compared with nonsyndromic clefts (11/58; 19.0%).

Furthermore, a potential relationship between ASA score and fistula risk was not detected (see Table 3.5).

	No Fistula	**Fistula**	
ASA classification			p = 0.208 *
ASA I	36 (80.0%)	9 (20.0%)	
ASA II	28 (90.3%)	3 (9.7%)	
ASA III	1 (50.0%)	1 (50.0%)	

Table 3.5 – Relationship Between ASA Score and Oronasal Fistula Risk. *[Abbreviations: ASA = American Society of Anesthesiologists; * Chi-square test]*

Within the control group, utilization of a surgical microscope resulted in a significantly decreased risk of oronasal fistulas (1/15 (6.7%) versus 8/21 (38.1%); p = 0.036; *Fisher's exact test*).

3.4 Secondary Outcomes – Perioperative Measures

3.4.1 Duration of Surgery

The mean (± standard deviation, SD) DOS in children allocated to the Sommerlad group accounted for 138.4 (±36.6) minutes. By comparison, the mean DOS in children of the control group was 127.2 (±59.8) minutes. There was no significant difference between the two groups (see Table 3.6, page 50). However, after exclusion of the CL/P patients from the control group since these individuals were managed using the all-in-one approach (i.e., they received concomitant cleft lip repair), the mean DOS became significantly shorter (94.6 ±34.0 minutes; p < 0.001).

In both groups combined, ASA status had no effect (p = 0.820; *ANOVA*) on the mean DOS (130.8 ±46.7 minutes with ASA I, 137.4 ±66.0 minutes with ASA II, 124.0 ±25.5 minutes with ASA III). The absence or presence of associated congenital anomalies also did not influence DOS (133.1 ±52.5 versus 133.7 ±36.4 minutes; p = 0.965; *Student's t-test*). Kendall's tau-b correlation coefficient failed to detect any relationship between the children's age and DOS (τ = 0.022; p = 0.779).

	Sommerlad group	**Control group**	
DOS (*minutes*)			p = 0.334 *
Mean (±SD)	138.4 (±36.6)	127.2 (±59.8)	
Range	82–221	49–278	
LOS (*days*)			p < 0.001 †
Median (IQR)	4 (2)	5.5 (4)	
Range	2–9	2–9	
Adverse events			p = 0.801 ‡
Yes	12 (28.6%)	9 (25.0%)	
No	30 (71.4%)	27 (75.0%)	

Table 3.6 – Perioperative Measures. *[Abbreviations: DOS = duration of surgery; IQR = inter-quartile range; LOS = length of in-hospital stay; SD = standard deviation; * Student's t-test; † Mann-Whitney U-test; ‡ Fisher's exact test]*

Within the Sommerlad group, intraoperative administration of TXA resulted in significantly prolonged surgical procedures (146.4 ±35.0 versus 104.4 ±20.6 minutes; p = 0.002; *Student's t-test*). Among patients of the control group, the use of a surgical microscope did not significantly contribute to a longer DOS (133.7 ±65.3 versus 122.6 ±56.8 minutes; p = 0.296; *Student's t-test*).

3.4.2 Length of In-Hospital Stay

The median LOS in children who underwent SR-IVVP accounted for 4 (IQR 2) days. When compared with the median LOS of 5.5 (IQR 4) days in patients belonging to the control group, a statistically significant difference became evident (see Table 3.6).

In both groups combined, ASA scores were not significantly related to the median length of hospitalization (see Table 3.7). However, children with syndromic clefts (i.e., the presence of associated congenital anomalies) stayed significantly longer in hospital than children with nonsyndromic clefts (i.e., 6 (IQR 5) versus 4 (IQR 1) days; $p = 0.009$; *Mann-Whitney U-test*). The children's age at the time of surgical repair showed a weak inverse correlation to the median LOS ($\tau = -0.368$; $p < 0.001$; *Kendall's tau-b correlation coefficient*). The average DOS, on the other hand, did not correlate to length of hospitalization ($\tau = 0.123$; $p = 0.145$; *Kendall's tau-b correlation coefficient*).

	ASA I	**ASA II**	**ASA III**	
LOS (*days*)				$p = 0.171$ *
Median (IQR)	4 (2)	5 (4)	5.5 (-)	
Range	2–9	2–9	5–6	

Table 3.7 – Relationship Between ASA Score and Length of Hospitalization. *[Abbreviations: ASA = American Society of Anesthesiologists; IQR = interquartile range; LOS = length of in-hospital stay; * Kruskal-Wallis test]*

3.4.3 Post-operative Adverse Events

Post-operative adverse events (e.g., fever, infection, or bleeding; see Figure 3.3, page 52) occurred in twelve out of the 42 girls and boys who underwent SR-IVVP (28.6%). By comparison, one fourth of the children who were assigned to the control group experienced post-surgical adverse events (9/36; 25.0%). This difference was not statistically significant (see Table 3.6).

In both groups combined, the occurrence of adverse events following surgery was associated with both significantly longer DOS (166.8 ±48.8 versus 120.9 ±42.8 minutes; $p < 0.001$; *Student's t-test*) and LOS (5 (IQR 5) versus 4 (IQR 1) days; $p = 0.041$; *Mann-Whitney U-test*).

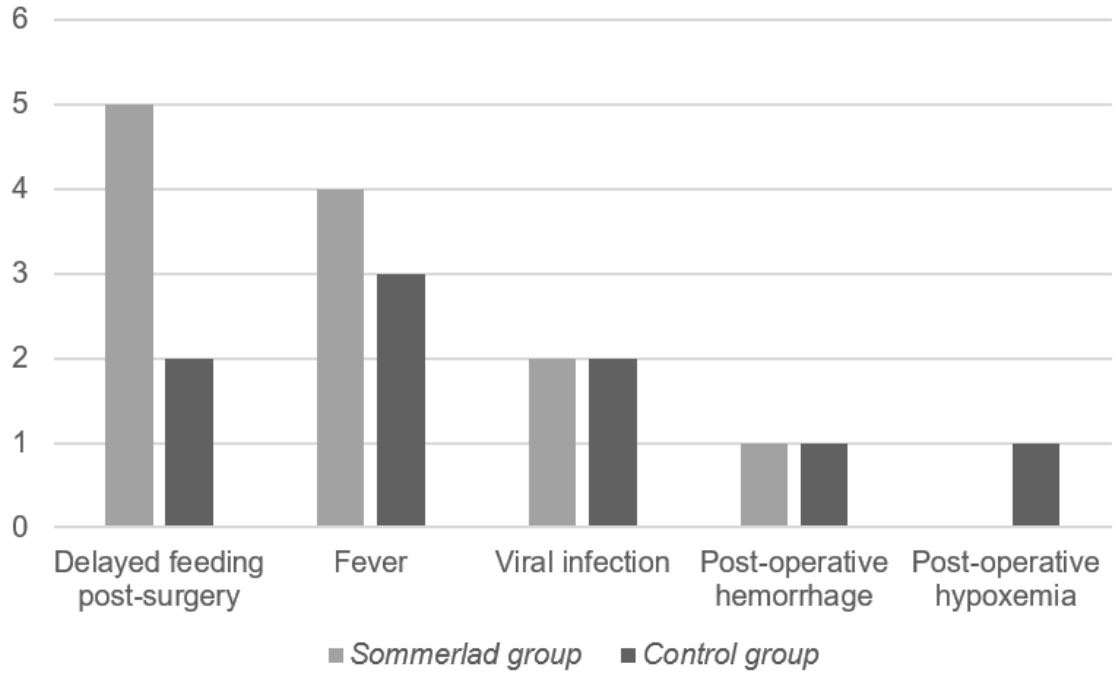

Figure 3.3 – Spectrum of Observed Post-operative Adverse Events.

The differences regarding the median age of children with (9.5 (IQR 4.8) months) and without (9.1 (IQR 5.6) months) post-operative adverse events did not reach the level of statistical significance (p = 0.834; *Mann-Whitney U-test*). The presence of associated congenital anomalies, however, resulted in a significantly increased risk of experiencing post-surgical adverse events when compared with nonsyndromic clefts (9/20 (45.0%) versus 12/58 (25.9%); p = 0.044; *Fisher's exact test*).

3.4.4 Complementary Surgical Procedures

Among all children who underwent SR-IVVP for primary CP repair (i.e., the Sommerlad group), complementary surgical approaches (e.g., LLR, BFPF, and/or A-stitch) were employed in roughly three out of four patients (31/42; 73.8%).

Between children who received SR-IVVP alone and those who received SR-IVVP plus complementary surgical procedures, significant differences regarding age at time of surgery, cleft type, cleft severity, and DOS were observed (see Table 3.8, page 52). On average, children who underwent SR-IVVP plus LLR, BFPF, and/or A-stitch were approximately one month younger than those children who did not.

Moreover, CL/P and complete clefts required extensive surgery (i.e., SR-IVVP plus complementary surgical procedures) more often than CP and incomplete clefts, respectively. The decision to augment SR-IVVP with the already described procedures resulted in longer DOS (see Figure 3.4).

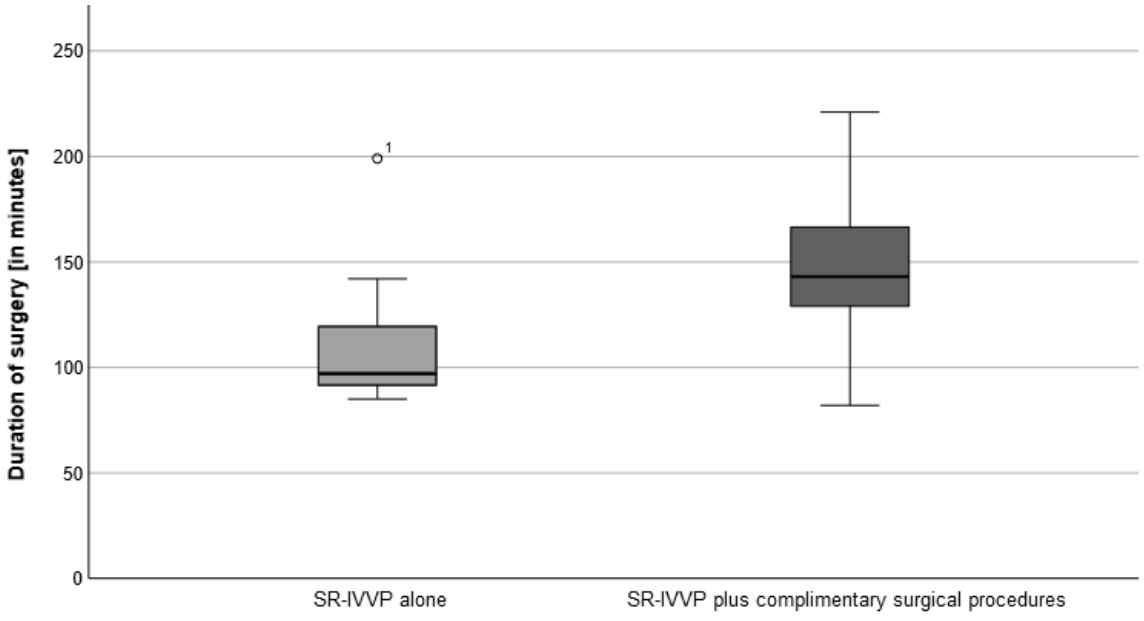

Figure 3.4 – Impact of Complementary Surgical Procedures on DOS. *[Abbreviations: DOS = duration of surgery; SR-IVVP = Sommerlad radical intravelar veloplasty]*

As opposed to those variables, presence or absence of associated congenital abnormalities, median length of hospitalization, post-operative adverse events, and oronasal fistula occurrence risk demonstrated no statistically significant differences between the aforementioned subgroups (see Table 3.8, page 54).

	SR-IVVP alone	SR-IVVP plus CSP	
Age (*months*)			*p* = 0.045 *
Median (IQR)	11.5 (5.5)	10.0 (2.2)	
Range	8.5–43.0	7.8–13.8	
Cleft type			*p* = 0.007 †
CL/P	0 (0.0%)	14 (45.2%)	
Isolated cleft palate	11 (100.0%)	17 (54.8%)	
Syndromic cleft?			*p* > 0.999 †
Yes	2 (18.2%)	7 (22.6%)	
No	9 (81.8%)	24 (77.4%)	
Severity			*p* = 0.003 †
Incomplete	9 (81.8%)	8 (25.8%)	
Complete	2 (18.2%)	23 (74.2%)	
Oronasal fistula			*p* = 0.558 †
Yes	0 (0.0%)	4 (12.9%)	
No	11 (100.0%)	27 (87.1%)	
DOS (*minutes*)			*p* = 0.003 ‡
Mean (±SD)	111.5 (±33.9)	147.9 (±33.0)	
LOS (*days*)			*p* = 0.730 *
Median (IQR)	4 (1)	4 (2)	
Range	3–5	2–9	
Adverse events			*p* = 0.133 †
Yes	1 (9.1%)	11 (35.5%)	
No	10 (90.9%)	20 (64.5%)	

Table 3.8 – SR-IVVP Versus SR-IVVP plus Complementary Procedures. *[Abbreviations: CL/P = cleft lip with or without cleft palate; CSP = complementary surgical procedures; IQR = interquartile range; SD = standard deviation; SR-IVVP = Sommerlad radical intravelar veloplasty; * Mann-Whitney U-test; † Fisher's exact test; ‡ Student's t-test]*

4 Discussion

OFCs describe a spectrum of congenital malformations limited to the upper lip and/or the palate that include both CL/P and CP.[1,2] Combined, they represent the most common congenital anomaly of the craniofacial region.[13] OFCs have the potential to substantially influence the affected individuals' long-term health, socioeconomic and psychosocial wellbeing as well as overall quality of life.[4,6] Thus, multidisciplinary treatment addressing the manifold issues associated with OFCs is initiated shortly after birth and frequently extends into adulthood.[4,5] The surgical management of palatal clefts aims to restore the functional impairments (e.g., speech dysfunction) resulting from the underlying anatomical defect through closure of the continuity between oral and nasal cavity as well as reconstitution of the aberrantly inserted velar muscles.[2,229] Thus, speech assessment protocols (e.g., the Great Ormond Street Speech Assessment, GOS.SP.ASS) are valuable tools to judge the long-term success of primary CP repair.[238,245] The evaluation of post-operative occurrence of oronasal fistulas, on the other hand, usually only requires three months of follow-up and is therefore an excellent short-term quality indicator of primary palatoplasty.[241,246]

SR-IVVP can be understood as a modification of conventional IVVP which involves comparably more radical levator muscle retropositioning through transection of the tensor tendon or extensive dissection of the velar muscles from the oral and nasal mucosa, thus theoretically yielding improved palatal function.[2,236,247] As a matter of fact, multiple studies were able to demonstrate that SR-IVVP is associated with superb results in terms of oronasal fistula incidence, speech development, and middle ear outcomes.[246,248-251]

In this study, the incidence of oronasal fistulas following primary CP repair using SR-IVVP at the *Division of Oral and Maxillofacial Surgery* in Graz, Austria was retrospectively examined. Also, secondary measures such as gender, age at time of surgery, cleft type, and cleft severity were assessed regarding their role as possible risk factors for the occurrence of oronasal fistulas.

4.1 Patient Demographics

According to the literature, CL/P is more common in boys (3:2 male-to-female predominance) while CP can be slightly more often observed in girls (5:4 female-to-male predominance).[17] After merger of both study groups, rudimentarily comparable gender distributions in terms of the two cleft types were observed.

Regarding the ideal time for primary CP repair, most surgeons follow the practice of executing surgery at an age of 10-12 months.[231] In his original description of SR-IVVP, Sommerlad stated that all patients were operated before they reached the age of 12 months.[236] Managing the balancing act between unfavorable speech and language development related to delayed surgical repair and potential interference with midface growth related to early palatoplasty is the main challenge of determining optimal timing of repair.[228] Those children who underwent SR-IVVP in Graz had a median age that fell within this time frame. On the contrary, children of the control group were significantly younger at the time of surgery. It is not unlikely that this effect can be ascribed to the concomitant repair of labial and palatal clefts in patients presenting with CL/P since CL repair is typically recommended to be performed at an approximate age of three months.[2] Published papers about the timing of single-stage CLP repair show considerable variation with reported mean ages including 3 months, 7 months, 9 months, and 14.4 months.[252,253]

The *ASA Physical Status Classification System* is a commonly used method to determine a patient's physical fitness prior to surgery.[254] In combination with other factors (e.g., age, type and complexity of surgical intervention, nutritional status), it can advantageously add to the preoperative evaluation of expectable risks and outcomes.[255] In this study, an overwhelming majority of children classified as either ASA I or ASA II (97.6% in the Sommerlad group and 97.2% in the control group, respectively). To the best of the author's knowledge, no reports regarding the ASA status of pediatric patients undergoing primary CP repair have been published. Lee and Peacock evaluated the risk for perioperative complications in cleft patients undergoing orthognathic surgery compared with noncleft patients. Although individuals allocated to the cleft group were less likely to be considered a normal healthy patient (i.e., ASA I), approximately six out of seven (86.8%) still

classified as either ASA I or ASA II.[256] The examined patient population, however, was on average 27.7 years old (17.7 years in cleft patients versus 28.6 years in noncleft patients) which limits its validity as a reference for interpretation of the observed ASA score distribution among infants receiving primary CP repair surgery. In spite of its importance with regard to normal speech development in children with palatal clefts, primary palatoplasty is not essential for survival. As a matter of fact, Sándor-Bajusz et al. observed notable delays in the timing of CP repair in patients with syndromic clefts. Main causes of postponement of primary palatoplasty were airway issues and feeding problems. In other cases, cardiorespiratory and urogenital interventions were prioritized over surgical cleft closure.[116] Furthermore, Crockett and Goudy reported significant deferral of CP surgery in patients with PRS for the sake of avoiding airway obstruction.[228] Against the background of palatoplasties being highly elective procedures, it is probable that very few patients scheduled for primary CP repair do not classify as either ASA I or ASA II.

4.2 Cleft Characteristics

Referring to the U.S. population-based estimates for major birth defects, CL/P contributes to approximately 60 percent of OFCs whereas CP makes up for the remaining cases.[13] In this study, both groups (i.e., Sommerlad and control group) featuered a larger share of children with CP (66.7% and 63.9%, respectively). This discrepancy, however, is not surprising since the focus on primary CP repair resulted in a selection bias and exclusion of individuals with isolated labial clefts.

OFCs that occur in conjunction with additional physical or cognitive abnormalities (e.g., heart defects) are referred to as syndromic clefts.[35] They contribute to roughly 30 percent of CL/P and about 50 percent of CP cases.[115] VWS is rated as the most common representative of syndromic OFCs.[35,38] In this study, the prevalence of associated congenital anomalies was higher among children with CP in comparison to children with CL/P. However, the observed proportions did not quite reach the abovementioned likes of textbook descriptions. Different population-based studies from all around the world revealed sizable variability concerning the frequency of associated malformations in OFCs (e.g., 2.9% in

China, 4.1% in Hungary, 7.6% in India, 7.7% in Iran, 21.0% in Sweden, 21.1% in Burkina Faso, 22.0% in South Africa, 36.7% in France, and 38.8% in the United Kingdom).[116,257-260] According to Venkatesh, significant underestimation of the true frequency of syndromic clefts is probable when spontaneous abortions, elective terminations, stillborn fetuses, and early deaths of affected babies are disregarded.[257] VWS has repeatedly been described as the most prevalent form of syndromic OFCs.[35,38] This finding was also confirmed by Gallagher and colleagues.[261] In this study, however, PRS contributed to more than half of the observed syndromic clefts. Similarly, the retrospective study of Sándor-Bajusz et al. detected that PRS comprised 50 percent of all clefts with associated anomalies.[116] In another study from Norway, PRS was recorded in 11.7 percent of all OFC patients and 38.3 percent of patients with associated anomalies.[262]

With regard to the laterality of OFCs, unilateral clefts are found to affect the left side considerably more often than the right side, and unilateral clefts in general are about twice as common as bilateral clefts.[15] Data from this study supports these descriptions. Left predominance in unilateral OFCs has also been observed by others.[263,264] More frequent occurrence of left-sided unilateral clefts is indicative of directional (i.e., systematic preference of a trait to one or the other side during development) rather than fluctuating asymmetry (i.e., random variation resulting in a trait to equally affect the left or ride sight).[265] Clefts on the ride sight are associated with comparably more pronounced lateral lip element hypoplasia as well as greater deficiency of lateral lip element vertical height and vermillion height, thus suggesting increased severity.[264] In fact, a global survey of clefts surgeons has shown that right-sided clefts are perceived to pose a greater surgical challenge than left-sided ones.[266]

4.3 Oronasal Fistula Risk

Oronasal fistulas are defined as an abnormal oronasal communications resulting from “failure of healing or […] breakdown in the primary surgical repair of the palate”.[243] They rank among the most frequently encountered complications of CP surgery.[267] Symptomatic fistulas can cause nasal air escape, nasal regurgitation, speech impairment (i.e., hypernasality), and VPD.[267-269] Further

consequences of oronasal fistulas include scarring that may impede maxillary growth, collapse of adjacent tissues, and social stigmatization.[270] The occurrence of oronasal fistulas following CP surgery is primarily ascribed to cleft closure under tension.[267] Indeed, Simpson et al. recognized tension-free repair as the probably most important factor for minimization of the risk of oronasal fistula.[268] Losee and colleagues went even further and introduced an algorithm for limiting fistulas following palatoplasty in OFC patients which encourages the use of relaxing incisions (e.g., LLRs), complete IVVP, full mobilization of the tensor tendon at the level of the pterygoid hamulus, complete dissection of the greater palatine neurovascular bundle (including the option of greater palatine foraminal osteotomy), and utilization of acellular dermal matrix to achieve adequate reconstruction of the nasal lining as well as sufficient two-layer closure.[271] Completely asymptomatic fistulas may simply be observed. Upon manifestation of symptoms, however, appropriate management becomes necessary.[272] Whereas the treatment of anterior fistulas (i.e., fistulas in the region of the alveolar ridge) can be usually postponed until they are closed in the mixed dentition with simultaneous bone grafting, posterior fistulas (i.e., fistulas at the junction between hard and soft palate) typically require surgical management through secondary palatoplasty in a timely manner.[273] A number of different surgical approaches and techniques for the repair of oronasal fistulas (e.g., two-layer closure of with advancement of local tissues, utilization of acellular dermal matrix grafts, or interposition of amniotic membrane allografts) have been described so far, with no definite consensus having been found yet.[274-277] Under special circumstances (e.g., repeated failure of fistula repair through secondary palatoplasty and local flap techniques), even microvascular tissue transfer may become a suitable option. In this context, Zemann et al. advocate the radial free forearm flap as the flap of choice.[273]

A comprehensive review by Hardwicke et al. which included more than 9,000 patients from 44 different studies found that the overall incidence of oronasal fistulas following primary CP repair is 8.6 percent (95% confidence interval, 6.4-11.1%).[278] The observed fistula rate from this study's Sommerlad group (9.5%) fell within this range. Reporting their respective experience with fistula formation after SR-IVVP, Mapar et al. noted a similar frequency of 7.5%.[279] An even lower

fistula rate (4.7%) after Sommerlad palatopasty was disclosed by Becker and Hansson.[246] The incidence of oronasal fistulas in this study's control group amounted to 25.0 percent. Since these patients underwent conventional IVVP which employs less extensive mobilization of velar muscles when compared with SR-IVVP.[2,236,247] The thereby resulting increased tension during closure of the palatal cleft may explain for the observed higher fistula frequency.

Regarding the anatomical distribution of oronasal fistulas (based upon the *Pittsburgh Fistula Classification System*), a meta-analysis by Bykowski et al. defined the junction between hard and soft palate (i.e., type III) and the hard palate (i.e., type IV) as the most common locations in which 50.0 and 32.6 percent of all fistulas occurred, respectively.[242,280] Cumulated appearance of oronasal fistulas at the hard palate-soft palate junction can be ascribed to the dynamic character of this area which regularly leads to cleft closure under tension.[280] Among patients of this study's control group, the recorded localization of fistulas rudimentarily corresponded to the abovementioned descriptions (type III in 22.2%, type IV 44.4%). In contrast, the anatomical distribution of fistulas in patients who were allocated to the Sommerlad group was distinctly different (no type III fistulas, type IV 25.0%). It is likely that this discrepancy is related to the limited sample size, thus representing a chance finding.

With reference to the risk of post-operative formation of oronasal fistulas, cleft type and cleft severity have been identified as possible risk factors. As a matter of fact, CL/P and complete clefts resulted in a higher likelihood of fistulas than CP and incomplete clefts, respectively.[235,278,281,282] Data from this study is in accordance with these reports. Gender, on the other hand, does not influence the frequency of fistulas following primary CP repair.[282-285] A potential relationship between age at the time of surgery and post-operative fistula incidence has also been denied by multiple authors.[235,282,284,285] However, Pollard et al. defined advanced age at CP repair as a protective factor whilst Aldaghir et al. associated earlier surgery with less likely development of fistulas.(241,283) Furthermore, the presence of associated comorbidities or syndromes as another possible risk factor for the post-operative occurrence of fistulas in OFC patients was repetitively disproven.[235,282,284] Only Saothonglang et al. described syndromic clefts as

predictive factors for oronasal fistulas.[281] In this study, gender, age at time of surgical repair, and association with other congenital abnormalities did not significant contribute to the observed frequency of post-operative fistulas. Cleft width, which has not been examined in this study, was not related to a higher fistula risk according to Yuan et al. and Mahoney et al., whereas Saothonglang and colleagues described it as another predictive factor.[281,285,286]

Among children of the control group, the utilization of a surgical microscope resulted in significantly less oronasal fistulas following primary CP repair. Despite the existence of multiple studies on advantages and disadvantages of the implementation of microscopy in cleft surgery, no reports regarding the possible effects on post-operative fistula rate have been published so far. However, the use of surgical microscopes for repair of OFCs has been repeatedly cherished for its improved visualization of the anatomical structures of interest which in turn facilitates more precise dissection.[287-289] Therefore, a protective effect of surgical microscopes regarding oronasal fistula risk can be suspected.

Last but not least, use of acellular dermal matrix during initial CP repair is another factor that is suspected to minimize the risk of fistulas following primary palatoplasty.[290]

4.4 Perioperative Factors

4.4.1 Duration of Surgery

The mean DOS accounted for 138.4 and 127.2 minutes in the Sommerlad group and control group, respectively. For comparison purposes, a study by Blough et al. which included 3,616 patients undergoing primary palatoplasty reported an average operative time of 135.4 minutes.[291] In this study, ASA status, absence or presence of associated comorbidities or syndromes, and age at the time of surgery did not significantly influence DOS.

TXA was administered in approximately four out of five children of the Sommerlad group and was associated with significantly longer DOS. TXA is a synthetic derivative of the amino acid lysine that possesses antifibrinolytic properties

through blockage of lysine binding sites on plasminogen molecules, thus inhibiting plasminogen activation which subsequently leads to stabilization of the preformed fibrin meshwork produced by secondary hemostasis.[292] Durga et al. conducted a prospective, randomized clinical study in which the effects of TXA on the surgical field in primary palatoplasty was examined. Intravenous bolus administration of 10 mg/kg TXA fifteen minutes prior to incision led to improved intraoperative visibility as well as greater surgeon's satisfaction with the surgical field.[293] According to the systematic review by Sheil et al., further studies confirmed the beneficial impact of TXA on blood loss and quality of surgical field.[294] Local (i.e., topical) use of TXA was found to yield similar results regarding blood loss minimization while also reducing the risk of adverse effects associated with systemic exposure (e.g., venous thromboembolism, seizures).[295,296] Although Durga et al. were unable to find a statistically significant difference in the DOS between the TXA and the placebo group, it is at a first glance counterintuitive that administration of TXA should result in longer operating times as it was in fact observed in this thesis paper's study.[293] However, children allocated to the Sommerlad group were only then given TXA when profuse bleeding substantially impeded the overall visibility of the surgical field. Thus, the observation that TXA administration correlated with prolonged DOS can be interpreted as an epitome of selection bias.

4.4.2 Length of In-Hospital Stay

Median LOS following SR-IVVP was 4 days while children of the control group stayed significantly longer in hospital (5.5 days). By comparison, among 3,616 primary palatoplasty patients evaluated by Blough et al., the average length of hospitalization was less than two days.[291] Against that backdrop, a median LOS of 4 or 5.5 days may appear unreasonably long. However, the publicly funded Austrian health care system allows doctors to keep the children in hospital until their parents or legal guardians feel secure enough to offer sufficient post-operative care without professional supervision.

Data from this study did not reveal a relationship between LOS and ASA score, whereas Blough et al. observed more prolonged hospitalization with patients with ASA III or higher.[291] Significant longer LOS for children with syndromic clefts was

found after critical analysis of the data from Graz. Similarly, Fitzsimons et al. reported that children without additional anomalies spent on average 2.2 days less in hospital for cleft-related care than children with additional anomalies.[297] This study's inverse correlation between LOS and age at the time of surgery indicated that younger children have a tendency to stay slightly longer in hospital. Considering the τ-value of -0.368, this correlation can be interpreted as negligible. Likewise, Izadi and Haers as well as Peck et al. also disregarded age in the context of post-operative LOS as insignificant.[298,299]

4.4.3 Post-operative Adverse Events

Post-operative adverse events occurred in approximately every fourth patient in both the Sommerlad group and the control group. Other studies reported much lower complication rates that ranged from 3.4 to 7.6 percent.[291,299,300] Uncertainty regarding the true definition of an adverse event following primary palatoplasty may explain for this discrepancy. For instance, this study also listed delayed feeding post-surgery and fever as complications. Following their exclusion, the adjusted complication rate (i.e., 7.1% in the Sommerlad group and 11.1% in the control group) was considerably closer to the abovementioned observations in the literature.

Of all noted adverse events in this study, only one case of post-operative hemorrhage required reoperation. Another child presenting with post-operative hypoxemia was monitored in the pediatric intensive care unit for five days.

Children of the Sommerlad group as well as the control group had a higher risk of developing post-operative adverse events with increased DOS. The presence of associated congenital abnormalities also contributed to the likelihood of adverse effects. Age at time of surgery, however, was not associated with an increased risk of experiencing post-surgical adverse events. On the contrary, Peck et al. described a significantly higher complication rate in children undergoing CP repair before the age of six months.[299]

4.4.4 Complementary Surgical Procedures

Complementary surgical procedures such as LLRs, BFPFs, and A-stitch were employed in the vast majority of patients who underwent SR-IVVP. Their application served the purpose of reducing tension during clef closure, thereby minimizing the risk of oronasal fistulas. Since these procedures require additional surgical steps, it is easy to understand why they were associated with significantly longer DOS. Overall, CL/P and complete clefts resulted in a considerably higher rate of complementary surgical procedures. Regarding the frequency of oronasal fistulas following primary palatoplasty, however, no statistically significant difference between children who received any of the aforementioned additional procedures and those who did not could be found.

Sufficient mobility of the mucoperiosteal flaps to facilitate tension-free closure has been named as the main reason for the application of LLRs during primary CP repair.[196,271] As a matter of fact, Losee et al. specifically addressed LLRs as part of their algorithm for limiting post-operative oronasal fistulas.[271] On the contrary, Sommerlad claimed that radical mobilization of the velar muscles during SR-IVVP makes LLRs unnecessary for the most part.[236] According to Sakran et al., avoidance of relaxing incisions began to be emphasized when evidence suggested that they could inhibit maxillofacial growth.[237] Nonetheless, different opinions regarding the value of LLRs continue to exist.[192]

The buccal fat pad belongs to the group of deep fat compartments of the face and is situated between the superficial musculoaponeurotic system and the buccinator muscle.[301] Multiple maxillofacial surgical procedures that may successfully use BFPFs have been described.[302] In the context of primary CP repair, it has been repetitively advocated as an adjunctive procedure which can reduce the rate of post-operative oronasal fistulas.[303,304] Advantages of BFPFs include the fat pad's excellent vascularity, minimal morbidity following easy harvest through simple procedures, and maintenance of facial function.[302,303] Regarding the safety of buccal fat pad harvest, Rohrich and Jalalabadi coined the "Five Ds". Strict adherence to this uncomplicated five-step technique should enable surgeons to yield both safe and effective results.[305] Addressing the concerns over possible facial esthetic impairments following use of the buccal fat pad in CP surgery,

Bennett et al. came to the conclusion “that there is no statistically or clinically significant volume difference”, thus ruling out the risk of iatrogenic facial asymmetry.[306] Nonetheless, Rohrich et al. remarked that potential long-term effects such as accelerated facial aging have not been satisfactorily examined yet. Consequently, buccal fat pad excision should be reserved for appropriately selected patients.[307] On a related note, Echlin et al. acknowledge that flap harvest usually leaves two-thirds of the buccal fat pad within the cheek which in turn protects against unwanted changes in esthetics of the face.[301] Alternative to its utilization as a complementary surgical procedure during primary palatoplasty, the buccal fat pad can also be used as a free graft for surgical closure of already existent fistulas.[301,308]

4.5 Perioperative Management

On the basis of studies that have shown as association between certain pathogens and oronasal fistula formation, some cleft surgeons have argued in favor of administration of perioperative antibiotics at the time of palatoplasty.[309,310] Unfortunately, no consensus or formal recommendations regarding surgical antibiotic prophylaxis in palatoplasty exist.[310,311] Rottgers et al. recommend the pre-operative administration of antibiotic agents that provide coverage against representatives of the diverse oral flora (e.g., ampicillin/sulbactam).[310] Likewise, Pfaff et al. state that the use of pre-operative antibiotics in patients who are scheduled to undergo CP repair is supported by the literature.[311] However, the practice of placing patients on prolonged post-operative antibiotic courses, as it is currently handled in Graz, remains questionable.[310,311] Jodeh et al. were unable to find evidence that prophylactic antibiotics reduce the risk of oronasal fistulas.[309] Considering the possible local and systemic morbidities associated with perioperative infections, surgical antibiotic prophylaxis is encouraged nonetheless.[310]

In regard to the appropriate perioperative pain management in CP surgery, nonopioid analgesics such as acetaminophen or nonsteroidal anti-inflammatory drugs (e.g., ibuprofen) should be prioritized.[312] Since children affected by OFCs typically have to undergo multiple surgeries from infancy until early adulthood, the

potential long-term neurocognitive and psychomotor effects associated with exposure to chronic opioid therapy have to be carefully considered.[313] Pre-incisional nerve blocks with long-acting anesthetics (e.g., bupivacaine) result in improved post-operative pain management and are superior to pre-incisional surgical-site infiltrations. Nerve blocks commonly employed for palatoplasty include maxillary, sphenopalatine, and greater/lesser nasopalatine nerve blocks.[312]

4.6 Limitations

Regarding possible limitations of this study, larger sample sizes would most likely have had a favorable effect on statistical analysis. For instance, it is possible that the rates of oronasal fistulas between the Sommerlad group and control group are in fact significantly different from each other. In that case, the actually observed *p*-value of 0.125 would simply have indicated an insufficient sample size. Against this backdrop, execution of an *a priori* power analysis as a means to calculate the correct sample size would have been beneficial as well. However, the sample size was predetermined by the number of eligible primary CP repairs that were carried out at the *Division of Oral and Maxillofacial Surgery* in Graz, Austria up to the present point in time.

Moreover, the retrospective design of the study has to be critically mentioned. It is a matter of common knowledge that retrospective studies have significant disadvantages such as multiple sources of bias (e.g., selection bias, loss of follow-up).[314] Thus, a prospective study extending over a time period of several years may provide more reliable data.

In summary, this study leaves room for improvement. However, the abovementioned suggestions regarding an alternative study design would have gone beyond the scope of a curricular thesis paper. Nonetheless, they should be considered if further studies intending to assess the quality of primary palatoplasty were to be planned.

4.7 Conclusion

In their 16-year review of clinical practice patterns in CP repair in the U.S., Kearney et al. found that IVVP increased in use whilst other palatoplasty techniques (e.g., von Langenbeck, Furlow) decreased.[300] In this context, Sommerlad's modification of IVVP (i.e., SR-IVVP) has to be specifically mentioned as its principles facilitate the achievement of satisfactory functional results as well as minimization of the need for secondary palatoplasty.[315]

The findings of this thesis paper's study demonstrate that the adoption of SR-IVVP as the standard primary CP repair technique at the *Division of Oral and Maxillofacial Surgery* in Graz, Austria resulted in an oronasal fistula incidence that corresponds to the published international standard. Although not reaching the level of statistical significance, SR-IVVP was also associated with less frequent fistula formation than conventional IVVP. Taking all observations into consideration, it can be concluded that SR-IVVP represents a safe and effective method for primary palatoplasty.

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