EGAS MONIZ SCHOOL of HEALTH & SCIENCE | INSTITUTO UNIVERSITÁRIO EGAS MONIZ

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MESTRADO INTEGRADO EM MEDICINA DENTÁRIA

PIERRE ROBIN SYNDROME : DIAGNOSIS AND OROFACIAL MANIFESTATIONS

Trabalho submetido por

MOHAMED ALI DOUSS

para a obtenção do grau de Mestre em Medicina Dentária

Julho de 2024

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Prof. Doutor José Manuel Furtado

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ABSTRACT

This narrative review provides an overview of the current understanding of Pierre Robin Syndrome (PRS) as a genetic disease. The gene SRY-box 9 (SOX9) is identified as the most common genetic factor associated with PRS, syndromic or not. Additionally, it discusses modern strategies for prenatal ultrasound diagnosis, emphasizing its significance in the early detection of micro anomalies related to possible genetic syndromes. The interaction between oral conditions and dental phenotypes of PRS is also evaluated, underscoring the importance of oral health. Finally, the critical role of the dentist in the comprehensive care of individuals with PRS is addressed, highlighting their involvement in multidisciplinary approaches and continuous management of oral and dental health to improve patients' quality of life.

Key-words: Micrognathia, Glossoptosis, Cleft Palate, Airway Obstruction

RESUMO

Esta revisão narrativa proporciona uma visão geral da compreensão atual da Síndrome de Pierre Robin (SPR) como uma doença genética. Explora-se o gene SOX9 (SRY-box 9) como sendo o fator genético mais comum associado à SPR, sindrómica ou não. Além disso, discutem-se as mais recentes estratégias de diagnóstico pré-natal ecográfico, destacando a sua relevância na deteção precoce de microanomalias relacionadas com possíveis síndromes genéticas. Avalia-se também a interação entre condições orais e os fenótipos dentários da SPR, realçando a importância da saúde oral. Finalmente, destaca-se o papel crucial do médico dentista na abordagem multidisciplinar e na gestão contínua da saúde oral e dentária dos pacientes com SPR, visando melhorar sua qualidade de vida.

Palavras-chave: Micrognatia, Glossoptose, Fenda palatina, Obstrução das vias aéreas

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LIST OF ABBREVIATIONS

AHI - Apnea-Hypopnea Index

AI - Artificial Intelligence

AO - Airway Obstruction

BMP - Bone Morphogenetic Protein

BWS - Beckwith-Wiedemann Syndrome

CAD - Computer-Aided Design

CAM - Computer-Aided Manufacturing.

CBCT - Cone Beam Computed Tomography

CHARGE - Coloboma, Heart defects, Atresia choanae, Growth retardation, Genital abnormalities, and Ear abnormalities

CMA - Chromosomal Microarray Analysis

COL- Collagen

COL2A1 - Collagen Type II Alpha 1 Chain

CPAP - Continuous Positive Airway Pressure

CT- Computerized tomography

DNA - Deoxyribonucleic Acid

EIF4A3 - Eukaryotic Initiation Factor 4A-III

ERK - Extracellular Signal-Regulated Kinase

EUROCAT- European Network of Population-Based Registries of Congenital Anomalies

FAS- Fetal Alcohol Syndrome

FISH - Fluorescence *In Situ* Hybridization

GWAS- Genome-Wide Association Studies

JI - Jaw Index

KCNJ2- Potassium Inwardly Rectifying Channel Subfamily J Member 2

MAPK - Mitogen-activated protein Kinase

MDO - Mandibular Distraction Osteogenesis

MIT - Massachusetts Institute of Technology

MRI - Magnetic Resonance Imaging

NGS - Next-Generation Sequencing

NICU - Neonatal Intensive Care Unit

NPT - Nasopharyngeal Tube

nsPRS- Non-Syndromic Pierre Robin Sequence

OMIM - Online Mendelian Inheritance in Man database

OSA - Obstructive Sleep Apnea

PEBP - Pre-epiglottis Baton Plate

PNDS - National Diagnostic and Care Protocol

PRS – Pierre Robin Syndrome / Pierre Robin Sequence

PSG - Polysomnography

RBM - RNA-Binding Motif protein

SNRPB - Small Nuclear Ribonucleoprotein Polypeptides B et B'

SOX9- SRY-box 9

SPR- Síndrome de Pierre Robin

sPRS - Syndromic Pierre Robin Sequence

TARP - Talipes Equinovarus, Atrial Septal Defect, Robin Sequence, and Persistent Left Superior Vena Cava

TGDS - Thymidine Diphosphate-Glucose 4,6-Dehydratase

TLA - Tongue-Lip Adhesion

TPP -Tübingen Palatal Plate

UAO - Upper Airway Obstruction

US - Ultrasound

VCFS - Velocardiofacial Syndrome

WES - Whole Exome Sequencing

I. INTRODUCTION

Pierre Robin Syndrome (PRS) is a congenital disorder characterized by micrognathia, cleft palate, and glossoptosis. These conditions collectively lead to significant challenges in feeding and breathing for affected individuals. Understanding these challenges is crucial for developing effective treatment strategies and providing comprehensive care.

This narrative review provides an overview of the current understanding of PRS as a genetic disease, focusing on its genetic bases, prenatal diagnosis, clinical characterization, and treatment strategies. (Palaska et al, 2022; Varadarajan et al, 2021)

Our text further delves into modern approaches to prenatal ultrasound (US) diagnosis, particularly in the context of orofacial developmental anomalies. With its potential for early PRS detection and management, this innovative method instills hope and optimism in PRS research and care (Bruce et al, 2023; Venchikova et al, 2022).

It explores the possibilities presented by micro anomalies in fetal facial development for the prenatal diagnosis of a spectrum of genetic syndromes. (Guan et al, 2020; Islam et al, 2021; Venchikova et al, 2022)

Moreover, the interplay between oral conditions, dental phenotypes, and PRS is examined, underscoring the significance of addressing the oral health aspects of individuals with PRS. (Yekula et al, 2020,Bartzela et al, n.d.; Yekula et al, 2020)

The narrative concludes with the critical role of dentists in the comprehensive care of individuals with this syndrome. Their involvement extends from early diagnosis and assessment to ongoing dental and oral health management, focusing on improving these patients' quality of life. (Cascone et al, 2023; Herring et al, 2020; Yen et al, 2020)

We consulted competent databases such as PubMed, Mendeley, Google Scholar, Wiley, Orphanet, rare diseases, and OMIM, focusing on articles published from January 2020 to April 2024. Relevant information was selected from articles covering genetic markers, clinical aspects, and treatment approaches, and we synthesized these findings to offer a comprehensive narrative overview.

II. DEVELOPMENT

1. Definition of the Pierre Robin Syndrome

1.1. History of Pierre Robin Syndrome

Delving into the annals of medical history, we encounter the remarkable contribution of Pierre Robin, a French physician. In 1923, he was the first to document a condition characterized by mandibular hypoplasia and a tongue that fell backward, leading to breathing difficulties in children. It was not until 1934 that he linked cleft palate to this condition, eventually resulting in the syndrome being named after him. This pivotal discovery underscores the profound role of medical breakthroughs in enhancing our understanding and treatment of diverse health conditions. (Varadarajan et al, 2021)

1.2. Definition of Pierre Robin Syndrome

The Pierre-Robin syndrome is an association of abnormal embryonic development resulting in the appearance of the anatomical triad:

- Micrognathia (Underdevelopment) or Retrognathia (Retroposition) of the mandible.
- Glossoptosis (Posterior displacement of the tongue).
- Airway Obstruction (AO)

These signs are frequently associated with Cleft Palate (U-shaped palate) and other extraoral symptoms (Fig.1). (Alsaeed et al, 2023; Stoll et al, 2023)

In 1982, it was admitted that the term "sequence" best corresponds to the physiopathology of this anomaly. The notion of sequence implies that glossoptosis, upper airway obstruction, and cleft palate are secondary to fetal retrognathism.

There are two types: Non-Syndromic PRS (nsPRS) and Syndromic PRS associated with other syndromes (sPRS). Studies have shown varying genetic mutations associated with both forms. (Herrera Farha et al, 2022; Perrine et al, 2020; Varadarajan et al, 2021)

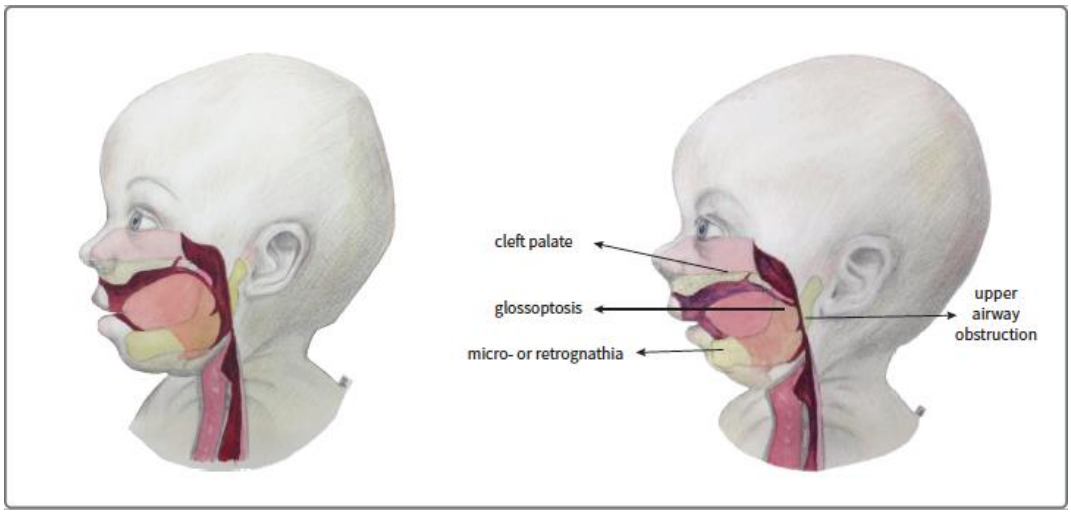

Figure 1. Presentation of a neonate child with normal upper respiratory tract anatomy (LEFT) and Pierre Robin Sequence (RIGHT). Adapted from (Železnik et al, 2022)

1.3. Classification of Pierre Robin Syndrome

1.3.1. Depending on the symptoms

1.3.1.1. Isolated Pierre Robin Sequence

In 50 % of PRS cases, the principal features— small jaw, glossoptosis, and upper airway obstruction (UAO) — occur by themselves and are frequently associated with a cleft palate. This form is called the "isolated Pierre Robin Sequence" or "Non-syndromic Pierre Robin Sequence" (nsPRS). (Železnik et al, 2022).

However, for others, these features are part of a broader syndrome affecting other parts of the body. We qualify it as a "syndromic Pierre Robin Sequence" (sPRS). (Bartzela et al, 2021; Varadarajan et al, 2021; Yekula et al, 2020)

The diagnosis allows the clinicians to decide between the different forms of PRS.

1.3.1.2. Syndromic Pierre Robin Sequence

About 34 syndromes have been reported to be associated with PRS (Table.1). We ranked the most relevant by frequency, mentioning their Online Mendelian Inheritance in Man database number (OMIM). (Al-Qattan & Almohrij, 2022; Varadarajan et al, 2021).

Table 1 – Clinical Symptoms of the Syndromic forms of PRS.
Adapted from (Al-Qattan & Almohrij, 2022; Varadarajan et al, 2021)

SYNDROME	OMIM	RELEVANT BIBLIOGRAPHY	CLINICAL FEATURES IN ADDITION TO THE TRIAD OF PRS
STICKLER SYNDROME Type I (around 16% of cases)	**#108300**	- Al-Qattan & Almohrij, 2022 - Cascone et al, 2023 - Maria Yolanda Yunga Picón et al, 2023 - Perrine et al, 2020 - Stoll et al, 2023 - Varadarajan et al, 2021	- Flat midface, - Long philtrum, - Epicanthus, - Prominent eyes, - Severe myopia from the outset, - Retinal detachments, cataracts, - Ligamentous hyperlaxity - Neurosensory hearing loss
RICHIERI-COSTA–PEREIRA SYNDROME (Around 8% of cases)	**#268305**	**- AL-QATTAN & ALMOHRIJ, 2022**	- Missing lower central incisors - Preaxial ray deficiency
CATEL-MANTZKE SYNDROME (Around 5.5% OF CASES)	**#268305**	**- AL-QATTAN & ALMOHRIJ, 2022**	- Clinodactyly - Hyperphalangism
CAMPOMELIC / ACAMPOMELIC DYSPLASIA WITH OR WITHOUT SEX REVERSAL (Around 4.7% OF CASES)	**#114290**	**- AL-QATTAN & ALMOHRIJ, 2022)**	- Scapular Hypoplasia - Hypoplastic thoracic cage - Short lower limbs
TALIPES EQUINOVARUS, ATRIAL SEPTAL DEFECT, ROBIN SEQUENCE, AND PERSISTENT LEFT SUPERIOR VENA CAVA TARP SYNDROME (AROUND 3% OF CASES)	**#311900**	**- AL-QATTAN & ALMOHRIJ, 2022)**	- Talipes equinovarus - Atrial septal defect - Persistence of the left superior vena cava. - Hypoplastic radii
CEREBRO-COSTO-MANDIBULAR SYNDROME (AROUND 2.7% OF CASES)	**#117650**	**- AL-QATTAN & ALMOHRIJ, 2022)**	- Microcephaly - Posterior rib defects - Intellectual disability

It is also important to mention that around 9 % of patients with Pierre Robin Sequence (PRS) who present additional chromosomal anomalies or defects but without an identified associated syndrome belong to a third group named the "PRS-plus group." (Cascone et al, 2023; Varadarajan et al, 2021 Karempelis et al, 2020)

1.3.2. Depending on the severity of the symptoms

Different forms of PRS have been defined according to patients' malformations."Couly" made the first classification based on the severity of the symptoms in 1988 (Table.2). It was revised by Caouette-Laberge in 1994. (Maria Yolanda Yunga-Picón et al, 2023)

Maria Yolanda Yunga-Picón et al. introduced the "Vancouver classification" for children affected by PRS. It is the most practical classification since it differentiates patients into four grades of increasing severity of symptoms from 0 to 3 (Table.3). It also guides the therapeutic plan. (Maria Yolanda Yunga-Picón et al, 2023)

1.3.2.1. The Classification of Couly

Table 2- Couly's classification. Adapted from (Cascone et al, 2023)

Grade	Features
1	The baby is newly born and has PRS traits. There are no noticeable breathing difficulties, and feeding is going well.
2	Baby has PRS traits and occasional breathing difficulties (like noisy breathing). Breathing problems start when the baby feeds.
3	Baby has PRS traits and severe breathing difficulties. The baby cannot be fed by mouth.

1.3.2.2.The Vancouver Classification

Table 3- Vancouver's classification. Adapted from (Cascone et al, 2023)

Grade	Features
0	Jaw with a slight difference of less than 10 mm between the upper and lower jaws and mild tongue displacement. No breathing problems. Regular eating habits. Better response to surgical treatments and show improvement when facing downward.
1	Jaw and a difference of less than 10 mm between the upper and lower jaws. Tongue moderately displaced, leading to eating challenges that require the use of a nasogastric tube. While there are no issues, oxygen levels may drop, especially when lying face down. Surgical tongue repositioning through procedures like tongue lip adhesion is sometimes considered adequate.
2	Micrognathia, with a 10 mm difference between the upper and lower jaws. Severe tongue displacement leads to oxygen levels even when lying face down, and feeding difficulties necessitate tube use. Changes in breathing patterns are also noted. The recommended surgical method for this grade is distraction.
3	Micrognathia significantly affects the airway. A tracheostomy is sometimes required when the airway is significantly compromised.

1.4. Etiology

While the exact embryological basis of the Robin sequence remains incompletely understood, it is believed to result from genetic and environmental factors.

1.4.1. The Embryological Basis and Etiopathogenesis of PRS

During early embryonic development, the face and anterior neck regions are derived from transient embryonic pharyngeal (branchial) arches, crucial in shaping the facial skeleton. Here are some key points related to the embryological basis of the Robin sequence (Fig.2).

- **The Pharyngeal Arches**

During the third and fourth weeks of embryonic implantation, the arches form as a series of bulges on the lateral surface of the embryonic skull. They contain numerous types of cells that grow into the oropharyngeal tract. (Toro-Tobon et al, 2023). The first and second pharyngeal arches, crucial in their role, will form the viscerocranium, the very foundation of the facial skeleton, while the embryonic germ layers (the ectoderm, mesoderm, and endoderm) will build the pharyngeal arches. During development, every layer will differentiate into oropharyngeal structures, such as pharyngeal epithelia, cartilage, muscles, blood vessels, and nerves. (Casale et al, 2024; Čverha et al, 2023)

- **Neural crest cells**

The neural crest is a vertebrate-specific migratory population of **multipotent stem cells**. These cells originate in the region between the neural and non-neural ectoderm while forming the **neural tube**, eventually developing into the central nervous system. Neural crest cells play a crucial role in adequately developing the mesenchyme (connective tissue) in the pharyngeal region. (Čverha et al, 2023)

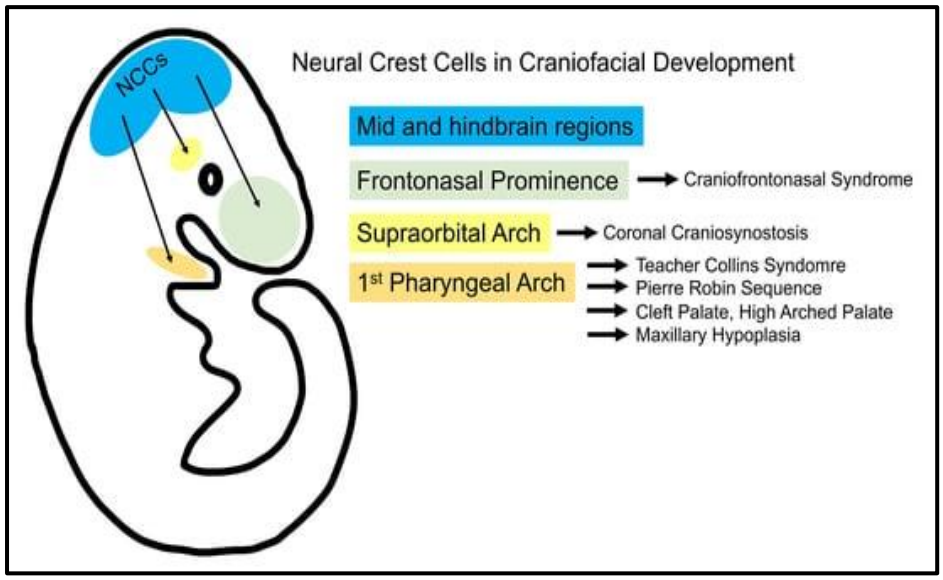

Figure 2. Cranial Neural Crest Cells and Their Role in the Pathogenesis Of Craniofacial Anomalie. Adapted from(Siismets & Hatch, 2020)

PRS results from genetic mutations that impede cranial neural crest cell migration and proliferation, leading to craniofacial abnormalities like cleft palate, micrognathia, and tongue malformations. It is worth noting that mutations affecting BMP (Bone Morphogenetic Protein) signaling, particularly BMP2 loss, can significantly disrupt craniofacial development, thereby contributing to PRS. Equally important, disruptions in the ERK/MAPK (Extracellular Signal-Regulated Kinase / Mitogen-Activated Protein Kinase) pathway within neural crest cells have been identified as another crucial factor in the pathogenesis of PRS, providing a comprehensive understanding of the genetic factors involved. These genetic factors intricately connect the embryonic development of the palate, tongue, and mandible. (Čverha et al, 2023), (Antonaci & Wheeler, 2022), (Toro-Tobon et al, 2023), (Siismets & Hatch, 2020)

1.4.2. PRS and Genetics

The cause of PRS, whether in isolation or as part of a syndrome, has been frequently discussed. Previous studies have identified chromosome 2, 4, 11, and 17 mutations as potential contributors to nsPRS. Particularly, mutations in SOX9 or Potassium Inwardly Rectifying Channel Subfamily J Member 2 (KCNJ2) on chromosome 17 have been linked to facial structure and cartilage development, shedding light on the genetic basis of PRS. On the other hand, syndromic PRS encompasses 34 associated syndromes, with Stickler syndrome being the most prevalent. This syndrome is characterized by Collagen (COL)

gene mutations, which significantly influence collagen formation. (Baxter & Shanks, 2024; Maria Yolanda Yunga-Picón et al, 2023)

The following table summarizes the clinical presentations and associated gene mutations for both nsPRS and sPRS (Table.4).

Table 4 - Associated gene mutations for both Non-syndromic and Syndromic PRS.

CLINICAL FORM	MUTATION
Non-Syndromic PRS	**SOX9**: the most frequently mutated gene (*locus*17q24)
Syndromic PRS	**1. Stickler Syndrome type I**: an autosomal dominant syndrome caused by mutations in the *Collagen Type II Alpha 1 Chain* (*COL2A1)* gene, which encodes collagen type II **2. Richieri-Costa–Pereira Syndrome**: inherited as autosomal recessive by biallelic expansion of a complex repeated motif in the 5' untranslated region of the *Eukaryotic Initiation Factor 4A-III (EIF4A3)* gene. **3. Catel–Manzke Syndrome**: inherited as autosomal recessive and is caused by *Thymidine Diphosphate-Glucose 4,6-Dehydratase (TGDS)* gene mutations **4. Campomelic and Acampomelic Dysplasia**: autosomal dominant syndrome is caused by *SOX9* mutations **5. TARP Syndrome**: inherited as X-linked recessive and is caused by *RNA-binding protein (RBM10))* gene mutations **6. Cerebro-Costo-Mandibular Syndrome**: autosomal dominant syndrome due to *Small Nuclear Ribonucleoprotein PolypeptidesB et B' (SNRPB)* mutation

Earlier research discovered and calculated the frequency of the different types of mutation observed. (Varadarajan et al, 2021).

We organized them by frequency in the table below (Table.5):

Table 5 - Different types of genetic mutations observed in PRS and their frequency. Adapted from (Al-Qattan & Almohrij, 2022)

TYPE OF MUTATION	FREQUENCY
Deletion	47%
Translocation	20%
Duplication	12%
Single nucleotide mutation	9%
Missense mutation	6%
Breakpoint mutation	5%
Splicing defect mutation	4%
Insertion	2%
Inversion	1%

1.4.2.1. Role of SOX9 gene (SRY-box 9)

Micrognathia is the primary anomaly in PRS, with SOX9 emerging as the central figure governing chondrogenesis in the mandibular cartilage. Recognizing these aspects prompted the hypothesis that this gene may play a role in the pathogenesis of PRS, even in cases where other gene mutations are responsible for syndromes. (Eustáquio et al, 2020)

In nsPRS cases, SOX9 mutations are the most prevalent and underlie campomelic dysplasia for other syndromes associated with PRS. The pathogenesis might be linked to the interplay between SOX9 and the proteins encoded by the causative genes of those syndromes. (Al-Qattan & Almohrij, 2022; Palaska et al, 2022; Varadarajan et al, 2021).

1.4.2.2. SOX9 Pathogenesis

The SOX9 gene plays a critical role in the development of facial structures. Mutations in SOX9 can directly cause nsPRS, where PRS occurs without any other associated conditions.

Chromosomal abnormalities near the SOX9 gene can disrupt its regulation, leading to developmental misexpression of SOX9.

Studies have shown that dysregulation of the SOX9 gene is associated with PRS, influencing the normal development of various structures, including the palate and facial features. Mutations in the SOX9 gene prevent the production of functional SOX9 protein, affecting the genes essential for normal development and contributing to the manifestation of PRS. (Long et al, 2020)

SOX9 also has other actions during development, such as modulation of cartilage precursors of various skeletal elements and sex determination. Thus, mutations of this gene are expected to cause skeletal defects in all syndromic patients (Table.6). (Stoll et al, 2023; Al-Qattan & Almohrij, 2022; Dash et al, 2021)

The most important ones are represented in the following table.

Table 6 - Skeletal defects caused by the most frequent syndromes.
Adapted from (Al-Qattan & Almohrij, 2022)

SYNDROME	SKELETAL DEFECT
Stickler (type I)	Spondyloepiphyseal dysplasia
Catel–Manzke	Bilateral hyperphalangism and clinodactyly of index fingers
TARP	Hypoplastic radius, Talipes equinovarus
Richieri-Costa–Periera	Preaxial ray deficiency
Campomelic/ Acampomelic dysplasia	Hypoplastic scapulae, short lower limbs, Abnormal hypoplastic thoracic cage,
Cerebro-costo-mandibular	Posterior rib defects

The Pierre Robin Sequence (PRS) development initiates with micrognathia, which creates an imbalance between tongue and oral cavity volumes. This relatively large tongue disrupts the typical vertical-to-horizontal movement of developing palatal shelves, forming a cleft palate. Following birth, the oversized tongue contributes to respiratory and feeding challenges. A current review suggests that SOX9 and its interactions likely play a role in the pathogenesis of clinical features in sPRS. (Cascone et al, 2023; Perrine et al, 2020)

However, it is essential to note the complexity of PRS development. Firstly, gene mutations are not identifiable in patients with nsPRS, indicating the probable involvement of other environmental (intrauterine) and intrinsic factors. Secondly, in sPRS cases,

SOX9 is the primary factor only in *Campomelic Dysplasia.* This complexity, where different genes or proteins take precedence in other syndromes, although interactions with SOX9 may offer insights into the pathogenesis, presents a fascinating challenge for further research. Ultimately, this connection is derived from a comprehensive literature search in basic science, elucidating the molecular interactions of SOX9 and causative genes in developing clinical symptoms.

1.5. Pathophysiology

Three theories of the pathophysiology of Pierre Robin syndrome have been suggested:

- **The Mechanical theory**

It is the most widely accepted theory. Mandibular hypoplasia occurs between the seventh and eleventh weeks of gestation, resulting in the tongue being maintained in a high position in the oral cavity, leading to cleft palate through non-fusion of the palatal processes. This theory explains the formation of the U-shaped cleft palate and its non-association with the cleft lip in PRS. A lack of amniotic fluid causes oligohydramnios, which causes chin compression, blocking the tongue between the palatal processes and preventing them from fusion. (Herrera Farha et al, 2022; Perrine et al, 2020).

- **The theory of neurological maturation**

Delayed neurological maturation is noted in the musculature of the tongue, pharyngeal pillars, and palate, as well as delayed conduction of the hypoglossal nerve. In this case, the tongue does not promote mandible expansion or palatal shelf fusion, developing micrognathia and breathing problems. (Perrine et al, 2020)

- **The mandibular compression theory**

Multigravida pregnancy, oligohydramnios, and uterine abnormalities can all impede mandibular growth. These circumstances all limit the flexed fetal head's typical range of extension. When the fetal chin presses over the sternum, it restricts mandibular growth. Consequently, the tongue cannot move downwards or forwards, inhibiting palatal surface elevation and fusion. The major outcomes include micrognathia, cleft palate, and airway constriction. (Maria Yolanda Yunga-Picón et al, 2023)

1.6. Epidemiology

The incidence of PRS is challenging to assess accurately, as it varies widely from one author to another; the difference is due to difficulties in defining the syndrome. The

European Network for the Surveillance of Congenital Anomalies (EUROCAT) estimates that the total prevalence of PRS is 12 per 100000 births in the populations covered by EUROCAT registries, with 94.1% being live births (Santoro et al, 2023)

According to anterior and recent studies, PRS affects approximately 1/8,500 to 1/14,000 newborns annually. (Baxter & Shanks, 2024)Approximately 50% of PRS cases are non-syndromic. (Yekula et al, 2020)

Both Patients with chromosomic anomalies or with syndromic form have a higher mortality rate, especially when the Cardiac or Nervous system is involved. (Baxter & Shanks, 2024; Eustáquio et al, 2020; Yunyan Z, 2022)

2. Positive Diagnosis of Pierre Robin Syndrome

2.1. Prenatal diagnosis

2.1.1. General

Prenatal diagnosis of PRS is rarely made by chance. Retrognathia, the most straightforward element of the triad, can be detected on second-trimester morphological ultrasound by observing an accurate fetal profile. Fetal glossoptosis detection is of the utmost importance in PRS diagnosis, as the posterior displacement of the tongue can lead to neonatal respiratory distress. (Čverha et al, 2023)

Indirect signs like moderate hydramnios (excess amniotic fluid) or small stomach size may suggest the diagnosis, but they are not definitive (pathognomonic). (Cang et al, 2023; de Souza et al, 2023)

Improvements in prenatal imaging techniques, mainly 3D ultrasound, should increase the percentage of antenatal PRS diagnoses. If PRS is suspected, looking for associated anomalies in the face, heart, skeleton, or brain is crucial. A fetal karyotype (chromosome analysis) may also be recommended. (Hsiao et al, 2022)

Antenatal identification of a Pierre Robin sequence syndromic form is challenging and often requires family history investigation and specialist consultation. (Boothe et al, 2020)

2.1.2. Medical and Radiological Examinations

The questionnaire will provide information about the couple's family, personal, surgical, obstetric history, and family consanguinity. If, on ultrasound, micro retrognathism and/or verticalization of the tongue and/or tip of the tongue above the palate are present, PRS

must be suspected, mainly if it is associated with hydramnios (an excess of amniotic fluid indicating swallowing disorders). (Baxter & Shanks, 2024)

Ultrasound allows us to visualize the development of the fetus and is a commonplace examination because it is neither dangerous nor toxic. It shows the shape but does not evaluate functional capacities. (Bruce et al, 2023; Guan et al, 2020; Islam et al, 2021)

Other examinations can be carried out during pregnancy, such as computerized tomography (CT) scans or Magnetic resonance imaging (MRI), to visualize the tongue's position in the oral cavity and its relationship with surrounding structures (Fig.3). In the case of glossoptosis, the tongue occupies a posterior position throughout the scan session, which lasts between twenty and thirty minutes and never shows contact between the tip of the tongue and the anterior mandibular alveolar ridge during lingual movements. (Cang et al, 2023)

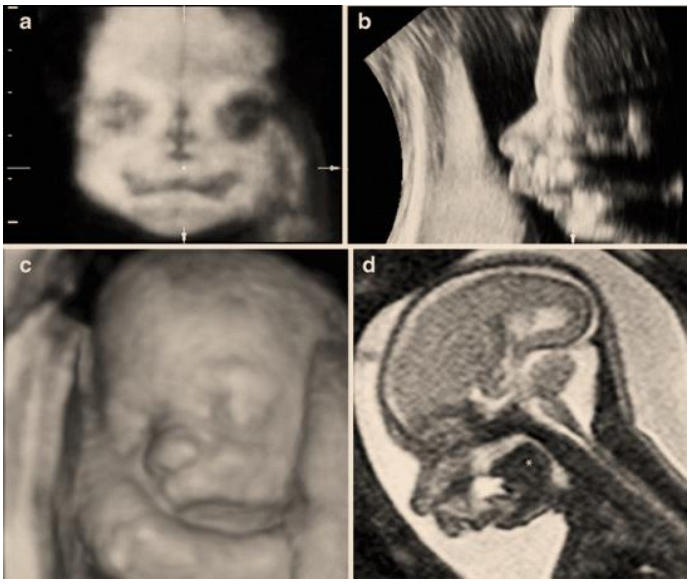

Figure 3. 3D Ultrasound and MRI in PRS.
a,b- Multiplanar coronal (a) and sagittal (b) 3D US.
c- morphology US scan: severe micrognathia.
d- MRI at 29 weeks: a high-arched cleft palate
and posterior displacement of the tongue, leading to the diagnosis of PRS.
Adapted from (Gonçalves, 2016)

2.1.3. Genetic Diagnosis

Pierre Robin Sequence (PRS) often presents without a clear genetic cause (sporadic).

Diverse genetic mutations associated with nsPRS and sPRS variations have been recognized. Importantly, PRS and its genetic indicators can be identified during the first

trimester of pregnancy, offering the potential for early detection of the anomaly. (Varadarajan et al, 2021)

Genetic diagnosis methods for Pierre Robin Sequence (PRS) involve various techniques:

- **DNA Sequencing**: utilizing DNA sequencing techniques, both Sanger sequencing and Next-Generation Sequencing (NGS), can be employed to analyze specific genes associated with PRS, such as SOX9, to identify mutations or variations. (Satam et al, 2023)
- **Fluorescence *In Situ* Hybridization (FISH)**: frequently used to detect specific chromosomal abnormalities, such as microdeletions or translocations, can sometimes be linked to PRS. (Gu et al, 2022; Wang et al, 2022)
- **Chromosomal Microarray Analysis (CMA)**: a high-resolution technique used to detect chromosomal abnormalities associated with PRS, aiding in identifying large deletions or duplications that may contribute to the condition. (Huang et al, 2021)
- **Whole Exome Sequencing (WES)**: allows for the comprehensive analysis of protein-coding regions of the genome, enabling the identification of rare genetic variants that may underlie PRS in individuals with no clear genetic cause. (Manickam et al, 2021; Mone et al, 2023)
- **Targeted Gene Panel Testing**: targeted gene panels focusing on genes associated with craniofacial development and syndromic forms of PRS can be used to screen for mutations in specific genes involved in the anomaly. (Antonaci & Wheeler, 2022)
- **Genome-Wide Association Studies (GWAS)**: can be employed to identify common genetic variants associated with PRS susceptibility or severity, offering a broader perspective on the genetic factors contributing to the condition. (Chen et al, 2022; Yang et al, 2022)

Integrating genetic testing results with clinical data and phenotypic information can enhance the interpretation of genetic findings and aid in correlating specific mutations with clinical manifestations of PRS.

2.1.4. Announcing the diagnosis

The diagnosis announcement should be a vital part of the antenatal consultation. Ultrasound gives us the time to explain the type of lesions and their treatment to the parents. (Guan et al, 2020)

Chromosomal Microarray Analysis (CMA) can provide crucial information as an initial step in prenatal diagnosis in high-risk pregnancies where ultrasound scans or prenatal screening tests reveal concerning results. This analysis helps detect chromosomal abnormalities that other screening methods may have missed. (Hsiao et al, 2022; Huang et al, 2021)

Prenatal diagnosis plays a crucial role by:

Empowering parents psychologically: Early detection of malformations allows parents time to prepare emotionally and gather information.

Ensuring optimal birthing environment: if a respiratory complication is suspected, delivery can be recommended and planned at a hospital with a well-equipped Neonatal Intensive Care Unit (NICU) for immediate intervention. (Cascone et al, 2023)

The diagnosis of PRS in antenatal care leads to a delicate ethical discussion depending on the severity of the disorder and the prognosis. Medical termination of the pregnancy maybe considered, but above all, genetic counseling and antenatal diagnosis should be offered in subsequent pregnancies. (Hsiao et al, 2022; Santoro et al, 2023)

2.2. Neonatal diagnosis

2.2.1. Clinical examination

The diagnosis of a Pierre Robin sequence is essentially clinical at birth. In 2014, a multidisciplinary team of doctors participated in an international consensus conference in the Netherlands, discussing the most appropriate treatments for patients with PRS.

2.2.1.1. Initial problems

2.2.1.1.1. Anatomical disorders

Clinical experience and literature data identify retrognathism as a primary characteristic associated with two other signs: glossoptosis (with possible obstruction of the upper airways) and cleft palate. (Eustáquio et al, 2020)

- **Retrognathism**

The "bird's profile" or "shark's mouth" is the most visible sign at birth. The small mandible is in a retrusive position, located far behind the upper jaw. The mandibular angle is obtuse, and the chin appears flat, in continuity with the neck, without apparent distinction (Fig.4). Defining whether retrognathism or micrognathism can be complex to demonstrate. (Eustáquio et al, 2020).

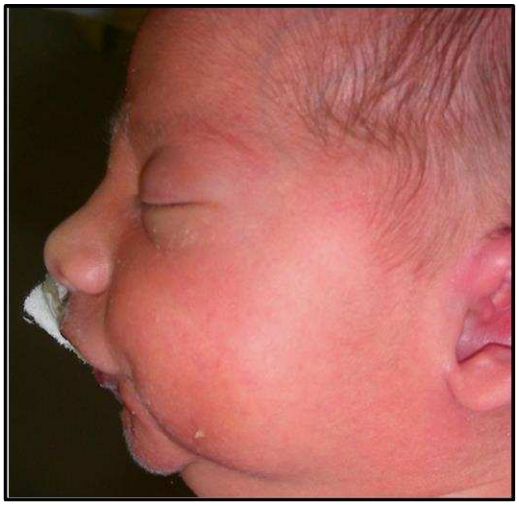

Figure 4. Chracateristic profile of severe mandibular micrognathia in a newborn PRS. Adapted from (Galluccio et al, 2019)

Analysis by teleradiography presents certain limitations due to the two-dimensional nature of the images obtained and the difficulty of placement and immobilization of the child who must undergo an instrumental investigation. Although the Cone Beam Computed Tomography (CBCT) scanning can create more accurate three-dimensional reconstructions, it exposes the patient to a higher radiation dose. For this reason, the diagnosis of micrognathia is still commonly clinical. (Maria Yolanda Yunga-Picón et al, 2023)

The "jaw index" (JI) makes the quantification of the retrognathism possible.

It is the product of the alveolar overjet multiplied by the ratio of the distance between the two tragi passing through the middle of the philtrum and the middle of the chin (Fig.5).

JI = Alveolar Overjet x (Maxillary arch / Mandibular arch) where:

- JI is the Jaw Index
- O: Alveolar overjet is the distance between the alveolar ridges of the upper and lower maxillae, measured in millimeters
- U: Maxillary arch is the length of the maxillary arch, measured in millimeters
- L: Mandibular arch is the length of the mandibular arch, measured in millimeters (Poets et al, 2022)

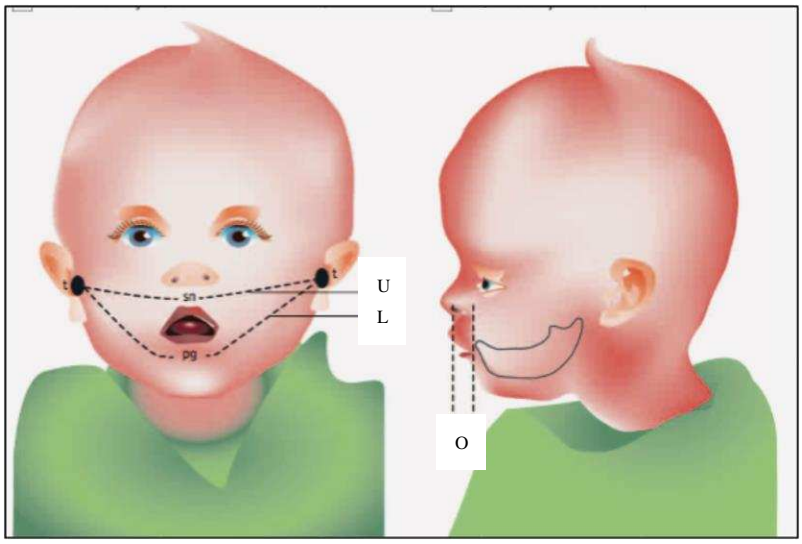

Figure 5. Jaw Index measurement. Adapted from (Pierre Robin Sequence 2021 National Diagnostic and Care Protocol (PNDS) September 2021 Reference Center for Rare Diseases of Pierre Robin Syndromes and Congenital Sucking-Swallowing Disorders (SPRATON) Health Sector Rare Diseases of Malformations of the Head, Neck and Teeth (TETECOU), n.d.)

- **<u>Glossoptosis</u>**

In addition to micrognathia, glossoptosis is another crucial element for diagnosing PRS, defined by posterior displacement of the base of the tongue. Generally, the tongue lies naturally above the hyoid bone, downward and forward. Conversely, in the Pierre Robin sequence, micrognathia reduces the available space, and the tongue occupies a high and backward position. (Prescher et al, 2022; Zaballa et al, 2023)

It can be found in varying degrees of severity and is the cause of upper airway obstruction. In the most severe cases, patients may experience abnormal breathing sounds, possibly accompanied by obstructive sleep apnea. (Poets et al, 2022)

The severity of micrognathia and glossoptosis becomes more apparent by the time of birth, leading to difficulties in breathing and feeding, which can result in neonatal lethality. (Dash et al, 2021)

The relationship between micrognathia and glossoptosis is still unclear. It means that assessing micrognathia alone may not accurately predict how much the airway is blocked. Before starting treatment, it is recommended to use an endoscope to check the airway, see if there is glossoptosis, and find where the blockage is.

A flexible nasolaryngoscope allows doctors to examine the upper airway and vocal cords and identify laryngomalacia. However, this procedure is complex because young patients often cry during the examination, making it hard to assess the glossoptosis's severity accurately. (Železnik et al, 2022)

Polysomnography is essential for accurately diagnosing and managing apnea, as it evaluates the degree of airway obstruction. (Maria Yolanda Yunga-Picón et al, 2023; Sharma et al, 2023)

Cardiorespiratory polygraphy during sleep in the initial months after birth objectively assesses respiratory disturbances and enables monitoring of the progression or regression of airway obstruction severity. This technique is beneficial in detecting and tracking changes in breathing patterns, which can help guide appropriate treatment interventions for infants with respiratory issues. By monitoring cardiorespiratory parameters during sleep, healthcare professionals can gain valuable insights into the infant's respiratory health and make informed decisions regarding their care. (Železnik et al, 2022)

- **Palatal Cleft**

The triad of PRS symptoms is sometimes associated with a U-shaped cleft palate. (Baxter & Shanks, 2024)

The limited space in the oral cavity, caused by its reduced volume, forces the tongue into a higher position, which restricts the growth of the lower jaw and disrupts the fusion of the two palatal shelves.

This incomplete fusion creates a U-shaped cleft palate (Fig.6). (Cascone et al, 2023)

It is also more observed in women than in male gender. (Al-Qattan & Almohrij, 2022)

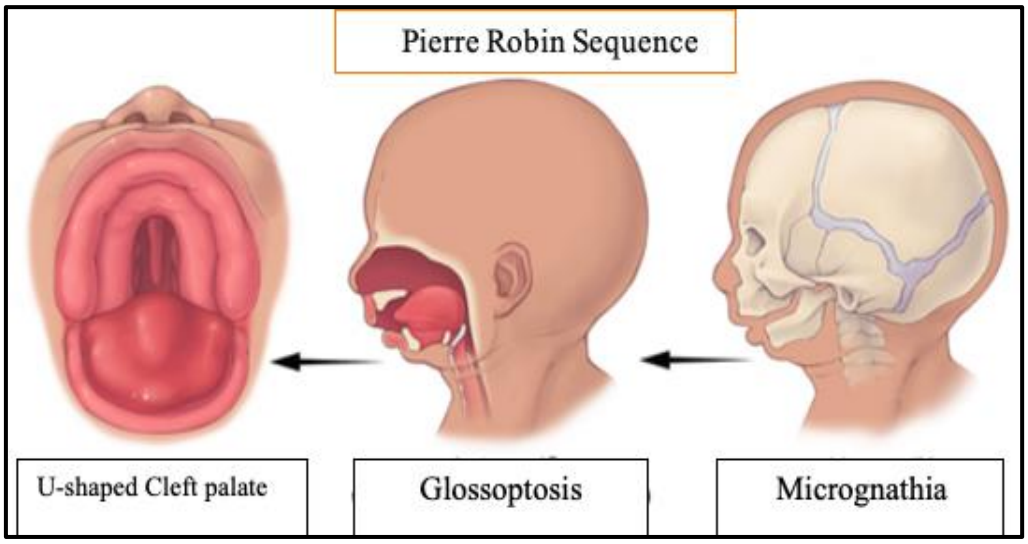

Figure 6. Pierre Robin Sequence: craniofacial malformations.
Available in: https://quizlet.com/515203898/genetic-syndromes-flash-cards

2.2.1.1.2. Functional disorders

The semiological triad is associated with functional signs: difficulties in sucking and swallowing, breathing problems, and abnormality in gastroesophageal motility.

Functional disorders gradually decrease during the first two years of life, eventually disappearing.

- **Breathing**

This airway obstruction is usually caused by tongue collapse, cleft palate, and lack of voluntary control of the tongue musculature. In addition, mandibular micrognathia reduces the size of the mouth floor and forces a retraction of the tongue, which obstructs the airflow, particularly at the level of the hypopharynx. (Piotto et al, 2023; Poets et al, 2022)

In many cases, PRS constitutes a problem of neonatal respiratory distress, which will require emergency treatment with upper airway clearance techniques. These respiratory disorders vary from mild dysfunction to apnea, cyanosis, or respiratory failure. (Maria Yolanda Yunga-Picón et al, 2023; Železnik et al, 2022)

Obstructive sleep apnea (OSA) is a sleep disorder where breathing is interrupted because the upper airway is blocked, entirely or partially. People with specific facial malformations are more at risk for OSA. The gold standard test for diagnosing OSA in adults and children is polysomnography (PSG). This test also helps measure the severity of OSA using the apnea-hypopnea index (AHI). (Alsaeed et al, 2023)

- **Feeding – Swallowing**

In newborns, the Pierre Robin sequence leads to eating disorders linked to difficulties in coordinating both sucking and swallowing.

Feeding difficulties associated with airway obstruction and cleft palate prevent the formation of sufficient negative intraoral pressure required for aspiration of milk from the breast or bottle. The initiation of oral feeding in infants requires that the control of the sucking movement, swallowing, and breathing are well integrated and centrally coordinated)

During the oral sequence, the pharyngeal and esophageal swallowing phases must be coordinated with breathing to avoid aspiration.

Concerning sucking, the infant will rarely be able to achieve adequate feeding at the breast, while with a bottle, the feeding will be slowed down and, therefore, quantitatively too weak for the newborn to have adequate nutritional intake. (Železnik et al, 2022)

- **Digestive difficulties**

In 80% of the cases, doctors noticed esophagus motility disorder leading to gastroesophageal reflux. It corresponds to a return of the food bolus after meals and acid reflux during periods away from meals. This discomfort is increased due to a cleft palate, which causes reflux laryngitis (reflux through the nose). (Zaballa et al, 2023)

Esophageal dysfunction could also complicate the Pierre Robin sequence. This can be assessed more specifically by electromyography and esophageal manometry. These examinations detect dysfunction in motor coordination between the tongue, pharyngeal muscles, and esophagus. (Banhara et al, 2022)

2.2.1.1.3. Delayed complications

- **Speech therapists**

A clear association exists between air escape during speech and atypical articulation of words with nasal resonance in children with PRS. These children will show delayed language development. These phonatory disorders are due to the presence of the cleft palate, not to micrognathia. There is a close relationship between atypical speech articulation and velopharyngeal incompetence in air leakage through the nose during speech. (Palaska et al, 2022; Prescher et al, 2022)

- **Otolaryngology**

A significant proportion of children may have moderate hearing loss. Furthermore, cleft palate can affect speech development and result in speech disorders, including hypernasality and articulation difficulties. It is worth noting that over half of children with palatoschisis are prone to recurrent otitis media or otitis media with effusion, which can cause conductive hearing loss. (Železnik et al, 2022)

- **Intellectual impairment**

Prolonged airway obstruction can result in either acute or chronic hypoxia, leading to cerebral hypoxia with cognitive disability. (Eustáquio et al, 2020; Piotto et al, 2023)

- **Dental problems**

*Orthodontic disorders

A Retrospective longitudinal study directed by Palaska et al. in the USA concluded:

- Agenesis of one or more permanent teeth, severe crowding, and skeletal and/or dental dysplasia were frequently diagnosed.
- For patients aged 15 years and older, 34% had Angle's Class I malocclusion, 50% had Class II malocclusion, and 16% had Class III malocclusion.
- Interceptive guidance of occlusal development was often programmed through serial extractions of teeth.
- Treatment of Class II malocclusions and convex profiles was frequently needed. (Palaska et al, 2022)

The same analysis highlights the importance of orthodontic treatment in addressing dental and skeletal abnormalities during middle childhood and adolescence, focusing on interceptive guidance and correction of malocclusions. The data also suggest that some patients may require orthognathic surgery to correct severe malocclusions. (Palaska et al, 2022)

***Hypodontia**

A high incidence of tooth agenesis in children with cleft lip and palate is notorious, mainly affecting bilateral lower premolars, particularly bilateral lower premolars, as reported by Anderson et al, 2015), Smalen et al, 2017), and Mateo-Castillo et al, 2019).

The Pierre Robin sequence characterized by pronounced micrognathia and subsequent loss of space may contribute to dental agenesis. Both lack of space (mandibular hypoplasia) and genetic factors can create a potential link between dental abnormalities and craniofacial anomalies in this population. (Choi et al, 2023; Eustáquio et al, 2020; Lu et al, 2020)

A retrospective cohort analysis in the United Kingdom (UK) compared hypodontia in nonsyndromic isolated cleft palates and isolated cleft lips with the prevalence and patterns of hypodontia in nsPRS. The study involved three groups of kids: the first with isolated cleft palate, the second with isolated cleft lip, and a third group of nsPRS at Alder Hey Children's Hospital in the UK.

Orthopantomographs were used to evaluate hypodontia in the permanent dentition. According to the findings:

- The prevalence of hypodontia was higher in patients with PRS (47%) compared to those with isolated cleft palates (27%) and isolated cleft lips (19%).
- In 93% of hypodontia cases in PRS patients, there was at least one missing second premolar; in 50% of cases, bilateral agenesis of second premolars was discovered.
- Individuals with PRS and cleft palates have a higher chance of getting hypodontia compared to those who have isolated cleft palates.
- A frequently observed pattern among PRS patients with hypodontia is the bilateral absence of lower second premolars.
- The severity of hypodontia is greater in PRS patients compared to those with isolated cleft palates or isolated cleft lips. (Dillon Maria et al, 2022)

2.2.2.Radiological and EndoscopyExaminations

2.2.2.1. Prenatally

Ultrasound imaging is highly efficient in detecting PRS characteristics such as cleft palate, glossoptosis, and micrognathia, aiding in early diagnosis and prognosis assessment.Additionally, MRI can be used as an adjunct imaging modality in cases where ultrasound findings are ambiguous, providing detailed information on facial structures and aiding in diagnosing craniofacial abnormalities. However, due to cost considerations, MRI is not typically used as a first-line screening tool, but it can be valuable in cases where ultrasound results are inconclusive. (Cang et al, 2023; Guan et al, 2020)

2.2.2.2. Postnatally

Radiological exams and nasoendoscopy or bronchoscopy can assess airway obstructions in the upper and lower respiratory tracts, determining the severity of obstructive apneic events and guiding the timing of interventions. Continuous oxygen saturation monitoring, polysomnography, and growth charts are also utilized to assess respiratory and feeding functions, determine the need for nutritional support, and evaluate the severity of the condition. Radiological exams are essential in managing PRS, especially in severe cases requiring surgical interventions to address airway impairments and associated anomalies. (Baxter & Shanks, 2024)

3. Differential Diagnosis of Pierre Robin Syndrome

Identifying PRS from other conditions sharing similar facial characteristics is essential for accurate management. Below are some prevalent conditions to consider during the diagnostic process.

1. **Stickler Syndrome:** Stickler Syndrome, known for its autosomal dominant inheritance and collagen gene mutations, presents with micrognathia (a small jaw), cleft palate, and myopia (nearsightedness). (Boothe et al, 2020; Snead et al, 2020)
2. **Velocardiofacial Syndrome (VCFS),** also termed Shprintzen-Goldberg syndrome: VCFS, characterized by cleft palate, learning disabilities, and congenital heart defects, often shares facial features with PRS. Further insights into VCFS and its diagnostic considerations are discussed in a recent article by Guo et al. titled "Velocardiofacial Syndrome: Clinical Features and Diagnostic Challenges" (2022).
3. **Treacher Collins Syndrome (Mandibulofacial Dysostosis):** This syndrome, marked by ear, jaw, and cheekbone malformations, presents challenges in differential diagnosis with PRS. An article by Tonello et al. provides recent insights into this syndrome. (Tonello et al, 2023)
4. **Beckwith-Wiedemann Syndrome (BWS):** Recent research by Borjas Mendoza et al, 2024) sheds light on the features of BWS, including macroglossia and potential airway obstruction. BWS may resemble PRS but has distinctive characteristics. Borjas Mendoza et al, 2024)

5. **CHARGE Syndrome**: Characterized by various anomalies, including heart defects, growth retardation, and ear abnormalities, presents challenges in differentiation from PRS. (Baxter & Shanks, 2024)
6. **Fetal Alcohol Syndrome (FAS):** Recent insights into Fetal Alcohol Syndrome, its facial dysmorphisms, and growth patterns are discussed in an article by Vorgias et al. (Vorgias et al, 2023)
7. **Di George Syndrome:** For recent advancements in understanding DiGeorge Syndrome and its distinctive clinical features, refer to the article by Altshuler et al. (Altshuler et al, 2022).
8. **Childhood Sleep Apnea:** While childhood sleep apnea may manifest in some PRS cases due to airway obstruction, it is essential to consider recent research on sleep disorders in children directed by Gouthro and Slowik. (Gouthro & Slowik, 2024)

4. Therapy and Management of Orofacial Manifestations

4.1. Nonsurgical Management Of PRS

4.1.1. Prone Positioning

To alleviate upper airway obstruction in infants with Pierre Robin Sequence (PRS), placing them in the prone position (also known as ventral decubitus) is commonly recommended as a first-line treatment. This technique involves placing the child in this position to allow the mandible and tongue to fall anteriorly, reducing airway obstruction at the base of the tongue and improving oxygen saturation levels (Fig.7). While this method may provide short-term benefits for airway permeability and swallowing, it is not considered a definitive therapeutic method due to the lack of evidence supporting its long-term effectiveness. (Baxter & Shanks, 2024)

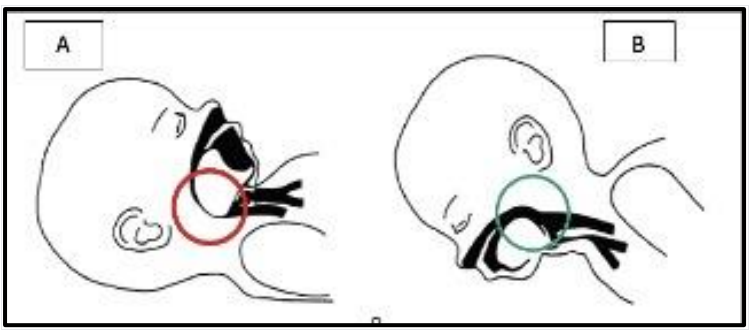

Figure 7. Effect of the Prone positioning on the airway patency in the illustration B. Adapted from (Čverha et al, 2023)

Some studies have reported that ventral decubitus effectively resolves airway obstruction in 40-70% of children with PRS. However, this technique may not be suitable for children with severe airway obstruction, as the success rate is limited. Some groups have suggested using lateral decubitus instead of ventral decubitus during sleep, as the prone position has been associated with an increased risk of sudden death. However, no evidence currently supports lateral decubitus as an effective method for improving airway obstruction. (Zaballa et al, 2023)

Managing upper airway obstruction in PRS is complex and requires a multidisciplinary approach. The most recent and relevant articles on this topic include a retrospective chart review of surgical and nonsurgical interventions for PRS at two children's hospitals, which found that interventions included prone positioning, tongue-lip adhesion, nasopharyngeal intubation, continuous positive airway pressure, tracheostomy, and mandibular distraction osteogenesis. The study also found that patients who underwent tracheostomy had a lower birth weight thannewborns with other interventions and that patients who underwent surgical interventions had longer intensive care unit stays. (Čverha et al, 2023)

Another article discusses the importance of and management of airway obstruction in PRS, especially in the context of potential neurocognitive, metabolic, and cardiovascular complications associated with untreated obstructive sleep apnea (OSA). It also highlights the need for serial monitoring and review for persistent or re-emergence of symptoms of airway obstruction throughout childhood. (Cascone et al, 2023; Eustáquio et al, 2020)

Overall, managing airway obstruction in PRS requires a comprehensive and individualized approach, considering the severity of the obstruction, associated anomalies, and patient characteristics. Objective documentation of the effect of ventral decubitus on airway obstruction, at least twice a day, through SpO2 levels and assessment of hypoventilation is crucial for evaluating its effectiveness and improving outcomes for children with PRS. (Čverha et al, 2023)

If this approach proves ineffective, our next step is inserting a nasopharyngeal tube (NPT) or utilizing respiratory support options such as continuous positive airway pressure (CPAP).

4.1.2. Nasopharyngeal Tube (NPT)

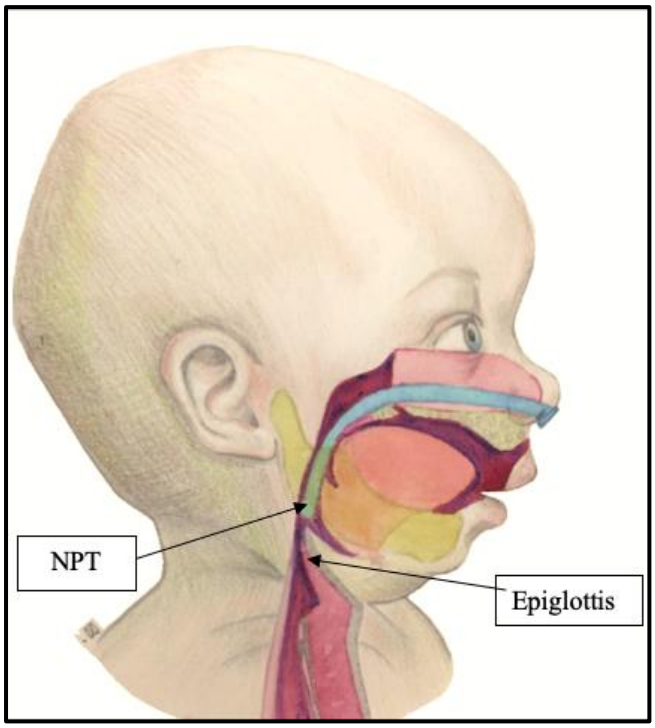

Figure 8. Position of an inserted nasopharyngeal tube.Adapted from (Železnik et al, 2022)

The tip of the NPT is inserted from the nose and directed to the base of the tongue, but just before the epiglottis. It opens the airway at the oropharynx, facilitating feeding and inhaling air. Obstruction may be relieved as the tube disrupts the junction between the tongue and the posterior pharynx (Fig.8).

The placement of the tube using endoscopy or radiography will facilitate the procedure. This technique allows for direct visualization and verification of its position.

This technique is complicated in children, where constant head movement can make keeping the device in a static position challenging.Displacement downwards may trigger the vomiting reflex and irritate the larynx. Displacement upwards may cause the tongue to obstruct the airway again. This technique has complications, including tube patency blockage by secretions and gastric content aspiration. (Železnik et al, 2022)

Nasopharyngeal airway clearance is a temporary measure while awaiting mandibular growth. Its outpatient use requires evidence that airway obstruction is reduced/alleviated, parental involvement in the process, and a specialized team available to support it. (Casale et al, 2024)

4.1.3. Tübingen Palatal Plate (TPP)

The Tübingen Palatal Plate (TPP) is a removable plate worn in the mouth that offers a gentle and highly effective way to treat airway obstruction in infants with PRS (Fig.9). It has three main parts :

- **A Palatal Plate:** covers the cleft palate and stabilizes the upper jaw. When correctly positioned, it simultaneously alleviates the upper airway by pushing the tongue forward and obturating the Cleft palate. However, the patient can breathe and eat normally. (Čverha et al, 2023; Poets et al, 2022)
- **A Velopharyngeal Extension:** This gentle extension reaches the pharynx, pushes the tongue forward, and helps to open the airway (Poets et al, 2022)
- **Extraoral Fixation Bows:** The bows are affixed to the forehead with tape to enhance the plate's retention, while a wire within the extension prevents any breakage that could lead to aspiration (Fig.10). (Knechtel et al, 2023)

The TPP is customized for each baby following a safe semi-digital workflow to avoid intubation or sedation. The plate can be comfortably worn during the day and night, with only brief removals for daily cleaning (Fig.11). Using the digital scan data, technicians create a custom design for the TPP with the help of computers. This computer-aided design (CAD) ensures a precise fit. The design is then sent to a 3D printer for production (CAM). (Knechtel et al, 2023)

In addition to improving airway function, Effert et al.'s study suggests that these appliances may promote faster lower jaw growth. (Effert et al, 2023)

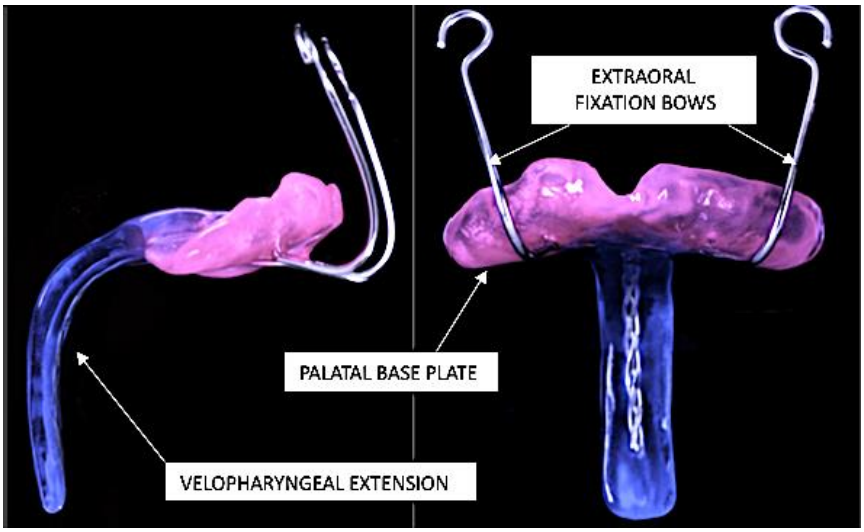

Figure 9. Tübingen palatal plate (TPP). Adapted from(Poets et al, 2022)

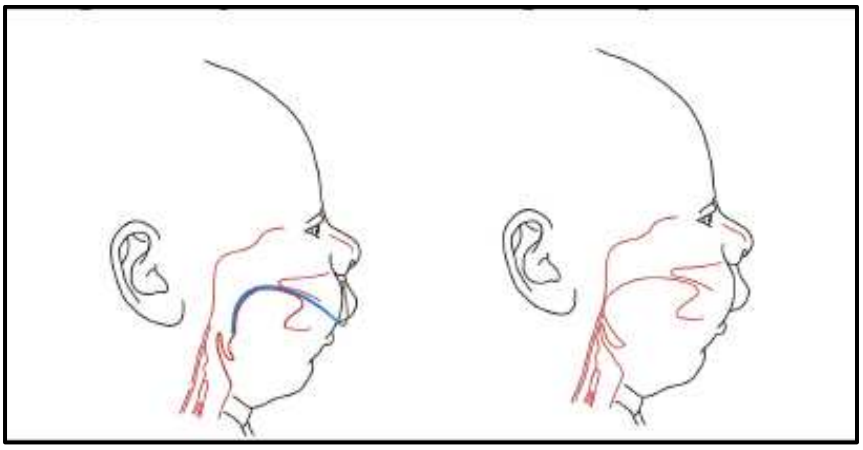

Figure 10. The effect of the Palatal Plate obturates the cleft palate and retracts the tongue. Adapted from (Čverha et al, 2023)

Figure 11. The extraoral fixation bows. Adapted from (Knechtel et al, 2023)

4.1.4. Pre-epiglottic Baton Plate (PEBP)

The pre-epiglottic baton plate (PEBP), commonly known as the Tübingen soft palate plate, is the most used customized orthodontic plate.

While traditional palatal plate therapy addresses palatal defects and guides medial maxillary development, recent adaptations with the PEBP now include a velar extension. This addition guides the tongue forward for a better position against the mandible. On the one hand, the continuous pressure exerted by the anterior tongue placement may stimulate bone remodeling and, consequently, mandibular growth. (Abbas et al, 2022; Wiechers et al, 2024)

Another significant benefit of the PEBP is its ability to ensure the tongue remains positioned away from the cleft, effectively narrowing the cleft width. This feature is precious in surgical procedures. These factors are crucial for achieving normal speech and overall development, a topic we plan to explore in subsequent studies. (Schmidt et al, 2021)

4.1.5. Pneumatic airway stenting with Continuous Positive Airway Pressure (CPAP)

Several studies have highlighted the beneficial effects of CPAP in reducing the strain on respiratory muscles and optimizing the ventilatory process. Despite these advantages, some centers have encountered challenges in utilizing CPAP to address airway obstruction in the PRS due to factors such as the technique's difficulty in very young children and the recent availability of a broader range of nasal mask sizes. Nonetheless, CPAP has shown success in numerous cases involving patients with micrognathism or post-palatoplasty airway obstruction, demonstrating significantly positive responses to therapy. (Zaballa et al, 2023)

However, it is worth noting that prolonged CPAP use has been associated with acquired maxillary hypoplasia. This complication underscores the importance for clinicians to be mindful of potential adverse effects when considering extended CPAP therapy. Consequently, in cases where traditional airway stenting methods like nasopharyngeal airways or nasal CPAP provide no growth stimulus for the mandible, complementary

rather than alternative approaches, such as the addition of high-flow nasal cannula alongside Tübingen Palatal Plate (TPP) treatment, may be incorporated to address persistent upper airway obstruction (UAO) during TPP treatment. While some groups advocate for CPAP as the preferred treatment for UAO in PRS, caution is warranted regarding its prolonged use due to the risk of maxillary hypoplasia. (Poets et al, 2022; Zaballa et al, 2023)

4.2. Surgical Therapy

Children affected by PRS often encounter issues with their palate, hindering their ability to thrive. Proper diagnosis and care for these children require a comprehensive approach involving surgical and nonsurgical treatments. A study by Côté et al. found that 68% of infants with PRS responded well to nonsurgical interventions. Surgical options for infants experiencing significant respiratory obstruction include tongue-lip adhesion and mandibular distraction osteogenesis. In severe cases where respiratory function is compromised, tracheostomy may be necessary. (Santoro et al, 2023)

4.2.1. Tongue-lip adhesion

Glossopexy, a surgical procedure that secures the tongue to the mandible, is crucial in managing the Pierre Robin Sequence (PRS). It has been shown to enhance feeding and alleviate airway obstruction, addressing critical challenges in neonatal care for PRS.

The surgical protocol involves suturing the tongue to the mucous membrane and muscle of the lower lip, addressing the glossoptosis when tracking the tongue forward. Advancements in surgical techniques and materials have improved safety and efficacy, as evidenced by low complication rates reported in recent studies (Fig.12). (Casale et al, 2024)

Multidisciplinary collaboration is essential for patient selection and timing, ensuring comprehensive care for infants with PRS. Glossopexis, thus, stands as a cornerstone in the evolving landscape of neonatal care and surgical innovation for craniofacial anomalies.

The advantage of early intervention is that it relieves immediate respiratory distress and positively impacts neurodevelopmental outcomes, reducing the risk of hypoxic-ischemic injury. (Casale et al, 2024)

This approach is frequently indicated in the isolated PRS as a provisional solution while the mandible grows. Potential complications encompass dehiscence, injury to Wharton's duct, lacerations, and the risk of infection. However, it reduces the need for invasive respiratory support like tracheostomy, enhancing long-term speech development and craniofacial growth outcomes. (Maria Yolanda Yunga-Picón et al, 2023)

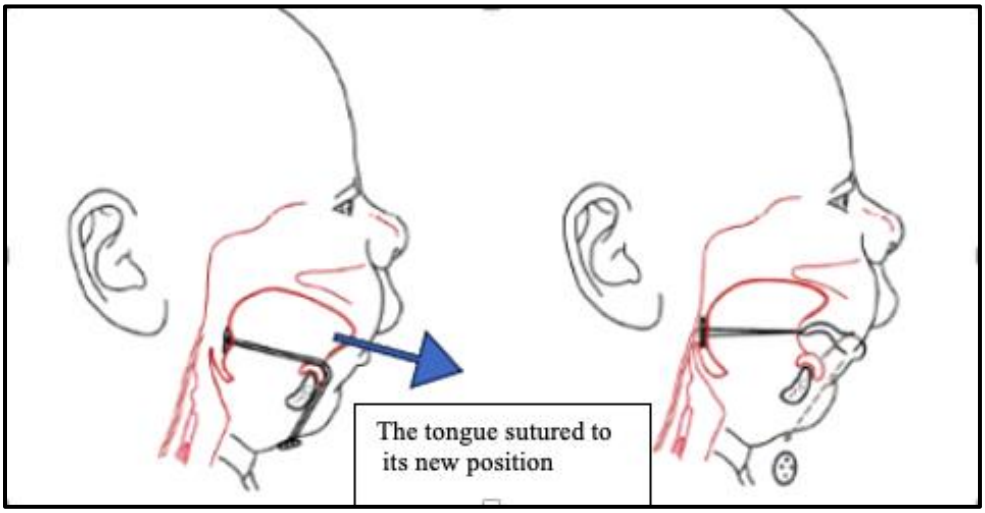

Figure 12. Tongue-Lip Adhesion (TLA) or Glossopexy
(Suturing the tongue to the mucous membrane and muscle of the lower lip to tract the tongue to an anterior position. Adapted from (Čverha et al, 2023)

4.2.2. Mandibular Distraction Osteogenesis (MDO)

In mild to moderate airway obstruction cases, initial management often involves prone positioning, mainly when there are episodic oxygen desaturations at rest or during feeding, signs of carbon dioxide retention, and chronic respiratory acidosis on blood gas analysis.

The MDO involves performing bilateral vertical osteotomy on the hypoplastic mandible associated with the placement of the distractor (Fig.13). It aims to elongate the mandible gradually and continuously 1–2 mm/day until reaching a Class III occlusion. Correcting micrognathia usually and gradually unlocks the pharyngeal airway.

There are two kinds of devices: The external distractor is preferred for its ease of placement and removal. However, it may be susceptible to movement due to external

forces and can lead to scarring at the insertion site. Children generally tolerate the internal distractor better, but its removal necessitates a second surgical time under general anesthesia. (Železnik et al, 2022)

If MDO allows a faster resolution of obstruction, clinicians report many risks, including general anesthesia. The Orofacial complications were Inferior alveolar nerve lesions, dental or follicle damage, and mucosal and bone defects. Scarring on the face was seen when the doctor indicated the external device. (Poets et al, 2022; Železnik et al, 2022)
These complications may interfere with the mandibular growth. (Čverha et al, 2023).

The classic osteodistraction has three successive phases: latency, activation, and consolidation.

- The latency phase occurs immediately after osteotomy, typically lasting 0 to 2 days.
- During the activation phase, mandibular distraction occurs at a specific rate, usually 1mm per day (0.5mm in the morning and 0.5mm in the evening). The desired length of mandibular distraction is assessed based on the initial defect to achieve optimal functionality and/or correct certain malocclusions such as open bite or asymmetry.
- Finally, the consolidation phase allows the mineralization of newly formed bone tissue for 6 to 12 weeks. (Poets et al, 2022)

Consolidation designates the timeframe allocated for bone regeneration and healing at the osteotomy site. Possible complications encompass infection, mandibular osteomyelitis, inferior alveolar nerve injury, bite deformities, and permanent dentition loss. (Abbas et al, 2022; Marston et al, 2022; Prescher et al, 2022)

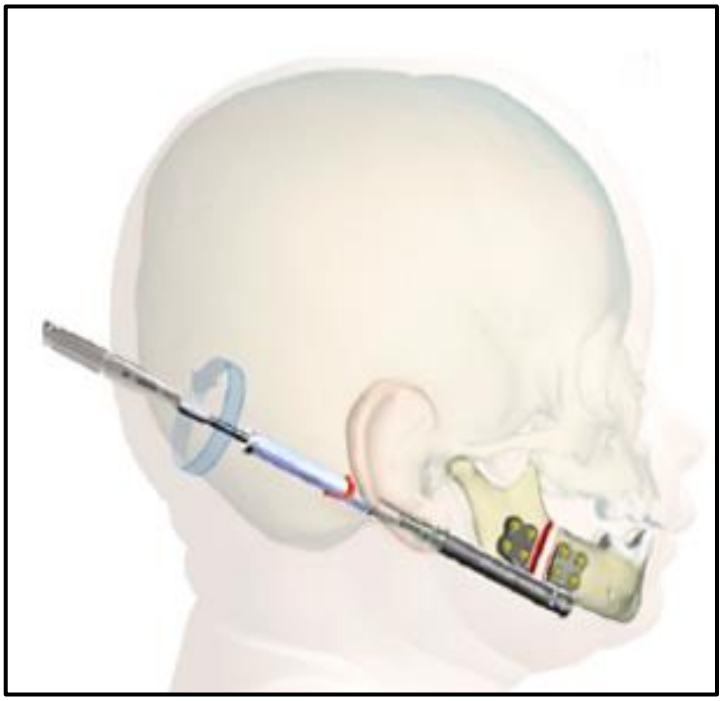

Figure 13. Mandibular Distraction Osteogenesis:
The distractor is screwed to the mandibula after osteotomy.
The activation of the device leads to the progressive lengthening of the mandibula.
Adapted from (Poets et al, 2022)

4.2.3. Tracheostomy

Before MDO became the first-line surgical treatment of Upper Airway Obstructions (UAO), tracheostomy was the gold standard technique. (Abbas et al, 2022)

The protocol involves cannulating the trachea directly through the anterior neck. (Baxter & Shanks, 2024).

Even if it is invasive, it remains the most efficient in relieving advanced cases of airway blockage (like in Grade 3 of Cole's classification of PRS) or when other conservative or surgical techniques are considered ineffective or contraindicated.

Tracheostomy is more common in syndromic PRS cases and is favorable for patients experiencing UAO at multiple sites. (Maria Yolanda Yunga-Picón et al, 2023) .

Associated complications comprise:

- esophageal injury, recurrent laryngeal nerve damage,
- cannula blockages, infection
- pneumothorax, pneumomediastinum,
- prolonged admission in intensive care units of the child. (Baxter & Shanks, 2024)

4.3. Revolution in PRS Treatment: Tissue Regeneration takes center stage

Scientists are on the verge of dramatically changing how Robin sequence (RS) is treated. Inspired by nature's designs, new regenerative dentistry tools pave the way for innovative surgeries focusing on growing new tissues. These advancements involve:

- **Biomimetic materials:** Imagine using materials that mimic bone structure to help the jaw grow properly. Biomimetic hydroxyapatite is making this a reality.
- **3D printing and bioprinting:** These technologies allow the creation of custom-made implants and scaffolds that perfectly fit each patient's needs, promoting bone regeneration.
- **Mesenchymal stem cells (MSCs):** These powerful cells from sources like bone marrow can be used to engineer new cartilage, addressing another aspect of RS. (Čverha et al, 2023)

Beyond Bone: A Holistic Approach

Further than treating hard bones, researchers are exploring ways to improve treatments for the soft tissues by engaging advanced tools such as:

- **Machine learning and AI:** Powerful computers are helping design even more effective orthodontic appliances and biomimetic materials.
- **Personalized medicine:** Tools like Style2Fab (developed at MIT) allow the creation of customized 3D-printed appliances for the patient, ensuring a perfect fit and improved comfort. (Čverha et al, 2023)

Minimally Invasive and More Effective

Harvesting patient's stem cells offers exciting possibilities for less invasive and more effective surgeries. 3D-printed appliances are being enhanced with:

- **Zinc coatings:** These coatings fight bacteria, reducing the risk of infections during treatment.
- **Antimicrobial biomaterials:** These materials further reduce the chance of infections, leading to better treatment outcomes.
- **Finite element analysis:** This technology helps design implants and appliances with the optimal shape to minimize stress on surrounding tissues.

These advancements hold immense promise for the future of RS treatment. We can offer patients more practical, comfortable, and long-lasting solutions by harnessing the power of regeneration and personalization. (Čverha et al, 2023)

III. CONCLUSION

Pierre Robin is a real sequence since the mandibular micrognathia gives the tongue a vertical posterior position before the fusion of the palatal processes, which are separated, creating the cleft palate. When the tongue becomes wedged in the palatal region and the nasal cavities posteriorly, it obstructs the upper airway and is responsible for neonatal respiratory distress.

Furthermore, feeding challenges arise due to issues with suction and swallowing. The presence of a cleft palate often leads to problems such as ear infections and hearing issues. Left untreated, the tongue's position can result in speech difficulties and even neurological problems due to insufficient oxygen.

A cleft palate can lead to two primary issues - seromucousotitis and conductive deafness. If accompanied by glossoptosis, which is challenging to treat, it can result in phonatory disorders during preschool. Moreover, hypoxemic cerebral distress caused by oxygen deprivation often leads to neurological disorders and mental retardation.

The urgent and vital management of the Robin sequence focused primarily on airway patency and feeding support involving nonsurgical and surgical interventions.

Regenerative dentistry is revolutionizing the treatment of PRS. Using biomimetic hydroxyapatite materials and advanced techniques like bioprinting or 3D printing has opened new perspectives in surgical interventions.

Recent research indicates that mesenchymal stromal cells (MSCs) obtained from different sources, such as bone marrow, adipose tissue, and the umbilical cord, exhibit similar biological properties and potential for chondrogenesis. That makes them a hopeful choice for regenerating both hard and soft tissues. This technique can repair the skeletal issues thatunderlie the sequence.

For patients, the hurdles posed by the intricacy of their condition can make conventional surgical interventions problematic.

However, biomimetic principles hold the promise ofcreating novel, nonsurgical techniques. The less invasive the intervention, the greater the quality of life attainable for the patients.

To ensure the best possible outcome, parents and infants must receive the support of a knowledgeable and diverse team of medical professionals. This team can provide an early diagnosis of the syndrome, assess the severity of symptoms, and create a comprehensive treatment plan.

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