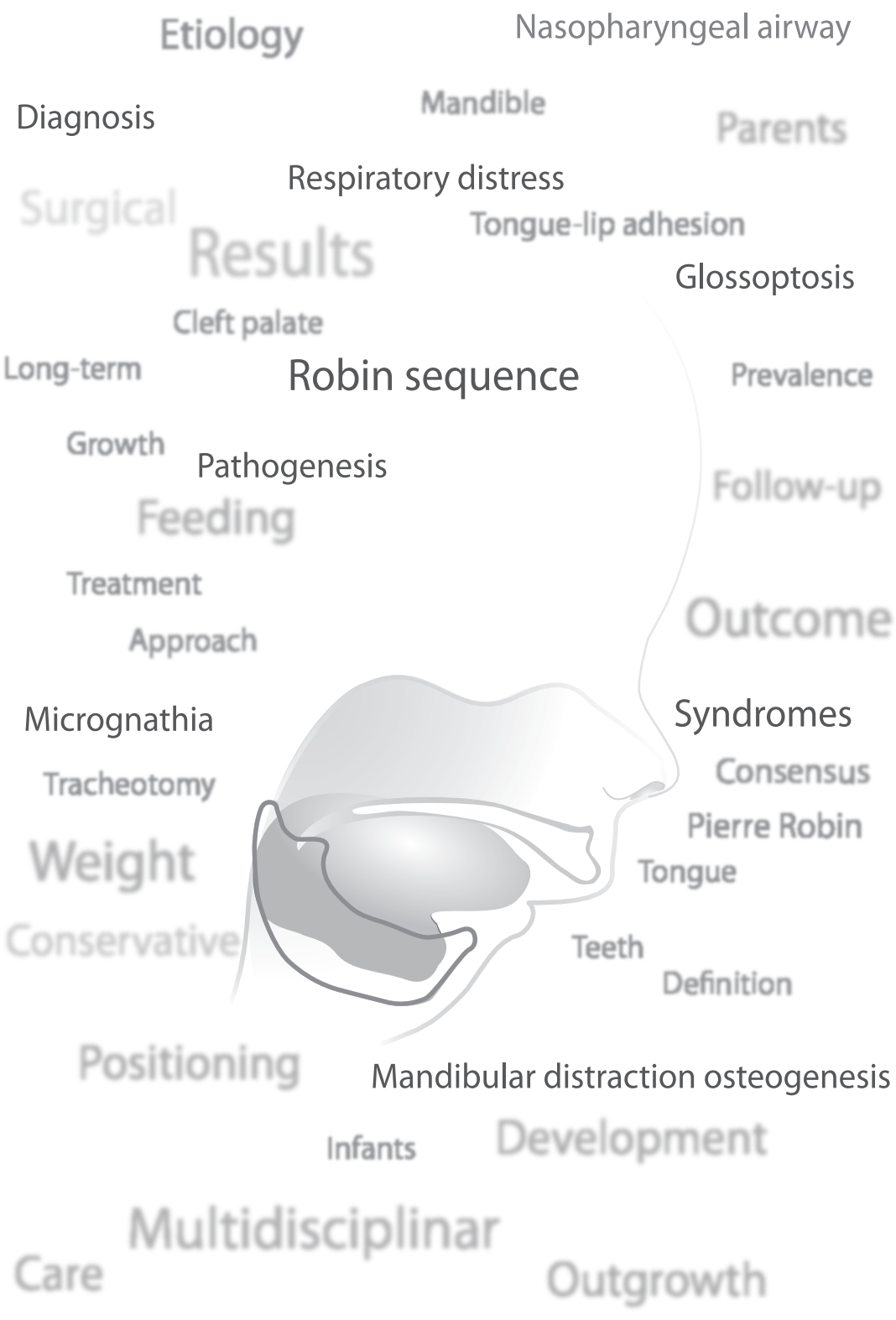
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Care
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PROGRESS TOWARD UNDERSTANDING ROBIN SEQUENCE

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PROGRESS TOWARD UNDERSTANDING ROBIN SEQUENCE

Vooruitgang naar het begrijpen van Robin sequentie
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op
gezag van de rector magnificus, prof. dr. G.J. van der Zwaan,
ingevolge het besluit van het college voor promotie in het openbaar te verdedigen op

donderdag 11 juni 2015 des ochtends te 10.30 uur

door

Emma Constance Paes
geboren op 19 april 1984 te Mainz, Duitsland

Promotor:	Prof. dr. M. Kon
Copromotor:	Dr. C.C. Breugem

Voor Vic

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Robin sequence (RS), a congenital malformation named after the French stomatologist Pierre Robin[1], consists of the triad of micrognathia, subsequently leading to glossoptosis and varying degrees of upper airway obstruction. It occurs in about 1 in 8,000-14,000 newborns[2-4] and is associated with high morbidity. Mortality ranges from 2.2-26%.[5]

As with many disorders, studying its history will ultimately enhance our understanding of RS. In this general introduction, several aspects of the RS will be discussed to create greater awareness of the discrepancies of certain conceptions and highlight the most important controversies; subsequently, the aims of the thesis will be revealed at the end of this chapter.

HISTORICAL PERSPECTIVE

Pierre Robin was born in 1867 and, after completing his doctorate in 1899, became a professor at the School of Stomatology in Paris. From 1914, he was editor of the journal *Revue de Stomatologie*.[6, 7] Though the condition bears his name, Robin was not the first who described the symptoms; St. Hilaire already reported a case of micrognathia in 1822.[8] Thereafter, the triad was described by Fairburn[9] in1846 and Shukowsky[10] in 1911. Robin introduced the term *"glossoptosis"* and the subsequent respiratory difficulty due to a *"dysmorphic atresia of the mandible"* for the first time in 1923.[1] He presented a simple way to examine the upper airway obstruction and proposed an orthodontic apparatus (called a *"monobloc"*) as a treatment for children aged 3-4 and adults in order to restore the normal relationship between the upper and lower jaws. In a later report, in 1934, he described some cases of severe congenital "*mandibular hypotrophy*" leading to "*athrepsia*" and death in infants.[11] He wrote *"I had never seen babies live for more than sixteen or eighteen months who presented hypoplasia such that the lower maxilla was pushed more than 1 cm. behind the upper",* thereby creating awareness of the morbidity of the condition.[11] However, he also noted: *"I have been able to bring a great number of infants to a normal condition by orthostatic feeding, followed by the use of a monoblo*c".[11] In this report he also emphasized the need to hold a baby with glossoptosis in a prone position when it is agitated or stressed in order to *"prevent gurgling and other causes of respiratory disturbance"* (Fig. 1).[11] Robin published approximately 20 papers and a monograph about the disorder, but got carried away by his findings during this process,[8] stating that glossoptosis was present in about three out of five infants and it could predispose a scale of other disorders, such as scoliosis, appendicitis, or varices (Fig. 2). Overall, he deserves the credit for drawing attention to the condition and contributing to our current understanding of it. Pierre Robin died in Paris, in 1950, at the age of 83.[6, 7]

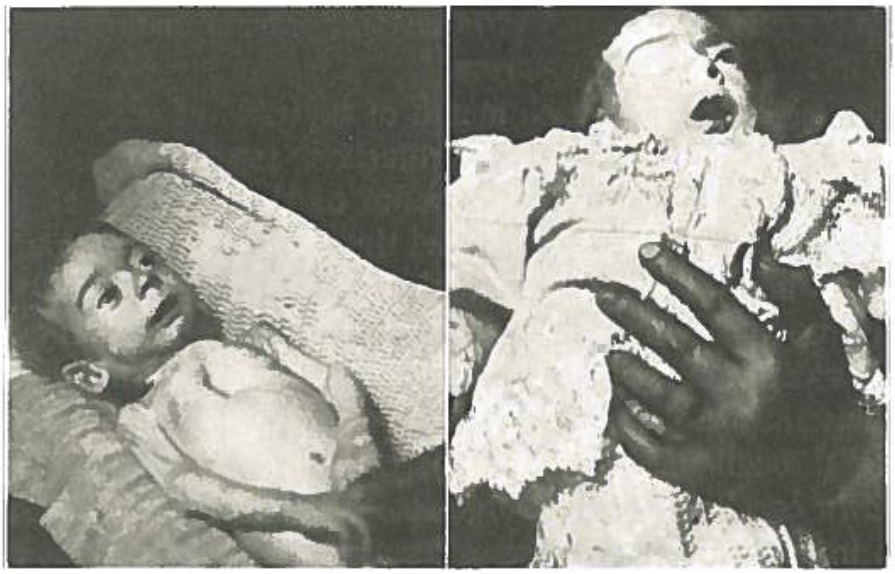

Figure 1 The "orthostatic feeding" treatment as presented the original article of Pierre Robin in 1934.[10] Adapted from Robin.[10]

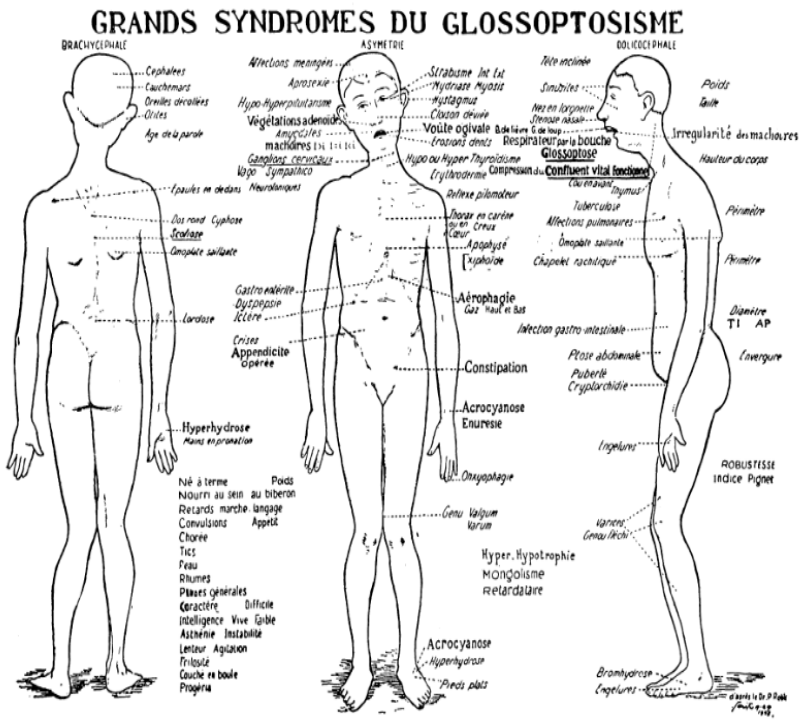

Figure 2 Other related problems that Robin described to be present in the infants. Adapted from Randall.[8]

DEFINITION

Micrognathia with concomitant airway obstruction was already described by St. Hillaire in 1822; however, Robin was the first to introduce the term *"glossoptosis"* to summarize the *"backward and downward fall of the base of the tongue,"* which he noticed was the consequence of the micrognathia.[1] In 1934, Robin described the presence of a wide U-shaped palatal cleft that he believed aggravated the glossoptosis.[11] Currently, there is still no consensus amongst clinicians regarding which features of the sequence should be included in the diagnosis of RS.[12-14] Some clinicians do not consider a cleft palate essential for diagnosis, while others would not include upper airway obstruction as required.[15] Recent analyses amongst members of the American Cleft Palate–Craniofacial Association demonstrated that 14 different definitions were identified, while a survey under Dutch and Belgian Cleft Palate team members demonstrated similar findings.[12-14] It seems obvious to adhere to the triad of characteristics as originally proposed by Robin in 1923;[1] however, the extent to which symptoms are present in infants is highly variable. Not all symptoms must be present at a certain moment, as RS is a dynamic problem, and symptoms could evolve at a later stage to become more obvious or severe.[16, 17]

Just as the symptoms necessary to diagnose the disorder remain controversial, so does the nomenclature of the condition itself. Until the mid-1970s, RS was called *Pierre Robin syndrome*.[18] However, some argued that there was no single identifiable pathogenesis, as occurs in a syndrome, but rather a nonspecific sequence of findings with etiological heterogeneity.[19] Hence, after a better understanding of the dysmorphology, the term *Pierre Robin anomalad* was introduced by Hanson and Smith[20] in 1975, and Cohen[21] in 1976. *Anomalad* was used to describe an etiologically nonspecific complex that could occur as a component of various syndromes or as an isolated symptom secondary to a deformational problem of the mandible.[19] Soon after, the term *Pierre Robin sequence,* proposed by an international working group, was generally accepted;[22] However, it is unusual to use the first name of the person the disease is named after in medicine. Hence, when adhering to the purist, it seems obvious that the condition should be called *Robin sequence*.[13]

The concept of a sequence is well known in medical genetics. Spranger et al.[23] define it as *"a pattern of multiple anomalies derived from a single known or presumed prior anomaly or mechanical factor."*[23] In RS, it is generally agreed that the small mandible is this prior anomaly, which subsequently leads to symptoms like glossoptosis and upper airway obstruction. It is, however, imperative to differentiate between the causative agents of the micrognathia to optimize the treatment strategy. In the majority of patients with the characteristics of RS, an associated syndrome or other malformations are present.[24] A syndrome is defined as multiple anomalies with a single common pathogenesis.[25] While micrognathia could lead to breathing problems, the presence of other anomalies in the same patient might cause these breathing problems. Hence, different mechanisms of obstruction can occur within the same syndrome, and micrognathia and glossoptosis do not necessarily have to be the (only) causes of the upper airway obstruction;[15, 26, 27] this led Cohen to establish a difference between a true *Robin sequence* and a *Robin complex* in 1999.[28]

Due to this causal and nosologic heterogeneity, Shprintzen questioned the merit of applying the diagnosis of RS at all, though he concluded that the eponym is too common to quit being used.[15] Yet, it is imperative that, if RS is regarded as a specific entity and definitive diagnosis, the search for other anomalies and syndromic diagnosis should not stop there.[15] The fact that accurate diagnosis of a syndrome is difficult in the neonatal period emphasizes the need for longitudinal follow-up.

ETIOLOGY

The currently accepted primary pathology of RS is congenital micrognathia. The abnormal development and position of the mandible leads to a high and retroposed position of the tongue, resting against the basicranium.[22] During normal embryogenesis, the tongue lies between the two palatal shelves until the mandible starts growing ventrally and inferiorly, thereby pulling the tongue in the same direction at approximately seven weeks post-conception. Subsequently, the palatal shelves begin their growth towards the midline to complete the palate closure during the 11th week of development.[16] However, the abnormal position of the tongue prevents this by interposing between the palatal shelves, resulting in a typical wide, U-shaped cleft palate[20] (Fig. 3). As an infant is an obligate nose breather, the glossoptosis that obstructs the posterior pharynx can lead to serious upper respiratory obstruction after birth.

The abnormal arrest in mandibular development is causally heterogeneous and can occur at many stages during the ingenious prenatal development of the mandible,[21, 29] possible causes include the following:

1. *Extrinsic abnormalities*. For up to six weeks, the fetus keeps its head in a flexed position onto the chest. Until the 12th gestational week, the head is gradually extended, facilitating a normal outgrowth of the mandible. Any factor that would lead to intrauterine restriction can theoretically prevent normal head extension, possibly leading to micrognathia. Examples include oligohydramnos, multiple birth, uterine abnormalities (tumors, etc.), an abnormal embryonic implantation site, or unstretched uterine muscles within a small uterus.[16, 21, 22]
2. *Intrinsic abnormalities*. Numerous syndromes present characteristic mandibular growth deficiencies,[22] such as Treacher Collins syndrome, in which infants express a highly specific hypoplastic mandible that includes a short mandibular ramus. In Stickler syndrome, a concave depression in the body of the mandible and a shortened ramus is seen. In contrast, in deletion 22q11.2 syndrome, the mandible is normally sized, but retrognathic in position due to the more obtuse cranial base angle.[30] There are many more syndromes in which the presence of mandibular hypoplasia was described, possibly occurring as a result of defects of both generation or growth of Meckel's cartilage in early mandibular outgrowth.[31] Associated anomalies can help direct the clinician towards a correct diagnosis beyond mandibular hypoplasia.[16, 22, 26]

3. *Neurologic or neuromuscular abnormalities*. Inhibited motion of the mandible during fetal development may also prevent the tongue from descending between the palatal shelves, as mandibular growth results from intrauterine oral motility.[32, 29] An anomaly of the prenatal activity of the brainstem, where the neuronal network that controls the cranial nerves is located, could thus explain the anatomic facial features seen in RS.[32-34] This could also onset or influence the severity of the respiratory obstruction and dysphagia due to a lack of voluntary control of the tongue, caused by underdeveloped tongue musculature or innervation. Any syndrome involving neurologic abnormalities, hypotonia, myotonia, or other neuromuscular abnormalities that would inhibit motion, can be a possible cause.[22]

Mandibular development is not only causally heterogeneous, but also phenotypically and pathogenetically variable.[26] More than 80 percent of the infants with RS have anomalies other than the micrognathia and airway obstruction.[15] Phenotypic variability is, for instance, illustrated by comparing the mandible of an infant with Treacher Collins syndrome to an infant with RS that does not suffer additional anomalies. In both conditions, the mandible is short but varies greatly in shape.[26] The symptoms seen in RS can originate from multiple mechanisms other than micrognathia and glossoptosis. For example, respiratory compromise in spondyloepiphyseal dysplasia could also be caused by tracheobronchomalacia, in addition to the upper airway obstruction caused by RS.[35] Other causes for respiratory compromise seen in infants with RS are, for example, neurological abnormalities, pharyngeal hypotonia, or choanal atresia.[12] The diversity of genetic aberrations associated with RS indicates that there are many pathways to reach the same outcome.[31] All of the above emphasizes the need for a thorough investigation of the underlying pathogenesis of this heterogeneous disorder and a longitudinal, multidisciplinary follow-up of the infants.[17] Knowledge of the underlying genetic diagnosis might influence decision-making in treatment strategies.

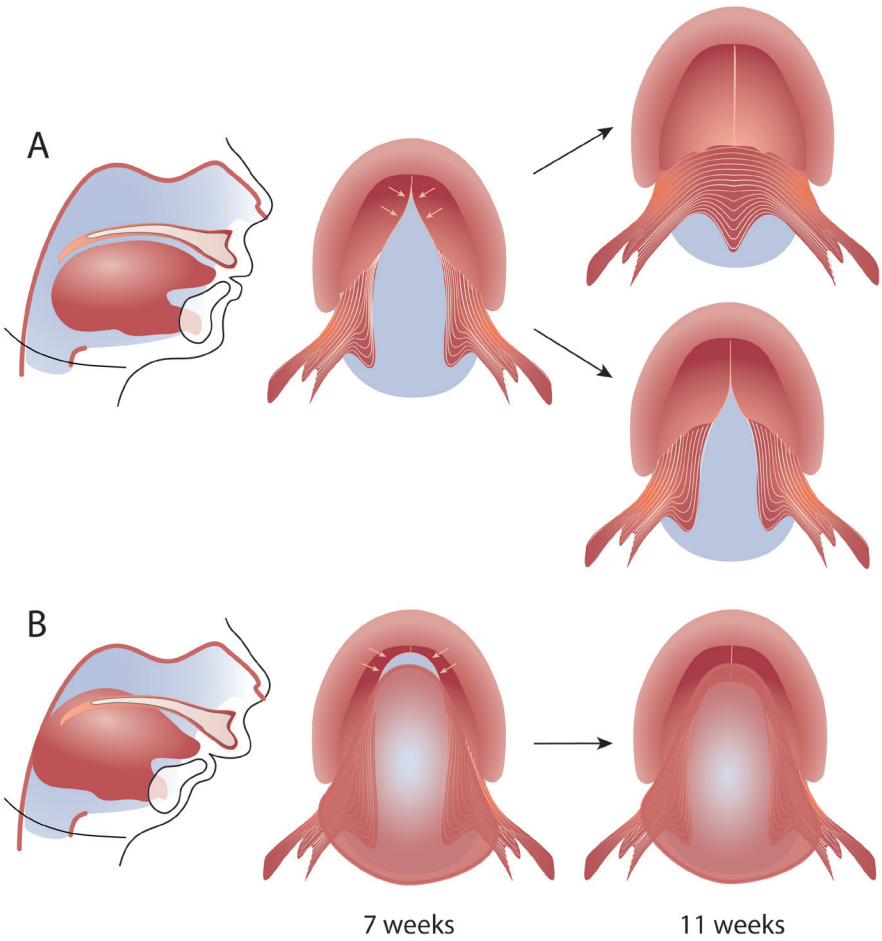

Figure 3 Development of the typical wide (U-shaped) cleft palate, as often seen in Robin sequence. Example of normal palatal closure, or development of a cleft palate (A), and development of a cleft palate as seen in RS; where micrognathia results in a posteriorly displaced tongue which is partially interposed between the closing lateral palatine shelves (B). Based on drawings from Hanson and Smith.[20]

SYMPTOMS AND DIAGNOSIS

As mentioned before, the expressed symptoms may vary in every child and depend on the underlying pathogenesis. Additionally, the airway-related symptoms are dynamic and don't have to be present at the same moment but can evolve during infancy.[16] In general, infants express a typical underdeveloped mandible (Fig. 4), though there is no easily applicable scale to measure this. Van der Haven et al. introduced the "jaw-index" in 1997 to measure micrognathia in newborns.[36] Other methods include lateral cephalograms[37] or 3D-CT scanning[38, 39], although these are not favored because of radiation exposure. Glossoptosis is another characteristic of the sequence. Sher

et al. described how true glossoptosis could be differentiated from other types of upper airway obstruction by utilizing flexible fiber optic nasopharyngoscopy;[40, 41] still, there are currently no easy, reproducible measurements to accurately diagnose micrognathia and glossoptosis.

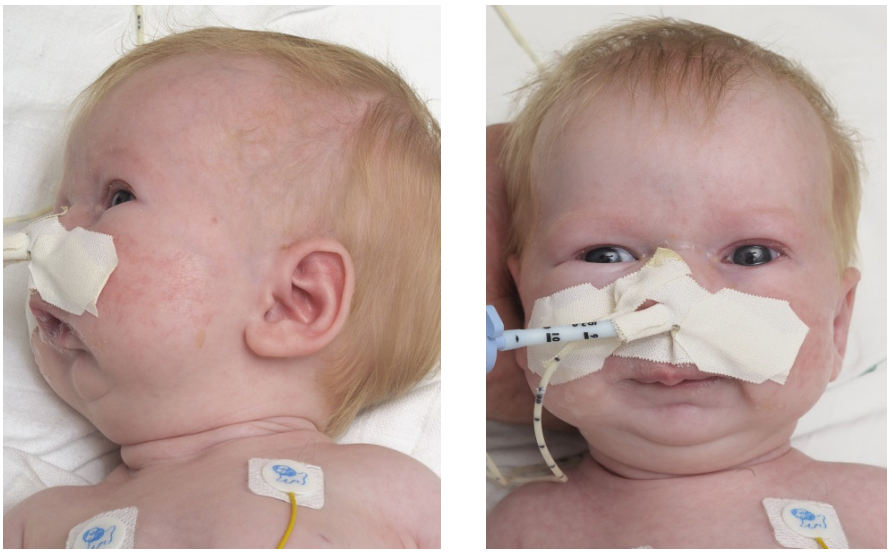

Figure 4 Example of the characteristic micrognathia seen in infants with Robin sequence.

Due to micrognathia and concomitant glossoptosis, the infants express varying degrees of upper airway obstruction. Severe cases will be obvious, where infants will be displaying increased respiratory efforts, such as agitation, altered consciousness level, dyspnea, the use of accessory respiratory muscles, tachypnea, snoring, or stridor.[17] In contrast, some infants will display upper airway obstruction only when they are sleeping and the tongue musculature is more relaxed, thereby more easily obstructing the pharynx.[16] This makes monitoring of oxygen saturation and bicarbonate levels essential for e diagnosis of the upper airway obstruction. On indication, possible other levels of airway obstruction need to be ruled out by additional investigation, such as flexible laryngotracheobronchoscopy or polysomnography.[17, 42]

Infants with RS also frequently express feeding difficulties, such as aspiration, gastro-oesophageal reflux, or swallowing difficulties.[43-46] The increased work of breathing, in combination with physiological abnormalities, impede the infant from successfully coordinating the actions of breathing, sucking, and swallowing. Feeding problems can be directly related to the glossoptosis[43], though oroesophageal motor disorders[33] have also been described as a cause. Concomitant CP or an additional syndrome can also negatively affect feeding. There is a considerable risk of failure to thrive in infants with RS;[47] consequently, these patients are often in need of nasogastric (NG) tube feeding.[48]

Mortality rates vary from 2.2-26% and are usually caused by severe upper airway obstruction, leading to obstructive apnea and secondary cardiac problems, failure to thrive, or other associated comorbidities related to the underlying pathogenesis.[49] Many institutional approaches have been described to date,[17, 50-52, 52, 53, 53-55] which generally include clinical observation, monitoring of CO_2 retention and oxygen saturation levels by continuous pulse oximetry, and assessment of feeding status.[17] Some institutions routinely perform polysomnography. The results are normally interpreted in a multidisciplinary team, yet there is still no consensus about what the ideal work up should entail; additionally, the interpretation of results varies.[17]

TREATMENT

Numerous treatment options have been described to date, but there is still controversy amongst physicians regarding which treatment should be applied and when.[16] In general, the treatment can be divided into conservative and surgical methods. The primary goal is to maintain a safe airway and have adequate weight gain, growth, and development.[17]

Conservative treatment

When there is no life-threatening respiratory obstruction, it is currently agreed that a non-surgical approach is preferred. The oldest established conservative method of treating upper airway obstruction is prone positioning, as described by Robin in 1934.[11] Placing the baby in this position will allow the mandible and tongue to fall forward and reduce airway obstruction at the tongue base level; however, signs of respiratory obstruction might not be visible in this position, increasing the risk of sudden infant death syndrome, and it is more difficult for the parents to interact with the child in this position.[56, 57] Other conservative methods include the nasopharyngeal airway (NPA), short-term endotracheal intubation, CPAP, [58] or the use of intraoral devices. In NPA treatment, an endotracheal tube is inserted (under endoscopic vision) into the nose, so that it ends just superior of the epiglottis and thus opens the obstructed nasopharyngeal space. Preceded by earlier reports[59, 60], Heaf et al. confirmed the benefits and demonstrated clinical improvement after NPA;[61] and others also demonstrated NPA's beneficial applications on feeding and airway problems.[55, 62] Possible drawbacks of NPA include blockage of the tube, dislodgment, irritation of the larynx by inadequate positioning, prolonged treatment duration, and parental burden of care.[56, 57] Intraoral devices, such as custom-made palatal plates, have been recently described;[53, 57, 63-65] a frequently used method is the pre-epiglottic baton plate (PEBP).[65, 66] The tongue is non-invasively moved forward by this orthopedic oral appliance, which subsequently widens the oropharynx; it is speculated, but unproven, that this protrusion of the tongue might stimulate mandibular growth.[66]

Surgical treatment

Surgical intervention is currently pursued if there is a severe airway obstruction that is not alleviated by conservative measures; however, as stated before, exact indications regarding when to proceed to more invasive therapy are highly variable amongst institutions. Consequently, the percentage of infants with RS that can be treated conservatively varies in the literature from 100%[42, 55, 67] to as low as 23%[68]. The kinds of interventions performed vary greatly amongst physicians and depend on the surgeon's education, skills, and preference.[69] Currently, there are five described surgical interventions: tracheotomy, tongue-lip adhesion, release of the muscles of the floor of the mouth, mandibular traction, and mandibular distraction osteogenesis.

For a long time, tracheostomy was considered the 'gold standard' for the treatment of severe respiratory distress in infants with RS;[70, 71] however, tracheostomy is related to a high percentage (51%-77%) of both early and late complications, such as (airway) infections, granulations, tracheocutaneous fistulae, interference with speech and language development, and feeding and swallowing difficulties.[72-74] Tracheostomy-related mortality, most commonly due to accidental decannulation and cannula obstruction, varies between 0.7%– 1.6%.[72, 75] The average age of decannulation in children with RS is 28 months, thereby exposing child and parents to a great medical and social burden[72, 74, 76] Additionally, a delay in speech and language development can develop.[77] Still, in cases of subglottic obstruction due to laryngo- or tracheomalacia, tracheostomy will obviously be the appropriate treatment option when severe respiratory distress is present.[16]

Tongue-lip adhesion (TLA), described as a surgical measure as early as 1902,[10] was popularized by Douglas in 1946;[78] and numerous following studies demonstrated its efficacy in protecting the airway[70, 79-82]. Modifications, such as a subperiostal detachment of the genioglossus, or usage of a bolster sutures tied over buttons, to improve outcomes have been described.[83, 84] Yet, opponents of TLA point to the complications and risks, such as dehiscence, scarring of tongue, lip, and salivary glands, chance of relapse after release of the adhesion, prolonged treatment duration, and delays in speech.[56, 85]

Delorme et al.[86] described subperiostal release of the insertion of the muscles of the floor of the mouth as a method to improve the airway, accomplished by an incision just behind the chin along the inner aspect of the mandible, thereby allowing the tongue base to move in a lower position and relieving the glossoptosis. Although good results were demonstrated by others, no long-term effects of this procedure are described to date.[87, 88]

Mandibular traction, first reported by Callister[89] in 1937 and slightly modified by Longmire[90] in 1949, is based on continuous traction on the mandible, either by springs connected to a halo-frame that surrounds the infant or by suspension weights (50-200 gram). These are connected to the mandible by a percutaneous fixated circumferential wire; no osteotomy is performed. Despite mandibular traction's reported successes in correcting micrognathia, this procedure was rapidly abandoned because of the required long-term immobilization and frequent development of temporomandibular joint ankyloses.[91]

Distraction osteogenesis was first introduced as a method to lengthen the lower extremities.[92-94] Application of the technique to the craniofacial skeleton should be credited to German craniofacial surgeons Wassmund[95] and Rosental[96] in 1926 and 1927, respectively. Mandibular Distraction Osteogenesis (MDO) seemed to be forgotten worldwide until 1972, when Sneyder presented an experimental report in a canine mandible,[97] followed by a clinical report from McCarthy et al.[98] in 1992, which described a rigid external device for distraction of the mandible in congenital deformities.[98] Since then, numerous reports were published, demonstrating the feasibility of MDO in relieving airway obstruction, the prevention of tracheotomies, or making successful decannulation possible.[99-101] The principle of MDO is based on the gradual lengthening of the micrognathic mandible, thereby advancing the tongue and consequently increasing pharyngeal space (Fig. 5).[17] There are two types of devices: external and internal distractors. The preference for using a certain device varies amongst different institutions.[101] The primary advantage of the external distractor is the ability to use multivector movements that can be adjusted during the distraction phase. In internal MDO, there is a smaller risk of pin-associated infections, hypertrophic scarring, and damage to the marginal mandibular branch of the facial nerve.[102-104] Moreover, it averts the disadvantages of a cumbersome external device during the distraction and consolidation period. The unidirectional movement of the internal distracters, however, requires more meticulous planning of osteotomies and vectors than external distracters, and does not allow fine adjustments of mandibular segments to correct any occlusal disharmony that occurs during the distraction process.[105] Internal curvilinear devices have been developed to obviate this problem.[106]

Both internal and external MDO require a second operative procedure for removal of the hardware, obviated by the use of an internal resorbable distractor. MDO with resorbable devices has been widely used in craniofacial surgery for several years;[107] Burstein et al. were the first to present this application in infants was in 2002.[108] Thereafter, its clinical feasibility in relieving upper airway obstruction, specifically in very young infants with RS, has been further demonstrated,[109, 110] though there are no documented long-term results for this method.

MDO has become popular in the surgical treatment of RS. Those in favour state that this is the only treatment that truly addresses the problem of the small mandible that causes the airway obstruction in RS.[16] However, the outgrowth potential is not influenced, making secondary procedures at a later stage sometimes inevitable.[111] Questions regarding the long-term outgrowth and stability of the mandible, the optimal vector, and the presence of tooth damage need to be elucidated.[57] Some authors, therefore, state that as long as the answers to these questions do not exist, MDO is reserved for failures of TLA only.[17, 51]

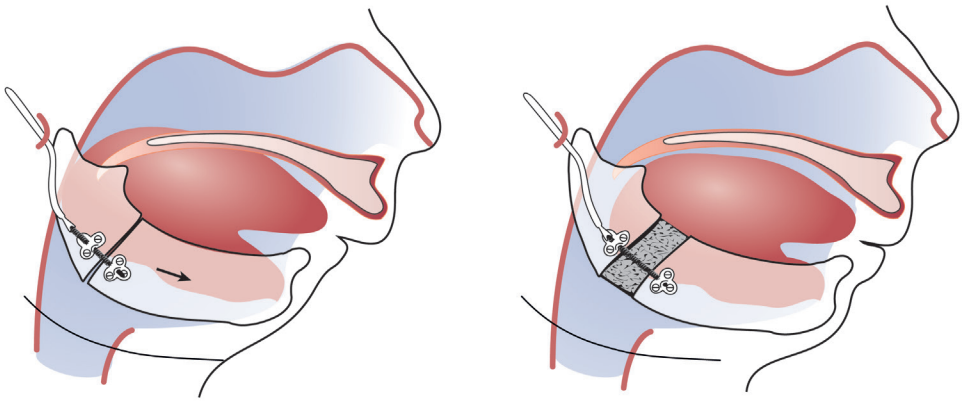

Figure 5 By gradually lengthening the micrognathic mandible, the tongue is advanced out of the pharyngeal space.

OUTLINE AND AIMS OF THE THESIS

In this thesis, we want to provide insight into several aspects of the RS. Our aim is to achieve a better understanding of this challenging group of patients which would then assist in the decision process for the treatment approach, in counseling the involved caregivers, and in managing parental expectations.

Data on RS epidemiology is scarce in the Netherlands. Therefore, in **chapter 2,** the frequency of RS in a CP population and the estimated birth prevalence in live births in the Netherlands, using distinct diagnostic criteria, is detailed. This was done in a multicentre study, including data from the Wilhelmina Children's Hospital in Utrecht, the Academic Medical Center/Emma Pediatric Hospital, and the VU Medical Center in Amsterdam from 2000-2010. Moreover, in **chapter 3**, the underlying pathogeneses are retrospectively analyzed. Over the study period of 1995-2013, all RS patients of the three aforementioned academic centres were re-evaluated with a team of clinical geneticists.

Regarding the optimal approach and different treatment strategies, there are inconsistencies. In **chapter 4**, after a retrospective analysis of the literature, a general overview and information on post-operative outcomes and the complications from the different type of distracters for the treatment of upper airway obstruction in RS is provided. The short-term results of MDO with an internal resorbable device, which has been applied in our institution since 2007, is revealed in **chapter 5**. Currently, there is a paucity of information regarding the long-term results of the internal mandibular distraction system. A detailed description of our experience with this method, during a minimal follow-up of five years, is provided in **chapter 6**. Specifically, the effect on the developing molars and the mandibular outgrowth is addressed and compared to a group of controls. A response to the study of Abel et al.,[62] in which the results of NPA applied to 104 infants with RS is discussed, is presented in **chapter 7**. As the medical system requires both functional outcomes and

cost-effectiveness, we conducted a cost analysis study between two frequently performed surgical interventions in our institution: distraction osteogenesis and tracheostomy (**chapter 8**).
In addition to the respiratory problems, infants with RS also frequently encounter feeding difficulties. Long-term data on growth in RS infants is lacking. In **chapter 9**, a retrospective analysis of weight in the first two years of life is shown. These data were compared to an isolated CP-only group. A systematic literature review was conducted to find reported feeding difficulties in RS patients; consequently, factors that influence feeding and growth in RS are identified.
In **chapter 10,** we present our experience of airway management in RS infants. Additionally, current approaches described in the literature were thoroughly analyzed. Through this, our multidisciplinary team developed recommendations and a pragmatic algorithm that can be applied as a fundament or guidance for other centres involved in the care of infants with RS.
In **chapter 11** the main results and conclusions of this thesis are described. Both the current knowledge and the remaining controversies are discussed and the future perspectives are presented.

In summary, the aims of this thesis are:

- To provide insight into the pathogenesis of RS, and assess the estimated birth prevalence in a large cohort of RS infants of three Dutch Academic centres.
- To provide insight into the different types of mandibular distraction and specifically reveal the short- and long-term outcomes of mandibular distraction osteogenesis with a resorbable device.
- To assess differences in cost between tracheotomy and mandibular distraction osteogenesis.
- To report the presence of feeding difficulties and growth in the first two years of life in infants with RS.
- To develop a pragmatic institutional approach for infants with RS.

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Birth prevalence of Robin sequence in the Netherlands from 2000-2010: a retrospective population-based study in a large Dutch cohort and review of the literature

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ABSTRACT

Background

The birth prevalence of Robin sequence (RS) is frequently cited to be 1 in 8,500 to 14,000 live births (range: 7,1-11,8 per 100.000), which is based on just a few epidemiological studies. The objective of this study is to contribute to the limited knowledge of the epidemiology of RS by determining the frequency of RS in a cleft palate (CP) population and the estimated birth prevalence in live births in the Netherlands, using distinct diagnostic criteria.

Methods

A retrospective population-based analysis of the National Cleft Registry was performed in order to obtain all CP patients registered in the Netherlands from 2000-2010, in addition to a thorough review of the medical records in three Dutch Academic Pediatric Hospitals for the same period. Furthermore, a systematic search of the literature was conducted to allow for comparison of our findings.

Results

The Dutch birth prevalence of RS was estimated to be 1:5,600 live births (or 17.7 per 100,000), with a slight female predominance. RS was estimated to occur in a third of the CP population and patients with RS had a more severe cleft grade than the general CP population. The literature search yielded 42 studies reporting the birth prevalence for RS, which varied between 1:3,900 and 1:122,400 (0.8-32.0 per 100,000), with a mean prevalence of 1:24,500 (8.0 per 100,000).

Conclusions

The birth prevalence of RS in the Netherlands was higher than reported for most other countries when similar diagnostic criteria were used, with a slight female predominance. A third of the general CP could be classified as RS.

INTRODUCTION

Although preceded by several earlier reports[1, 2], Robin sequence (RS) was first thoroughly described in 1923 by the French stomatologist Pierre Robin in a case series of patients with breathing problems, glossoptosis and micrognathia.[3] In a second article published in 1934, Robin included palatal clefts as a concomitant feature.[4]

Notwithstanding the reports by the physician whose name is affiliated to this condition, the debate concerning the essential characteristics has still not been settled. Since the 1960s the condition has been variously described as Pierre Robin syndrome, anomalad, complex or sequence.[5, 6] The main points of discussion in diagnosing RS are the requirement for a cleft palate, the determination of the presence and subsequent degree of micro- or retrognathia, glossoptosis and airway obstruction[7, 8] and the difficulty of diagnosing RS in patients with a syndrome diagnosis.[5, 6, 8-10]

RS is generally cited to occur with a frequency of 1 in 8,500 to 14,000 live births.[11, 12] Only recently two studies provided a more detailed insight in a Robin sequence population of the USA and Germany.[13, 14] The lack of research into the epidemiology of RS may be partly explained by the controversy in the literature about the essential characteristics to define RS. The conflicting choices made in this debate by researchers and clinicians both increase the difficulty of collecting unequivocal epidemiological data and greatly complicate the interpretation of what has been published so far. Since RS is associated with considerable morbidity and even mortality, the exact prevalence of RS is of great importance.

The objective of the present study is to contribute to the limited knowledge of the epidemiology of RS by (1) establishing an estimated birth prevalence RS among the Dutch population using clear diagnostic criteria, after determining the frequency of RS within a population of infants with a cleft palate of three Academic Pediatric Hospitals from the Netherlands and the usage of a Nationwide Cleft Registry and (2) by comparing these findings with previous reports from other countries produced by a comprehensive search of the literature.

MATERIALS AND METHODS

In the present study we chose to adhere to the following criteria to define RS: cleft palate without cleft lip or alveolus (CP), micro- or retrognathia and obstructive respiratory distress.

Two distinct data sources were employed to identify the number of patients born with RS, residing in the Netherlands at birth and not adopted, during the study period of 2000-2010: (1) the Dutch Cleft Registry, managed by the Dutch Association for Cleft Palate and Craniofacial Anomalies (NVSCA), (2) medical records of patients with diagnosed cleft palate of the Wilhelmina Children's Hospital (WCH) in Utrecht, the Academic Medical Center/Emma Pediatric Hospital (AMC) in Amsterdam and the VU Medical Center (VUMC) in Amsterdam. These sources will be separately discussed, followed by a description of the data extraction and analysis. Approval for this study was obtained from a local institutional review board (WAG/om/13/074747).

Dutch Cleft Registry

In the Netherlands all live-born children with an oral cleft are referred to one of the fourteen regional cleft palate teams for registration and treatment. There is no national center for Robin sequence and patients are referred to the geographically closest located cleft center. The Dutch Cleft Registry is an anonymous national database, launched by the NVSCA in 1997. All Dutch cleft palate teams report their new patients to this database and thereby contribute to a nation-wide registry of facial clefts and craniofacial anomalies to facilitate epidemiological and clinical research.[15, 16] The Dutch Cleft Register has proven to be a valuable tool for research because of its excellent validity on all three common oral cleft categories.[15] The primary center of referral completes the registration process, which prevents new patients from being registered twice. The standard recording form consists of a general section for infant/parental characteristics, checkboxes in which the type of oral cleft and associated craniofacial anomalies can be recorded in detail and space for verbatim descriptions and final diagnoses, including syndromes and chromosomal defects. In-depth information on the registry is found in Luijsterburg and Vermeij-Keers.[16]

First, all patients with a CP registered by the Dutch Cleft Registry from 2000-2010 were extracted. Furthermore, all individuals registered with the diagnosis RS -indicated by a verbatim description of the diagnosis added by a presentative of each of the fourteen Dutch regional cleft palate teams during registration- were extracted from the register for the same period (Table 1). No uniform definition is used in this Register to diagnose RS, thus reliability depends on the diagnosis made by the cleft team. Additionally, the extent of the CP was obtained from the database of the Dutch Cleft Registry (Table 2).

WCH/AMC/VUMC cohort

As the agreement on *associated anomalies* between the Dutch Cleft Registry and the patient's medical charts has proven to be moderate to poor, this second data source was used.[17] A retrospective and thorough review was conducted of the medical records of all CP patients registered at the Dutch Cleft Registry by the WCH, AMC and VUMC from 2000-2010, in order to manually identify the individuals with RS. During this search we adhered to the following characteristics to define RS: presence of a CP and micrognathia or retrognathia and obstructive respiratory distress. In addition to the extent of the cleft palate, the degree of respiratory distress and additional malformations could be retrieved (Table 1, 2). The presence of micro- or retrognathia was made after a thorough clinical evaluation by the cleft team members. Presence of respiratory distress was diagnosed after clinical observation and measurement of at least oxygen saturation and carbon dioxide levels. A flexible nasopharyngolaryngoscopy was performed to rule out other causes of upper airway obstruction. The severity of the respiratory distress was subsequently graded according to Printzlau and Andersen[12] (Table 2).

Table 1 Patient characteristics for all patients registered with a cleft palate from 2000-2010

		CP RS	Dutch Cleft Registry RS	WCH/AMC/VUMC
Patients				
Distribution	Total	1194	246	118
	Male	543 (45%)	102 (41%)	56 (47%)
	Female	644 (54%)	143 (58%)	62 (53%)
	Unknown	7 (1%)	1 (0%)	-
Male proportion	95% Confidence interval	42-48	35-48	39-56
Diagnostic criteria				
MG/RG		-	226 (92%)	118 (100%)
GT		-	3 (1%)	47 (55%)[B]
ORD	Total	-	48 (20%)	118 (100%)
	Grade I	-	-	21 (18%)
	Grade II	-	-	41 (35%)
	Grade III	-	-	56 (47%)
CP	Total	1194 (100%)	227 (92%)	118 (100%)[C]
	Grade I	143 (12%)	6 (3%)	1 (1%)
	Grade II	478 (40%)	50 (22%)	36 (31%)
	Grade III	276 (23%)	68 (30%)	36 (31%)
	Grade IV	297 (25%)	103 (45%)	44 (37%)
Test cleft grade (χ^2-test)[A]		Ref.	$\chi^2 = 64.7$ $p < 0.001$	$\chi^2 = 25.1$ $p < 0.001$

CP: Cleft Palate only, RS: Robin Sequence, MG/RG: Micrognathia/Retrognathia, ORD: Obstructive Respiratory Distress, GT: Glossoptosis, WCH: Wilhelmina Children's Hospital, AMC: Academic Medical Centre/ Emma Pediatric Hospital, VUMC: VU Medical Center
A: Test of cleft grade, H_0: distribution of cleft grade equal to that of CP
B: WCH/AMC (57% of 77 pts), data not retrievable for the VUMC
C: CP grade unknown in 1 patient

Data analyses

A distinct birth prevalence of RS was calculated, using the number of total live births for the period 2000-2010 from the Dutch Central Statistics Office.[18] Subsequently, a second estimate was calculated by extrapolating the *regional* RS:CP ratio of the WCH/AMC/VUMC patient cohort to the *national* level from the Dutch Cleft Registry database. Cleft grade was compared between the RS and CP groups. Statistical testing was conducted using a Chi-square test (IBM SPSS Statistics 20.0, IBM Inc., NY, USA) and calculations were performed using Microsoft Excel (Microsoft Inc., Redmond, WA, USA).

Table 2 Diagnostic classifications

Cleft palate grade*	Extension of cleft palate
1	Submucous cleft or bifid uvula
2	Soft palate
3	Soft palate and segment of the hard palate
4	Soft palate and hard palate up to incisive foramen

Grade of respiratory distress**	Description of respiratory distress
0	No respiratory problems
1	Mild: consistent respiratory problems during feeding but only intermittently during supine positioning
2	Moderate: consistent respiratory problems in the supine position and intermittently during sleep
3	Severe: respiratory problems at rest, even in prone position

** Modified "Jensen et al. cleft palate classification" (1988), according to the division made in the Dutch Cleft Registry database*
*** According to Printzlau and Andersen, 2004*

Systematic literature review

A comprehensive search in the PubMed and Embase database was conducted to identify previous studies into the epidemiology of RS published until September 2014 (Table 3). Studies specifically focusing on RS or presenting the epidemiological characteristics of populations with CP, or a wider spectrum of congenital anomalies, were included. The language of publication was not an exclusion criterion. Articles without a clear methodology, nor describing the number of patients with RS in their cohort, were excluded. For each study identified, information on the time period, research area, data source, definition of RS and number of patients enrolled was collected. The search was performed independently by two authors without any disagreement (DvN and EP).

Table 3 Search query for the literature search

PubMed	("robin"[Title/Abstract] OR "cleft"[Title/Abstract] OR "clefts"[Title/Abstract]) AND ("epidemiology"[Title/Abstract] OR "epidemiologic"[Title/Abstract]) OR "epidemiological" [Title/Abstract] OR "Birth prevalence"[Title/Abstract] OR "prevalence"[Title/Abstract])
EMBASE	(robin:ab,ti OR cleft:ab,ti OR clefts:ab,ti) AND (epidemiolog:ab,ti OR epidemiologic:ab,ti OR epidemiological:ab,ti OR Birth prevalence:ab,ti OR prevalence:ab,ti)

RESULTS

Birth prevalence – Dutch Cleft Registry

In the years 2000-2010 a total number of 1194 patients with CP were born and could be retrieved out of the Registry. Of these, 246 were labeled with the diagnose Robin sequence in the Dutch Cleft Registry. During 2000-2010 a total of 2,113,858 live births were recorded in the Netherlands.[18] This yields a birth incidence of 1:8,593 (11.6 per 100,000) (Table 4).

Table 4 Birth prevalence of Robin sequence in the Netherlands from 2000-2010

Database	Population	Cases per 100.000 live births		Ratio of births to cases	
		Point estimate	95% Confidence interval	Point estimate	95% Confidence interval
Dutch Cleft Registry	Total	11.6	10.2-13.1	8,593	9,820-7,638
	Male	9.4	7.6-11.2	10,615	13,171-8,890
	Female	13.9	11.6-16.1	7211	8,624-6,195
WCH/AMC/VUMC*	Total	17.7	-	5,891	-
	Male	16.5	-	6,163	-
	Female	18.8	-	5,687	-

** Containing at least cleft palate, micro- or retrognathia and obstructive respiratory distress in medical records*
WCH: Wilhelmina Children's Hospital, AMC: Academic Medical Centre/Emma Pediatric Hospital, VUMC: VU Medical Centre (Numbers calculated after extrapolation to national levels)

Birth prevalence – WCH/AMC/VUMC cohort

A total of 376 patients born with CP during 2000-2010 were registered and treated in the WCH/AMC/VUMC. One hundred-ten of these patients suffered from co-morbid micro- or retrognathia and obstructive respiratory distress and fulfilled our definition of RS. Forty-four of them were additionally diagnosed with glossoptosis; its presence or absence was poorly recorded for the remaining patients. One third (n=118, 31%) of the CP population (n=376) of the WCH/AMC/VUMC cohort suffered RS. After extrapolating this *regional* RS:CP ratio (of the WCH/AMC/VUMC cohort) to the *national* CP figure (of the Dutch Cleft Registry cohort) a birth prevalence of 1:5,641 (round off 1:5,600) or 17.7 per 100,000 was obtained. Similar calculations by gender showed a higher birth prevalence for women (Table 4).

Additional patient characteristics

A significant female predominance was observed in the CP and RS group of the NVSCA database, while a non-significant female predominance was seen in the WCH/AMC/VUMC group. On average a more severe cleft grade was found in the RS population than in CP (Table 1, Fig.1). Furthermore, RS patients experienced considerable respiratory distress, with 49% registered with severe difficulty breathing, even in the prone position (Table 1,2).

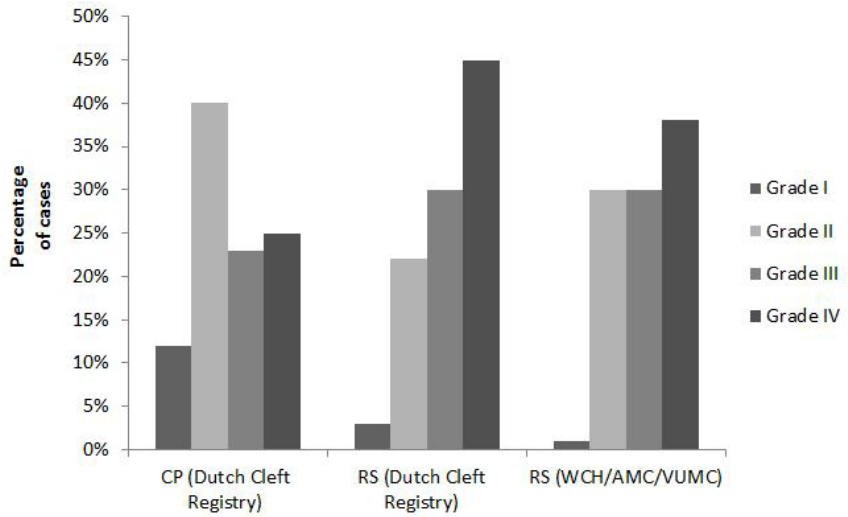

Figure 1 Distribution of the severity of the cleft in the patient groups. Cleft palate grade explained in table 2.

The diagnosis of the WCH/AMC/VUMC group are listed in Table 5. All individuals with a CP were assessed by a clinical geneticist, who is part of the cleft team. Cytogenetics or molecular genetics to investigate the possibility of chromosomal anomalies at 22q11.2, and a formal ophthalmological examination to check for ocular features of Stickler syndrome were performed routinely. If Stickler syndrome was suspected, DNA analysis for at least *COL2A1*, *COL11A1* and *COL11A2* was conducted. All RS patients were recently re-evaluated to confirm or re-asses the diagnosis. This revealed that 36% (n=43) of the patients had isolated RS, and the majority (n=75, 64%) suffered an underlying genetic disorder. In 15% (n=11) of these non-isolated RS infants a chromosome anomaly was found and in 44% (n=33) a Mendelian disorder. In 41% (n=31) an unknown cause was detected. If a chromosome imbalance was detected but uncertainty about its causal role remained, we grouped this patient in the unknown-cause group. In-depth information can be found in other work of our institutions.[59]

Table 5 Overview of the diagnoses in 118 patients with Robin sequence treated in the WCH/AMC/VUMC*

Underlying cause	Amount of patients (n)
Total	118
Isolated	43
Nonisolated	75
Chromosomal	11
Mendelian	33
Unknown cause	31

** A full description of these diagnoses is described in work by Basart et al.[59]*

Systematic literature review

The literature search and cross-referencing identified 42 articles with figures on the birth prevalence of RS and a description of data sources and methodology (Table 6). Only four studies specifically focused on RS[11-14], while the remaining 38 studies[19-42] presented the epidemiological characteristics of populations with CP or a wider spectrum of congenital anomalies. Different sources were used, but the majority of data was collected from medical records[43-54] or congenital malformation registries.[11, 12, 14, 20-23, 25, 26, 31, 33, 36-40, 42, 43, 45, 47, 55] Some (additionally) used birth certificates[19, 24, 27-30, 33-35, 39, 43-46, 48-54], the records of insurance companies[20, 32, 36, 38], an institute for speech disorders[56], a national healthcare system[41]. The diagnostic criteria for RS were specified in 19 studies[13, 21] but were variable. Most frequently, the criteria contained at least CP and micro- or retrognathia[11-14, 19, 20, 24, 25, 29, 33-35, 37, 38, 41, 46, 49, 53, 55] Only four studies fulfilled the criteria of CP, micro- or retrognathia and obstructive respiratory distress, as used in the current study.[13, 19, 24, 25, 33, 34, 46, 49, 53, 55]

A total of 2673 patients with RS were reported in all studies combined. The birth prevalence varied between 1:3,900 and 1:122,400 (.8-32.0 per 100,000) with a median of 1:14,500 (6.5 per 100,000) and mean of 1:24,500 (8.0 per 100,000). Although sixteen studies provided the number of male and female patients, no gender-specific birth prevalence for RS was presented in any study.

Table 6 Overview of the literature

	General population										Robin sequence	
Study	Period	Area of study	Source of data*	Type of births**	Diagnostic criteria Robin sequence***	Number of births (n)	Number of CP (n)	Total (n)	Male (n)	Female (n)	Cases per 100,000 births	Ratio of cases to births
Addor et al., 2003	1990-1999	Switzerland (Vaude)	CMR	-	CP, RG	77,259	60	11	-	-	14.2	7,024
Andersson et al., 2010	1960-2002	Norway (Oslo, 60% of all births)	BC, HR	L	CP, RG, AO	1,684,746	994	116	52	64	6.9	14,524
Bellis and Wohlgemuth,1999	1971-1990	Scotland (Southeast)	HR, statistics division NHS	-	-	356,733	149	53	29	24	14.9	6,731
Bister et al., 2011	1993-1997	UK (Cambridge)	HR	L,S	-	23,577	10	1	-	-	4.2	23,577
Bittar, 1998	1991-1993	Lebanon (South Beirut)	HR	L	-	3,865	-	1	-	-	25.9	3,865
Bush and Williams, 1983	1960-1982	UK (Liverpool)	HR	L	U-shaped CP, hospitalization for >28 days with RD and FD	1,048,800	-	110	63	47	5.0	9,535
Calzolari et al., 1988	1978-1986	Italy (Emilia Romagna)	CMR	L,S	CP, MG, GT	150,168	88	14	-	-	9.3	10,726
Chetpakdeechit et al., 2010	1975-2005	Sweden (Southwest)	HR, PR	L	CP, MG/RG	535,320	343	52	-	-	9.7	10,295
Chi, 1974	1964-1966	Australia (New South Wales)	HR	L	-	14,7042	56	7	-	-	4.8	21,006
Clementi et al., 2000	1996-1998	Europe (12 countries)	CMR	L, S, TOP	-	709,027	198	23	-	-	3.2	30,827
Cornel et al., 1992	1981-1988	Netherlands (Groningen, Drenthe)	CMR	L, S, TOP	-	73,879	48	7	-	-	9.5	10,554
Czeizel, 1980	1970-1976	Hungary (whole country)	CMR	-	CP (unspecified), abnormalities face, neck, skull region (unspecified), and digestive system	1,300,000	588	65	-	-	5.0	20,000
Czeizel and Hirschberg, 1997	1980s	Hungary	CMR	-	-	-	-	-	-	-	6.0	-
Dreise et al., 2011	2008-2009	Uganda (Kampala)	HR	L	-	26,186	1	1	0	1	3.8	26,186
Elahi et al., 2004	1998-2001	Pakistan (Northwest Frontier)	BC	L	-	61,156	28	3	-	-	4.9	20,385
FitzPatrick et al., 1994	1980-1984	Scotland (West)	HR, CMR	L, S	CP, MG	187,321	147	23	9	14	12.3	8,144
Genisca et al., 2009	1997-2004	USA (11 states)	CMR	L, S, TOP	CP, mandibular hypoplasia	2,731,809	1,194	279	-	-	10.2	9,791
Gilmore and Hofman, 1966	1943-1962	USA (Wisconsin)	CMR	L	MG	1,712,977	640	14	-	-	0.8	122,356
Greene et al., 1964	1956-1960	USA (California, Hawaii, Pennsylvania, Wisconsin)	HR, BC	L	-	3,578,438	1,270	49	-	-	1.4	73,029
Hagberg et al., 1998	1991-1995	Sweden (Stockholm)	HR, PR	L	Isolated CP, extreme RG, AO	122,148	90	10	2	8	8.2	12,215
Harville et al., 2007	1967-1998	Norway (whole country)	BC, HR	L, S	CP, "other (unspecified) facial anomalies"	1,847,312	1,227	24	-	-	1.3	76,971
Hewson and McNamara, 2000	1980-1996	Ireland (Galway, Mayo, Roscommon)	HR, CMR	L	-	92,318	37	6	2	4	6.5	15,386

Higurashi et al. 1990	1972-1985	Japan (Tokyo, single hospital)	HR	L	-	27,472	-	1	-	-	3.6	27,472
Ingalls et al., 1964	1959-1961	USA (Philadelphia, Allentown)	HR	L	-	91,463	30	3	1	2	3.3	30,488
Jenssen et al., 1988	1976-1981	Denmark	Records Institute for Speech Disorders	L	isolated CP, extreme RG, AO	359,027	186	14	7	7	3.9	25,645
Kim et al., 2002	1993	South-Korea (whole country)	Records medical insurance firms	L	-	715,817	107	7	-	-	1.0	102,260
Knox and Braithwaite, 1962	1949-1958	UK (Northumberland, Durham)	HR, SS	L	CP, MG	404,124	188	5	-	-	1.2	80,825
Kozelj, 1996	1973-1993	Slovenia (whole country)	HR, CMR	L	-	590,249	360	54	25	29	9.1	10,931
Lary and Paulozzi, 2001	1968-1995	USA (Atlanta metropolitan area)	CMR	L	-	853,456	-	65	43	22	7.6	13,130
Lilius, 1992	1975-1985	Finland (whole country)	HR, CMR	L	-	713,038	938	29	-	-	4.1	24,588
Milan et al., 1994	1981-1989	Italy (Emilia Romagna, Veneto, Friuli)	CMR	L, S	CP, MG, GT	561,539	503	36	15	21	6.4	15,598
Nazer et al., 2001	1991-1998	Chile (Santiago)	HR	L, S	-	22,957	12	2	-	-	8.7	11,479
Owens et al., 1985	1960-1982	UK (Liverpool, surrounding area)	CMR	-	-	325,727	153	27	-	-	8.3	12,064
Printzlau and Andersen, 2004	1990-1999	Denmark	CMR, HR	L	CP, RG/MG, RD	670,001	-	48	24	24	7.2	13,958
Paes et al., 2014	2000-2010	The Netherlands	HR, CMR	L	CP, RG/MG, RD	2,113,858	1,194	113	55	58	17.0	5,891
Robert et al., 1996	1973-1992	Central-East France, Sweden, California	CMR	-	CP, strong MG	5,143,793	2527	494	243	242	9.6	10,413
Sarkozi et al., 2005	1973-1982	Hungary (whole country)	CMR	L	-	1,667,166	632	101	-	-	6.1	16,507
Scott et al. 2014	2006-2009	USA (38-44 states)	NHS	L	CP, MG	1,654,805	-	529	267	260	32.0	3,128
Stoll et al., 2003	1996-1998	Europe (11 countries)	CMR	L, S, TOP	-	709,030	198	23	-	-	3.2	30,827
Tolarova and Cervenka, 1998	1983-1993	USA (California)	CMR	L, S	-	2,509,881	784	134	-	-	5.3	18,730
Vallino-Napoli et al., 2006	1983-2000	Australia (Victoria)	CMR	L, S, TOP	CP, MG	1,140,668	833	112	-	-	9.8	10,185
Vatlach et al. 2014	2011-2012	Germany	HR by prospective inclusion	L	RG/MG and CP/AO/GT/ FD/ weight< 3rd perc. at admission or RS-associated syndrome	662,712	-	82	38	44	12.4	8,082
Womersley and Stone, 1987	1974-1985	UK (Glasgow)	CMR	L, S, TOP	-	158,668	129	38	-	-	23.9	4,175

** Source of data: Hospital records (HR), Congenital malformation registry (CMR), Social services (SS), Birth certificates (BC), Population registry (PR), National Healthcare System (NHS)*
*** Type of births: life (L), stillborn (S), termination of pregnancy (TOP)*
**** Diagnostic criteria: Cleft Palate (CP), Retrognathia (RG), Micrognathia (MG), Airway Obstruction (AO), Respiratory Distress (RD), Feeding Difficulties (FD), Glossoptosis (GT)*

R1 R2 R3 R4 R5 R6 R7 R8 R9 R10 R11 R12 R13 R14 R15 R16 R17 R18 R19 R20 R21 R22 R23 R24 R25 R26 R27 R28 R29 R30 R31 R32 R33 R34 R35 R36 R37 R38 R39

DISCUSSION

The current study provides a reliable basis to make an estimate of the birth prevalence of Robin sequence in the Netherlands. Clear diagnostic criteria were used, in contrast to the highly variable criteria in the epidemiological literature described to date. Moreover, general clinical features that give more insight in the medical implications of RS were addressed.

Methodological issues

An estimate of the birth prevalence of RS in the Netherlands was produced by using two sources. This approach was the consequence of (1) the ongoing debate about the definition and diagnostic criteria of RS and (2) the lack of a national database, accurately recording the clinical characteristics of patients suspected of RS.

First, the disagreement among physicians about what constitutes RS, decreases the reliability of diagnosing RS in the Dutch Cleft Registry.[12, 20, 37, 41] Secondly, incomplete registration of the clinical characteristics of patients in the Registry, leads to a subsequent under registration. Recently, Rozendaal et al.[6, 7] performed a validation study of the Dutch Cleft Registry for the period 1997-2003 in which the recorded information for a random sample of 250 patients was compared to the information contained in the medical records of the regional cleft teams. They found a high level of agreement between the Registry and medical records considering the specific facial cleft diagnosis.[15, 17] However, they determined that 77% of associated craniofacial anomalies and 80% of congenital malformations in other organ systems were not registered with the Registry, mainly due to delayed diagnosis or deficient recording.[15] Accurate and complete recording depends on the knowledge and the willingness of physicians. However, mild congenital abnormalities are difficult to observe or may reveal themselves later in life. Moreover, as soon as the initial registration at the Dutch Registry is performed, additional changes can only be made within 24 hours. As a consequence, a diagnosis such a RS is likely to be underreported in the registry.

These reasons prompted us to include supplementary data from a thorough review of the patients records of three cleft centers in order to identify the individuals with CP, micro- or retrognathia and obstructive respiratory distress. The subsequent extrapolation of the regional RS:CP ratio to the national number of CP patients yielded a theoretical national birth prevalence for RS. Underlying this approach was the crucial assumption that the proportion of RS in the group treated by the regional cleft palate team was closely similar to the proportion on the national level. An important fact to this assumption is that there are no national referral center for infants with Robin sequence in the Netherlands. Patients born with a CP are referred to the closest cleft center, where they are registered in the Dutch Cleft Registry. Thus, there was no *a priori* selection of patients amongst regional cleft palate teams, and only patients who were *primarily* registered in the WCH, AMC or VUMC, and thus no referrals, were included. Hence, the resulting birth prevalence of 1:5,600 live births (or 17.7 per 100,000), represents a good and valid estimate of the data available for RS in the Netherlands.

Epidemiologic aspects

The estimated birth prevalence of RS in the Netherlands is more than double the 1:14,000 found for Denmark by Printzlau and Andersen, who used identical diagnostic criteria.[17] In that study newborn babies with a CP were seen by a cleft nurse at home after birth. Within the first 24 months of life they were seen by the physician, just before the palatoplasty. At that moment a possible micro- or retrognathia was evaluated. "As this could be anywhere in the first 24 months, it is conceivable that patients in which the symptoms resolved during this 24 months period prior to consultation by the physician, were subsequently missed." The Dutch birth prevalence is also higher than 1:8,500 obtained by Bush et al. for Liverpool[12] and 1:8,000 by Vatlach and co-workers for Germany[11]. However, both these studies utilized different and more strict diagnostic criteria, such as concomitant feeding problems or a minimal period of hospitalization. This could have excluded the less severe RS patients. Three reports described a higher birth prevalence than ours.[14] However, diagnostic criteria were either not specified or not comparable to ours, which could lead to an overestimation. In comparison with the epidemiological studies of CP populations that employed similar diagnostic criteria for RS as in the current study, the birth prevalence was lower in Denmark[13, 23, 54]1:25,600; 3.9 per 100.000), Sweden[41] (1:12,200; 8.2 per 100.000) and Norway[37] (1:14,500; 6.9 per 100.000). Although these studies use uniform criteria for defining RS, limitations in accurate classification of a patient as RS, may have accounted for the variation in birth prevalence. For example; how should one interpret an "extremely retrognathic mandible" as described by Hagberg and co-authors?[20] Moreover, other factors such as the accuracy of a certain registration method or possible genetic and environmental factors may have an influence. It has also been demonstrated that the incidence of cleft palate differs per location (for instance higher in Finland when compared to other parts in Europe), making it conceivable that the incidence of RS could also be different in different geographical areas.[37] Comparison with the other 37 epidemiological studies is hampered by the use of less stringent diagnostic criteria.

While this study observed a (non-significant) female predominance among RS patients of our WCH/AMC/VUMC cohort, no clear pattern emerges from the literature. The distribution of the severity of respiratory problems experienced in the population from the WCH/AMC/VUMC was roughly similar to that reported by Printzlau and Andersen.[57] Although in the present study the method of cleft grading differed from the Danish study, a complete cleft (grade 4) was defined similarly and was found in 38% of the Dutch patients compared to 15% of patients in Denmark.[12] A more severe cleft (grade 3/4) was seen in the RS population, compared to the CP population (Fig.1, Table 1). Similar to Printzlau and Andersen[20], we did not find a correlation between the respiratory distress in relation to the severity of the cleft. Forty-six % of the infants of our RS cohort group had non-isolated RS. According to others, the majority (19%) suffered Stickler (Table 5).[12]

Diagnostic criteria

As already described by Breugem et al.[12], but also illustrated by our literature search (Table 6), a widespread confusion exists about the definition of Robin sequence. The current study revealed that the least registered feature of RS in both the Dutch Cleft Registry and regional patient medical records was glossoptosis. This could be explained by the absence of a dedicated field or text box for glossoptosis on the registration form of the Dutch Cleft Registry, but also by uncertainty over what constitutes glossoptosis and the difficulty of establishing its presence. Etymologically derived from the Greek *glossa* (tongue) and *ptosis* (falling), glossoptosis implies a retraction or downward displacement of the "lazy" tongue with clinical significance as a cause of obstruction of the pharyngeal airway. In RS this symptom is part of a sequence caused by a retro- or micrognatic mandible, which, in turn, can lead to various degrees of respiratory distress. The difficulty in determining glossoptosis might be due to the fact that intra-oral inspection does not immediately reveal the presence of this feature, as it sometimes is a "dynamic" problem, and no easily applicable scale of measurement exists. Sphrintzen[6, 9] and Sher[10] showed that upper airway obstruction in patients with micro- or retrognathia does not necessarily indicate glossoptosis, since other causes for obstruction could be present (e.g. neurologic abnormalities, pharyngeal hypotonia or choanal atresia), which can be discerned by direct flexible laryngoscopy. Given the poor registration of glossoptosis and following Printzlau and Andersen[58], we chose to disregard this criterion in the diagnosis of RS as a requisite one. Hence, in the current study it was decided to label the CP patients with the diagnosis RS who would express at least micro- or retrognathia and obstructive respiratory distress.

Strengths and limitations

The main strength of this study is that it comprises the first presentation of the birth prevalence of RS in the Netherlands, based on a retrospective review of medical records and a national Cleft Registry using clear diagnostic criteria. This registry is known to be a reliable source. The current study emphasizes the difficulty and current controversies in how to define RS and the need for a common definition to facilitate comparison between different countries. Moreover, to our knowledge, it is the first to offer an overview of the previous literature on the epidemiology of RS following a systematic search. Finally, it clearly describes the basic characteristics of the RS population, such as cleft grade, gender, birth weight and gestational age and additional anomalies. Limitations include the use of the Dutch Cleft Registry which forced the inclusion of CP in the definition of RS, even though the first important report on the condition did not involve this feature.[12] Second, in order to establish a diagnosis of RS, the current study relied on the notes of a number of physicians which introduced an unknown degree of inter-observer variation. Third, given the retrospective character of the study slight inconsistencies in reporting were encountered during the review of the medical records. Finally, only 21% (n=256) of the patient medical records of the total Dutch CP population (n=1194) registered during the study period was screened. Consequently, an extrapolation step was needed to derive an estimate of the national birth prevalence. As previously mentioned, this is

possible due to the knowledge that patients born with a CP are referred to the closest cleft center, where they are registered in the Dutch Cleft Registry. Thus, there was no *a priori* selection of patients amongst regional cleft palate teams, and subsequently the distribution of CP and hence RS patients is expected to be equal in the Netherlands.

Despite the above mentioned issues, the current study provides an estimate of the birth prevalence of RS in the Netherlands by using data of the national cleft registry in combination with thoroughly studied medical records of a large number of patients of three dedicated cleft palate teams. Hereby we were able to offer new insights and could obtain additional data on other clinical aspects of RS which may be valuable in clinical practice and provide a basis for accurate counseling of parents.

CONCLUSIONS

Combining data from the Dutch Cleft Registry and the medical records of three regional cleft palate teams in the Netherlands this study produced an estimate of the Dutch birth prevalence of RS of 1:5,600 live births (or 17.7 per 100,000), with a non-significant female predominance, for the period 2000-2010. One third of the Dutch CP population was estimated to have comorbid RS and a more severe cleft grade was found in the RS population than in the overall CP population. This study provided a Dutch birth prevalence using strict predetermined criteria, hereby attempting to obviate the terminological confusion about the disorder. Still, comparing data in the current literature remains difficult due to other factors besides definition, such as the accuracy of a certain registration method or possible genetic and environmental factors.

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Etiology and Pathogenesis of Robin Sequence in a large Dutch Cohort

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ABSTRACT

Background

Robin sequence (RS) can be defined as the combination of micrognathia and upper airway obstruction/glossoptosis causing neonatal respiratory problems, with or without a cleft palate and either isolated or non-isolated. Pathogenesis varies widely. We hypothesize that optimal treatment depends on pathogenesis and that for this reason patients should be stratified according to diagnosis. Here, we aimed to evaluate diagnoses and (presumed) pathogeneses in an RS cohort.

Methods

Medical records of all RS patients who presented between 1995 and 2013 in three Dutch academic hospitals were evaluated. Four clinical geneticists re-evaluated the collected information, including initial diagnosis. Diagnoses were either confirmed, considered uncertain, or rejected. In case of an uncertain or rejected diagnosis, patients were re-evaluated. Subsequent results were re-discussed and a final conclusion was drawn.

Results

We included 191 RS patients. After re-evaluation and changing initial diagnoses in 48 of the 191 patients (25.1%), 37.7% of the cohort had isolated RS, 8.9% a chromosome anomaly, 29.3% a Mendelian disorder, and 24.1% no detectable cause. Twenty-two different Mendelian disorders were diagnosed, of which Stickler syndrome was the most frequent. Stratification of diagnoses according to (presumed) pathogenic mechanism in 73 non-isolated patients with a reliable diagnosis showed 43.9% to have a connective tissue dysplasia, 5.5% a neuromuscular disorder, 47.9% a multisystem disorder, and 2.7% an unknown mechanism.

Conclusions

We diagnosed more non-isolated RS patients compared to other studies. Re-evaluation changed the initial diagnosis in a quarter of the patients. We suggest standardized follow-up and re-evaluation of all RS patients. Despite the relative high diagnostic yield pathogenesis could be determined in only 59.7% (71/119) of the non-isolated patients, due to the limited insight in pathogenesis in many diagnosed entities. Further studies into pathogenesis of the various entities causing RS are indicated.

INTRODUCTION

Robin Sequence (RS) can be characterized by micrognathia, glossoptosis and neonatal respiratory problems, with or without a cleft palate.[1, 2] Numerous other definitions have also been used.[3] A recent questionnaire study among Dutch and Belgian cleft teams demonstrated that there is no consensus on the definition between teams and not even within a single team.[4] RS has been reported to have an incidence of approximately 1:8,000-1:14,000[5-7] but obviously the reliability of such figures is limited if the definitions used for RS are different.

Irrespective of the exact definition RS has been found to be etiologically heterogeneous and to occur both isolated and in combination with other congenital anomalies[8-11] Indeed many syndromes have been associated with RS, of which Stickler syndrome and 22q11.2 deletion have been reported to be the most common ones.[10] The severity of the micrognathia, respiratory and feeding problems vary widely amongst RS patients. There are several management strategies such as prone positioning[12-15], nasopharyngeal airway[13, 16, 17], tongue lip adhesion[18-21], mandibular distraction osteogenesis[21-26] and tracheostomy[14, 21, 27]. However, there is no consensus which strategy should be follow ed and which parameters in the patients should dictate the choice of management.[28]

We hypothesize that the cause of RS influences the results of management, and, thus, the cause for RS should influence the choice of the management strategy. In our opinion stratification of patients based on the cause for their RS is needed in evaluating the efficacy of the various management strategies. This urged us in initiating a retrospective analysis in a consecutive cohort of RS individuals seen in three academic hospitals in the Netherlands, with the aim to evaluate the causes and most likely pathogeneses for their RS.

METHODS

All consecutive RS patient born between 1995 and 2013 who presented in one of three tertiary hospitals (Academic Medical Centre; VU Medical Center; Wilhelmina Children's Hospital) were selected, using the local databases for individuals with clefting, those for surgical correction of the cleft palate, patients who underwent a tongue-lip adhesion or mandibular distraction or had been admitted to the paediatric department for polysomnography because of respiratory problems. Selection was based on the presence of micrognathia and upper airway obstruction causing neonatal respiratory problems. Referral to one of the three academic hospitals has been depending almost exclusively on their regions: each hospital serves a well-defined region. Patients with (isolated and non-isolated) cleft palate from each region are always referred to the clefting team of that region and registered in the National Dutch Cleft Registry Database.[29, 30] Coverage of individuals born in a region by that regional clefting team is close to 100%.[29]

The work-up and follow-up of newborns with a cleft palate and newborns with clefting plus respiratory problems/glossoptosis and micrognathia (RS) differed between the three centers. In all centers, standard additional investigations have been classical cytogenetic analysis with FISH

for a 22q11.2 deletion in the first years of our study period. Since 2008 array-CGH is routinely performed, and since 2012 next generation sequencing is used in a small number of patients. Additional molecular studies were dictated by clinical findings. In two centers re-evaluation is routinely performed repeatedly during the first 18 years of life, and if indicated further studies are initiated. In the third center re-evaluation occurs on request of the family or after referral by one of the physicians in charge.

From the hospital medical records of all RS patients the following information was obtained: duration of pregnancy; potential teratogenic influences; anthropometric data at birth; results of initial clinical examination by the pediatrician, plastic surgeon, ENT surgeon, and clinical geneticist; (neuro) radiological studies; cytogenetic/molecular genetic studies; initial genetic diagnosis; subsequent physical complications; motor, cognitive and speech development; and family history. The information was entered in an electronic OpenClinica database. In addition, pictures depicting patients at different ages were collected.

All information on RS patients was evaluated in meetings of four geneticists from the participating centers, experienced in evaluating RS patients (JMVH, SMM, MJHVDB, RCH). The initial diagnosis was discussed, and either confirmed, considered doubtful, or rejected. In patients with a doubtful or rejected diagnosis, diagnostic suggestions were made, the patient was re-evaluated by a clinical geneticist and on indication additional studies were performed, unless the patient was unavailable or declined further diagnostic testing. After completing the re-evaluations, the patients concerned were re-discussed in a follow-up meeting, at which time a final diagnosis was given.

Patients were grouped into isolated RS and non-isolated RS. The non-isolated patients were sub-divided according to etiology into chromosome imbalance, Mendelian disorder and unknown-cause. If a chromosome imbalance was detected but uncertainty about its causal role remained, we grouped this patient in the unknown-cause group. We used strict criteria for etiology.[31] An example of this is a non-isolated patient who has been reported to carry a mutation in *NGFR*.[32] Since a causal relationship between this *NGFR* variant and the phenotype remains uncertain, this individual was still put in the unknown-cause group.

Subsequently, the entities were re-grouped, according to the most likely pathogenic mechanism: an entity was tagged as a connective tissue disorder if all major signs and symptoms could be explained by abnormal functioning of connective tissue. An entity was tagged as neuromuscular disorder if the major signs and symptoms could be explained by abnormal functioning of the neuromuscular system. An entity was labeled as multisystem disorder if two or more organ systems showed anomalies, not explainable by a connective tissue disorder or neuromuscular disorder, and likely caused by a disturbed function of a developmental gene.[33, 34] Finally, a patient was placed in the unknown mechanism group, if the pathogenic mechanism behind the entity remained uncertain or unknown.

The medical ethical committee of the Academic Medical Centre in Amsterdam has approved the study (File numbers W12 092 and NL44491.018.13).

RESULTS

In the study period, 191 RS patients were identified (45.5% male). There seems to be a slight increase in the number of newly diagnosed RS patients from 2001 on (Fig. 1). Initially, 152 diagnoses had been made and in 39 RS patients no etiological diagnosis had been recognized. Re-evaluation of all patients changed the initial diagnoses in 48 cases (25.1%) (Table 1). The most frequent change (in 13 of the 49) was a change from isolated RS to a non-isolated RS, often because patients had been found to have additional abnormalities at a later age, that usually were not or only with great difficulty detectable in infancy.

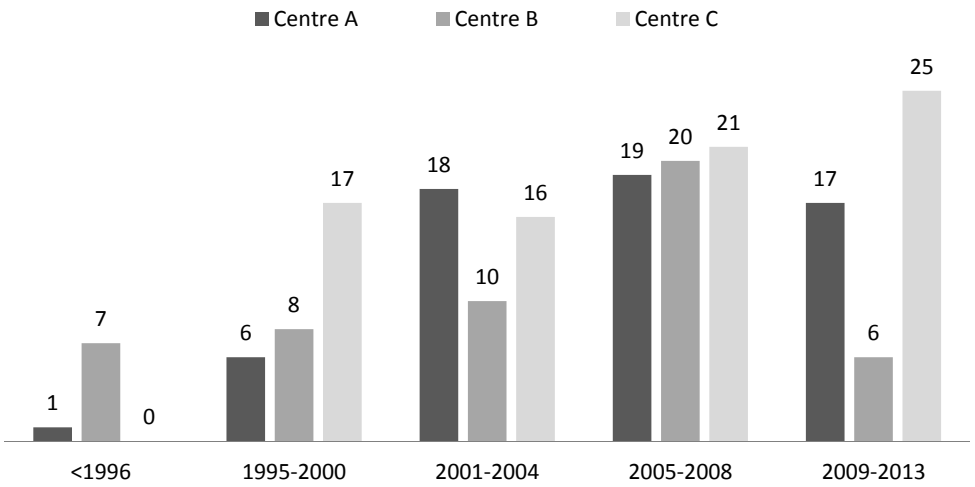

Figure 1 Number of Robin sequence patients per time period evaluated in the 3 participating centers.

Table 1 Change in diagnosis in 48 of 191 Robin sequence patients after re-evaluation

	Before reevaluation		After reevaluation	
	Group	Syndrome	Group	Syndrome
Center A	Isolated		Mendelian	Non-ocular Stickler
	Mendelian	Meier-Gorlin	Unknown	
	Mendelian	Oculo-auriculo-vertebral	Unknown	
	Mendelian	Nager	Mendelian	Acrofacial dysostosis
	Mendelian	Bohring-Opitz	Unknown*	*NGFR* mutation
	Mendelian	Stickler	Isolated	
	Chromosomal	46,XX, dup4p15.32, del6p21.2	Unknown*	46,XX, dup4p15.32, del6p21.2
	Chromosomal	46,XY, dup1q21.1	Unknown*	46,XY, dup1q21.1
	Unknown		Mendelian	Stickler
	Unknown		Mendelian	Schillbach-Rott
	Unknown		Isolated	
	Unknown		Mendelian	RAD21- Cornelia de Lange-Like
	Unknown		Mendelian	Schilbach-Rott
	Unknown		Mendelian	Fronto-metaphyseal dysplasia with keloids
Center B	Isolated		Unknown	
	Isolated		Unknown	
	Mendelian	Fragile X	Isolated	
	Mendelian	VATER association	Unknown	
	Mendelian	Stickler	Unknown	
	Mendelian	Peters-Plus	Mendelian	X-linked Ohdo (MED12)
	Chromosomal	46,XX, t(17;18)(p11.2;q21.1) mat	Unknown*	46,XX, t(17;18)(p11.2;q21.1) mat
	Unknown		Mendelian	CDG(I)II
	Unknown		Mendelian	X-linked Ohdo (MED12)
	Unknown		Chromosomal	46, XX, del 2q33.1-2q33.1 dn
Center C	Isolated		Mendelian	Stickler
	Isolated		Mendelian	Stickler
	Isolated		Mendelian	Auriculo-condylar
	Isolated		Mendelian	Yunis-Varon
	Isolated		Unknown*	46,XX, dupXp21.1, dup3p14.1 (pat)
	Isolated		Unknown	
	Isolated		Unknown	
	Isolated		Unknown	
	Isolated		Unknown	
	Isolated		Unknown	
	Chromosomal	46,XY, del3q22.2-q22.3	Unknown*	46,XY, del3q22.2-q22.3
	Chromosomal	7q36.3 duplication	Unknown	
	Mendelian	1p36 deletion	Chromosomal	46,XX, der(1)t(1;19)(p36.31;q13.42) pat
	Mendelian	Auriculo-condylar	Mendelian	Hyperphosphatasia-intellectual disability (PIGV)
	Mendelian	Spondylo-epiphyseal dysplasia	Unknown	
	Mendelian	HFM spectrum	Mendelian	Oculo-auriculo-vertebral
	Mendelian	Stickler	Isolated	
	Mendelian	Stickler	Isolated	
	Mendelian	Stickler	Unknown	
	Mendelian	Stickler	Isolated	
	Mendelian	Stickler-like	Unknown	
	Unknown		Unknown*	46,XX, dup 9p22.2-p22.3 dn
	Unknown		Unknown*	46,XY, dup 5q23.1, dup Xp22 31
	Unknown		Isolated	

Etiology

We grouped our patients according to etiology after the reevaluation. Seventy-two patients (37.7%) had an isolated form of RS (Table 2). In two isolated patients the RS was familial (only the two probands have been included in this study). Of the 119 non-isolated patients, 14.3% (17/119) had a proven chromosomal abnormality that likely explained the phenotype (Table 3). A Mendelian disorder was diagnosed in 47.1% (n=56) of the patients, of which Stickler syndrome (n=27) was the most frequently diagnosed entity (Table 2). The other 21 diagnosed Mendelian entities are tabulated in Table 4. Ten of the diagnosed Mendelian entities have been reported before in combination with RS, four entities have been described in combination with micrognathia but without upper-airway obstruction, and eight entities have not been described before in patients with either RS or micrognathia. In six patients a genetic abnormality was found that potentially could explain the RS, but proof remained insufficient to tag these abnormalities as such (Table 1 and 3).

Cognition

Cognition could not be determined in some due to early demise (n=4) or loss to follow-up (n=3). In the remaining 184 patients 73.4% had no intellectual disability (ID), 2.7% followed a borderline development, and 23.9% had a clear ID. In the isolated group no ID was diagnosed, and no individual with isolated RS had a cerebral palsy either. If only the non-isolated group (n= 112, in whom data were available) is evaluated, 39.3% (n=44) had ID and 4.5% (n=5) a borderline development. We had information on the developmental level of 42 of the 46 patients with an unknown cause for their RS: almost half of them (45.2%; n=19) had ID.

Table 2 Overview of causes in 191 Robin sequence patients

Underlying cause n=61			Centre A n=51	Centre B n=79	Centre C n=191	Total %	
Abnormality	Isolated		25	19	28	72	37.7
	Non isolated	Chromosomal	8	5	4	17	8.9
		Mendelian					
		Stickler	8	8	11	27	14.1
		Other	12	5	12	29	15.2
		Total	20	13	23	56	29.3
		Unknown Cause	8	14	24	46	24.1

Table 3 Chromosome anomalies detected in 23 of 191 Robin sequence patients and the (potential) link to cause Robin sequence

Patient ID	Karyogram	Effective chromosome imbalances	Other information	Pathogenicity
1	46,XX,der(6)t(6;9)(p21.3;q22)ins(6;13)(p21.3;q?21q31), der(9)t(6;9),der(13) ins (6;13)dn.arr cgh 1q21.1(143753734-143932665->144800622-144981936)x1 pat, 13q21.3 3q22.2(69505103-69672969->75611371-75786398)x1, 13q22.3(76677851-76898317->77477206- 77651205)x1 dn	Unbalanced translocation del 13q21.33q22.2 (6.1 Mb) del 13q22.3 (800kb)	None	Pathogenic
2	46,XX, ish,del(4)(p16.3) dn	del4p16.3 (~1.5Mb)	Clinically Wolf-Hirschhorn s.	Pathogenic
25	46,XY, t(8;17)(q24.12;q24) dn	Balanced translocation	8q24 involved in orofacial clefting[45] 17q24 involved in familial RS[46]	Possibly pathogenic
33	45, XO	del X	Clinically Turner s.	Pathogenic
44	46,XY, arr[hg19] 9p24.1(5,165,708-Fish 9q24(RP11-207C16-).arr9p24.1(5155708-6262575)x1 dn	del 9q24.1 (1.1Mb)	None	Likely pathogenic
46	46,XY.ish der(14)t(14;16)(p11;p12.3)(RG191K2+)	Unbalanced translocation del 14p11-1pter (~200-400 Mb) dup 16pter-16p12.3 (19.3 Mb)	16p involved in orofacial clefting[47]	Pathogenic
47	46,XX,del(5)(p14).arr 5p15.33p14.3(72,539-20,160,366)x1	del 5p15.33p14.3 (20.1 Mb)	Clinically cri-du-chat s.	Pathogenic
48	46,XY, arr Yq11.223q11.23(23283651-2573772222)x0, chr22q11.21q11.23(20043011-22973937)x1dn	del 22q11.21q11.23 (2.9 Mb) Yq11.223q11.23 (2.4 Mb)	Clinically velocardiofacial s.	Pathogenic
56	46,XY, dup1q21.1	dup1q21.1 (2.8 Mb)	Parents not available, 1q21 involved in orofacial clefting[48]	Uncertain
106	46,XX, der(13)t(13;21)(q12;q22)	Unbalanced translocation dup 13pter-13q12 (~20 Mb) del 21pter-21q22 (~25-45 Mb)	21q22.11 involved in RS[10]	Pathogenic
124	46,XY, der(18)t(13;18)(q32.3;q21.33) mat	Unbalanced translocation dup 13q32.3-qter (~15 Mb) del 18q21.33-qter (~18 Mb)	18q21 involved in orofacial clefting[49]	Pathogenic
131	46,XX, t(17;18)(p11.2;q21.1) mat	Apparently balanced translocation	17q21 involved in RS[42]	Uncertain
143	46, XX, del 22q11.2 dn	del 22q11.2 (1.5-3.0Mb)	Clinically velocardiofacial s.	Pathogenic
145	46,XX, del(2)(q33.1q33.1)(199,160,607-199,836,011) dup10q21.3 dn	del 2q33.1 (675 kb) dup 10q21.3 (730 kb)	*SATB2* (OMIM 608148) likely in part deleted at 2q33	Pathogenic

150	46,XX, der(1)t(1;15)(q42;q15) dn	Unbalanced translocation del 1q42 (~25 Mb) dup 15q15 (~62 Mb)	15q15 involved in velopharyngeal insufficiency[50]	Pathogenic
213	46,XX, arr cgh 1pter-p36.31(604268 -604327 ->5983938-5983997)x1; arr cgh 19q13.42-19qter(60551240 -60551299->63784327-63784382)x3	Unbalanced translocation del 1p36-pter (5.9 Mb) dup 19q13.4-qter (3.2 Mb)	father: ish t(1;19)(p36.31;q13.42)(wcp1+, wcp19+;wcp19+,wcp1+); 1p36 involved in orofacial clefting[51]	Pathogenic
223	46,XY, der(12(t(11;12)(q23.3;q24.3) mat	Unbalanced translocation del 11q23.3-qter (~15Mb) dup12q24.3-qter (~12Mb)	mother not available for phenotype analysis, 11q23 involved in RS [52]	Likely pathogenic
227	46,XY, arr 5q23.1(118,535,279-120,544,666)x3, arr Xp22.31(6,481,816-8,091,951)x2	dup 5q23.1 (2.1 Mb) dup Xp22 31 (1.6Mb)	5q23 involved in RS[53]	Uncertain
234	46,XX, del 4q31.3-q35 dn	del 4q31.3-q35 (~50Mb)	affected individual deceased 4q31 involved in RS[54]	Pathogenic
240	46,XX, dup 9p22.2-p22.3 dn	dup 9p22.2-p22.3 (142b)	9p22 involved in cleft palate and micrognathia[55]	Possibly pathogenic
242	47,XX, +idic(15)(q?13).ish idic(15)(q13) dn	idic(15)(q?13).ish idic(15)(q13) (~10Mb)	15q13.3 involved in orofacial clefting[56]	Pathogenic
265	46,XX, arr Xp21.1(37,223,446-37,534,533) x3,3p14.1(65,636,485-65,874,063)x3	dup Xp21.1 (311kb) dup 3p14.1 (234 Kb)	father not available for phenotype analysis, Xp21.1 involved in orofacial clefting[57]	Uncertain
270	46,XY.arrsnp 3q22.2q22.3(135702645-135702645)x1	del 3q22.2-q22.3 (2.19 Mb)	parents not available for karyotyping 3q22 earlier involved in RS[58]	Likely pathogenic

Pathogenetic mechanism

We stratified the 22 diagnosed Mendelian and 17 chromosomal entities according to their most likely pathogenic mechanism causing the RS and other abnormalities (Table 4). In the patients with a reliably diagnosed etiology the mechanism was a connective tissue dysplasia in 43.8% of the non-isolated patients (of which Stickler syndrome was by far the most common one), neuromuscular disorders in 5.5%, and a multisystem disorder in 47.9%. Finally, in 2.7% the pathogenic mechanism remained uncertain or unknown. Most of the chromosome imbalances found in the present cohort were large involving a large number of genes. This indicates that in most patients a combination of effects of disturbed function of dominantly acting genes is most likely, and therefore we grouped these patients in the multisystem disorder group.

Table 4 Most likely pathogenesis of the 73 patients with a reliably diagnosed Mendelian or chromosomal abnormality in 191 patients with Robin sequence

Pathogenic mechanism	n	Entity
Connective tissue disorder	27	Stickler s.*
	1	Spondylo-Epiphyseal Dysplasia
	1	Femoral Hypoplasia - Unusual Facies s.
	1	Fronto-Metaphyseal Dysplasia with keloids
	1	Van den Ende-Gupta s.
	1	Osteopathia striata with cranial sclerosis
Neuromuscular disorder	3	Moebius s.
	1	Carey-Fineman-Ziter s.
Multisystem disorder	17	Chromosomal anomalies **
	4	Treacher Collins s.
	2	Auricular Condylar s.
	2	X-linked Ohdo s. (MED12)
	1	Acrofaciale dysostosis
	1	CDG type II
	1	Fetal Alcohol s.
	1	Hyperphosphatasia - intellectual disability s. (PIGV)
	1	Kabuki s.
	1	Nager s.
	1	Oculo-Auricolo-Vertebral s.
	1	RAD21 - Cornelia de Lange- like s.
	1	Van der Woude s.***
	1	Yunis-Varon s.
Unknown mechanism	2	Schilbach-Rott s.

** Diagnosis based on: COL2A1 mutation (n=13), COL11A1 mutation (n=2), Family history + clinical presentation (n=6), Clinical presentation (n=6)*

*** Specification of the chromosomal abnormalities can be found in table III*

**** Unusual presentation of this syndrome as it usually does not show micrognathia; possibly another etiologic cause next to Van der Woude s. was present explaining the RS*

DISCUSSION

The present group of authors has formed a consortium in order to establish a research line for Robin sequence. We are re-evaluating and studying the main manifestations of RS in such a way that this allows objective determination of signs and symptoms, and will make future reliable meta-analyses possible: we use 3D facial scanning to determine the size of the mandible, follow its growth in time and identify other changes in facial morphology; we use polysomnography to determine the characteristics and degree of severity of upper airway obstructions; and we evaluate the value of flexible laryngoscopy to determine glossoptosis and compare this with the use of Cine-MRI of the nasopharyngeal region. The eventual aim of this RS research is to develop an evidence-based management strategy, using objective criteria, for optimal treatment of RS patients.

We hypothesize that RS patients with a variable etiology and pathogenesis will react differently to the various treatment modalities, and that a treatment should be stratified according to the etiology and pathogenesis of the RS. Of course this will need careful follow-up as results of the various management schemes can only be determined this way. Many hypotheses exist on the pathogenesis of RS. Frequently it has been suggested that the cause is a restricted intra-uterine growth preventing the mandible to grow, causing a display of the tongue between the palatal shelves and preventing their fusion.[6, 28, 35, 36] In this hypothesis the mandible is expected to show catch-up growth after birth when the restriction is relieved. We hypothesize that this can be the case in patients with isolated RS and that in non-isolated RS patients also other mechanisms are likely to act. For instance, a patient with RS due to a deformation is likely to demonstrate a significant spontaneous amelioration of the RS manifestations, while a patient with a dysplasia has developed the RS prenatally due to the abnormal tissue formation in the mandible, larynx and pharynx, and will continue having abnormal tissue postnatally. Possibly, in the former patient a conservative treatment such as prone positioning is justified, while in the latter patient a more aggressive strategy may be followed, and the surgeon needs to take into account that he/she could be operating on dysplastic tissue. In RS patients with neuromuscular disorders the respiratory problems may well be caused by the RS due to a lack of voluntary control of the tongue (either by muscular underdevelopment or insufficient tongue innervation) and a narrowing of the oropharynx by collapse of the pharyngeal wall.[12, 37] Tongue movements and pharynx wall stability may improve with age, and temporary alleviation of the respiratory problems may be the best management strategy. However, if a general insufficient functioning of muscles involved in respiration is present, improvement cannot be expected and an aggressive management strategy may be appropriate.

Etiology is a prerequisite to determine pathogenesis. This urged us to initiate the present study. The present cohort of 191 consecutive RS patients is relatively large compared to earlier studies[6, 10, 12, 16, 38] The bias in the acquisition of participants in the cohort is very small as referral for cleft palate respiratory treatment has almost exclusively been determined by geography and for the region referral is close to 100%.[29] Still, the databases from which patients were derived have led to inclusion

of mostly patients with a cleft palate (177/191) causing a possible overrepresentation of this group in our cohort. Furthermore we cannot exclude we have missed RS patients, without a cleft palate and only limited respiratory problems not necessitating admission, since these may not have been identified as having RS. The incidence over time seemingly indicates an increase over time (Fig. 2) but it is more likely that this is caused by better recognition of RS with time, and not by a true increase in incidence. We found significant value in re-evaluating patients, since a large portion of the patients received another diagnosis after re-evaluation. The re-evaluation allowed a change in diagnosis in 48 patients, and the ratio isolated: non-isolated changed from 40.3% vs. 59.7% to 38% vs. 62%. Other studies reported ratios comparable to our initial findings.[10, 21, 38] In the present cohort a low incidence of patients with a 22q11 deletion (n=2; 1.2%) is reported compared to previous studies in which incidences were higher such as 2.7%[38] and 13.3%[39]. We have no firm explanation for the lower incidence of 22q11 deletion in our cohort. One may speculate that diagnosing a patient as having a 22q11 deletion has impaired recognition of RS, even if all features are present. Alternatively RS has been over diagnosed in the past as in earlier studies polysomnography was not widely utilized, but coincidence cannot be excluded either.[38,39]

Within the present study group two centers re-evaluated all RS patients regularly in a standardized follow-up protocol, while the third center did this on request of the physician or parents. In the latter center the diagnosis was changed more frequently (30.4%) compared to the other two centers (23.0% and 19.6%, respectively). In the latter center, also more families declined re-evaluation, which may explain the higher number of unknown diagnoses compared to the other two centers. Still, in all three centers the change in diagnoses was of clinical importance. This may be explained by anomalies becoming more obvious with age, newly developed anomalies, newly available diagnostic studies (such as array CGH), and the peer review by four specialists experienced in evaluating RS patients. The present findings are in agreement with the findings of Izumi and co-workers, who reported on a change in diagnoses in 18% of patients due to re-evaluation after one year.[10] We assume that the presently reported higher frequency in diagnostic changes and the higher incidence of non-isolated RS patients are explainable by the longer follow-up time in our study. Indeed, the present numbers may still increase in time, since some of our patients still had only a limited time to follow-up. Possibly also the increase in quality of diagnostic tools in cytogenetic and molecular studies has played a role. Results of Izumi et al.[10] and of the current study demonstrate the usefulness of regular re-evaluation of patients with RS over a prolonged period of time, for instance 3-5 years, to ensure optimal diagnostics. In every team taking care of individuals with clefting and/or Robin sequence an experienced geneticist is essential for such optimal diagnostics and management.

The grouping of non-isolated RS patients according to their most likely pathogenic mechanism was possible in only 59.7% (n=71) of the presently reported patients, despite the relative high diagnostic yield of the present study. This mirrors our limited insight in pathogenesis of RS in general. SOX9 can be involved in the pathogenesis of isolated RS[40] and sometimes syndromic RS[41], and several other genes have been suggested as candidate genes for RS[42-44]. Except for the influence of SOX9

on chondrogenesis, firm data on pathogeneses are mostly lacking. The present study is a first step towards stratification of RS patients, which can be ameliorated by an increase in both diagnostics and in knowledge of pathogeneses. The increase in diagnostics is within reach due to the use of panels of genes potentially causing RS, by targeted next generation sequencing techniques. However, a better insight in pathogenetic mechanisms is more time consuming and likely will need a large number of basic functional studies.

CONCLUSIONS

In the present relatively large RS cohort, less isolated RS patients were diagnosed compared to earlier studies. Both known and (until now) unknown entities were found to go along with RS. Re-evaluation of newborns with RS over a prolonged period of time allowed adaptation of the initial diagnosis in a markedly high percentage of patients. We favor standard follow-up of all RS patients, specifically to (re-)evaluate diagnoses, during a prolonged period of time. The entities diagnosed in the present study are caused by differing pathogenetic mechanisms, which confirm that different pathogeneses for RS exist. Our present limited knowledge and insight in pathogenetic mechanisms urges for efforts to initiate pathogenetic studies, as optimal patient care may be depending on such studies.

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A systematic review on the outcome of mandibular distraction osteogenesis in infants suffering Robin sequence

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ABSTRACT

Background

Mandibular distraction osteogenesis (MDO) has been successfully applied in infants suffering RS with severe upper airway obstruction, but no comparative studies for the different types of MDO exist to date. Objective of the current study is to systematically review the published data considering this matter, providing a fundament for protocols and a more conscious treatment strategy for infants with RS in the near future..

Methods

For the period of January 1966 to January 2012 the Pubmed, EMBASE and Cochrane Library databases were searched. Abstracts were screened based on predetermined selection criteria. Relevant full text articles were retrieved. The articles were analyzed on type of MDO used, preoperative workup, patient characteristics, post-operative outcome and complications.

Results

The search yielded 109 articles. After checking abstracts and full texts on predetermined in- and exclusion criteria, twelve studies (four describing external MDO; five internal MDO; three both types) were extracted for further analyses.

Conclusions

Internal MDO seems very feasible in infants suffering RS, minimizing side effects such as hypertrophic scarring, nerve damage and extensive care needs, although the indications for usage are more limited compared to the external device. Corresponding protocols and long-term outcome studies are needed to make a better comparison and the use and indication of the different types of distraction even more distinct.

INTRODUCTION

Mandibular micrognathia with associated glossoptosis and airway obstruction, is the original trias of symptoms constituting the Robin Sequence (RS) described by Pierre Robin in 1923[1] RS may be an isolated condition but an associated syndrome such as Stickler's, Treacher Collins, Nager, velocardiofacial or hemifacial microsomia is present in about 45-80% of cases.[2-6] An additional cleft palate may exist, but is not a required feature to define the sequence.[6-12] In literature the phenomenon is described as Robin complex, Robin anomalad, Pierre Robin Syndrome or Robin sequence.[3, 13]Due to this discrepancy in the definition, reported incidences vary from 1 per 8500[14] to 14.000[15] births in the general population. Mortality, most commonly due to severe upper airway obstruction leading to obstructive apnea and cardiac problems, ranges from 2.2-26%.[16] To date several treatment strategies have been proposed, consisting of non-surgical and surgical options. The primary goal is to secure a safe airway in newborns with RS. When there is no life-threatening respiratory obstruction, a conservative approach is applied first. These consist of prone positioning techniques and close monitoring, nasopharyngeal airway, short term endotracheal intubation or intraoral devices.[6, 16-23] Although most RS cases can be adequately treated conservatively, up to 23% of infants have major respiratory obstruction necessitating surgical intervention, which can be challenging for caregivers.[24,25] Tongue lip adhesion, popularized by Douglas in 1946, has shown its efficacy in protecting the airway in acute respiratory compromise.[26-29] However, potential complications are scarring of lip, tongue or salivary glands, dehiscence of the adhesion and secondary procedures may be needed for definite management of the airway.[27, 30] In severe cases tracheostomy is used as a safe necessary temporary, or sometimes even as a long-term measure. [16, 31] Reported mortality rates (most commonly due to accidental decannulation and cannula obstruction) can be up to 6%, or even higher at a younger age and lower body weight at time of surgery.[32] It is related to a high percentage (43-65%) of complications such as granulations, tracheocutaneous fistulae, laryngeal/ tracheal stenosis or speech delay.[32-34] Besides, the average age at decannulation in neonates with RS is 28 months, during which an additional substantial social burden on the (grand) parents or caretakers of the child exists to constantly secure the child's airway.[35] Soon after the first widespread clinical use of external mandibular distraction osteogenesis (MDO) by McCarthy et al. in 1992, this technique was also successfully applied in infants suffering RS and was regarded as an alternative corrective treatment for a tracheostomy.[36] Since then, numerous reports have been published demonstrating its feasibility. However, an external device causes external scars and requires a second operative procedure for removal of the device and screws. The same disadvantage was noticed in the later developed (semi) buried non-resorbable devices, although scars and wound care were minimized.[5, 37] Subsequently, an internal resorbable distractor was presented in 2002.[38] This technique basically averts the need for a second operation and provides good clinical results[39, 40] also demonstrated in our institution.[41]

Recently Master et al. gave an extended literature overview of the encountered complications of MDO.[42] However, no clear distinction between the different types of distractors was made and it was not focused solely on infants with RS. Ow and Chueng presented a well conducted meta-analyses of the feasibility of MDO but also did not specify for infants with RS.[25] The purpose of the current study is to comprehensively review the literature regarding both internal and external MDO in infants suffering from RS, as this is a vulnerable patient group in which considerable morbidity and even mortality exists at the time a treatment proposal has to be made. At present, no critical systematic review comparing the extensive amount of published case reports about the different types of MDO in this patient group exists. We categorized the outcome per technique providing a clear summary, based on the current knowledge described in literature and our own experiences regarding MDO. This might help to choose a designated operative strategy and prevent complications in the future.

MATERIAL AND METHODS

Search strategy

A systematic literature search of the PubMed, MEDLINE and Cochrane databases was performed for January of 1966 to January of 2012, using specific keywords (Table 1). Duplicates were excluded and abstracts were screened, based on predetermined selection criteria. Relevant full text articles were retrieved and reference lists manually screened for additional articles. Subsequently the full text of these articles were critically analyzed (Figure 1). The search strategy was performed independently by two authors (E.P. and F.S).

Table 1 Key words used for the search of the three databases

PubMed	("mandibular"Title/Abstract OR "mandible"Title/Abstract OR "jaw"Title/Abstract OR "jawbone"Title/Abstract OR "chin"Title/Abstract) AND ("distraction"Title/Abstract OR "extend"Title/Abstract OR "extension"Title/Abstract OR "enlargement"Title/Abstract OR "distention"Title/Abstract OR "expansion"Title/Abstract OR "osteogenesis"Title/Abstract)
	AND
	("pierre"Title/Abstract OR "robin"Title/Abstract OR "sequence"Title/Abstract)
EMBASE	(mandibular:ab,ti OR mandible:ab,ti OR jaw:ab,ti OR jawbone:ab,ti OR chin:ab,ti) AND (distraction:ab,ti OR extend:ab,ti OR extension:ab,ti OR enlargement:ab,ti OR distention:ab,ti OR expansion:ab,ti OR osteogenesis:ab,ti)
	AND
	(pierre:ab,ti OR robin:ab,ti OR sequence:ab,ti)
Cochrane	(mandibular:ti,ab OR mandible:ti,ab OR jaw:ti,ab OR jawbone:ti,ab OR chin:ti,ab) AND (distraction:ti,ab OR extend:ti,ab OR extension:ti,ab OR enlargement:ti,ab OR distention:ti,ab OR expansion:ti,ab OR osteogenesis:ti,ab)
	AND
	(pierre:ti,ab OR robin:ti,ab OR sequence:ti,ab)

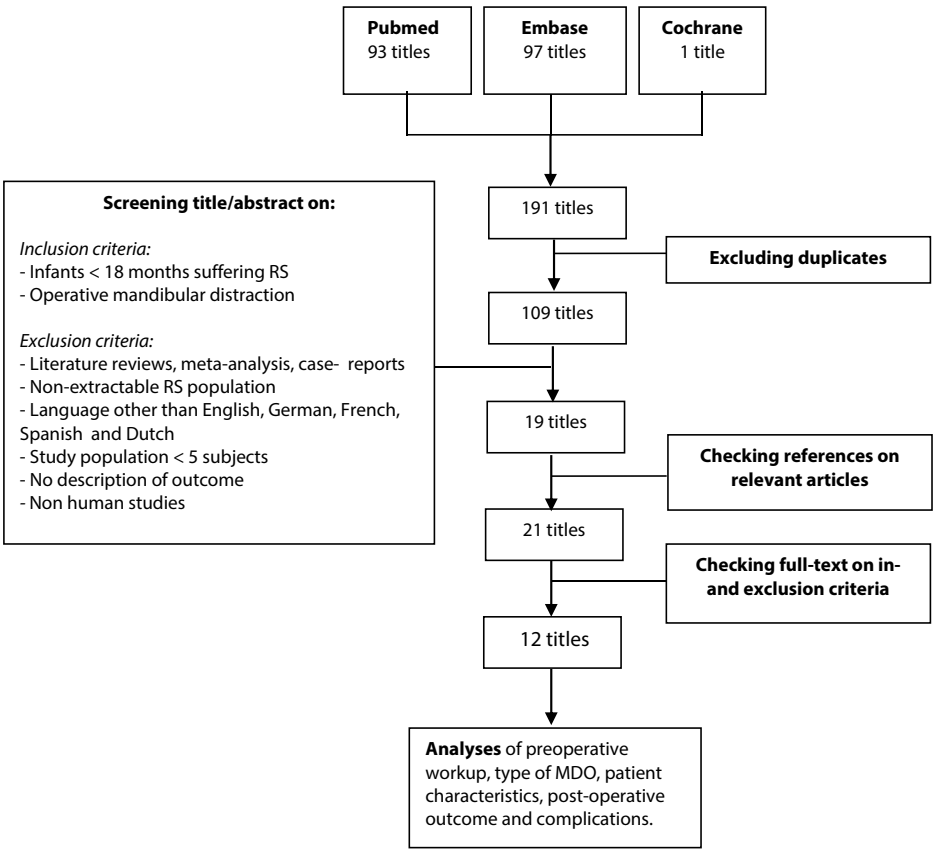

Figure 1 flowchart search strategy

In- and exclusion criteria

Prospective and retrospective case series, describing the outcome after external or internal mandibular distraction using resorbable or non-resorbable distraction device, in more than five infants aged <18 months suffering RS, were included for further assessment. Studies consisting of a mixed group of patients, in which those diagnosed with RS could not be extracted from the whole study group to analyze the outcome separately, were excluded. If there was double reporting of patients from the same center in different publications, the article describing the largest group was included. Articles that did not meet the selection criteria (description of preoperative workup, type of MDO used, patient characteristics, post-operative outcome and complications) were likewise excluded.

RESULTS

The literature search retrieved 191 titles. Following the criteria as described in detail in Figure 1, the search strategy finally yielded a total of twelve articles that were included for critical analyses. Four papers described the use of an external distractor[28, 43-45], three of an internal non-resorbable distractor[37, 46, 47], another three studies[5, 48, 49] described the use of both kinds of distractors and two of an internal resorbable distractor. [39, 41] There was no disagreement between the two assessors regarding the inclusion process.

A total of 212 patients underwent MDO over a period of 2004-2012. Of these 82% suffered isolated RS, 8% Stickler's syndrome, 2% Treacher Collins, 1% Opitz Syndrome and the rest varying syndromes. A full genetic evaluation was performed in all patients routinely. A cleft palate was seen in 79% of cases. Mean age of MDO varied from 8.6 weeks in external MDO, 9.6 in internal non-resorbable MDO and 8.3 weeks in resorbable MDO. Pre-operative a nasofiberoptic airway investigation was performed in all studies to rule out any other possible cause of airway obstruction. In some studies additionally bronchoscopy was done.[28, 46, 49] Except for one study[37], polysomnography was performed to rule out the presence of central apneas or as a parameter to compare pre- and post-operative outcome. Two others did not perform it if obvious upper airway obstruction was present even while the infant is awake.[41,45] Feeding status and observations, oxygen saturation monitoring, arterial blood gas measurement and radiographic imaging (cephalometry and/or 3D CT scans) were always carried out and also a multidisciplinary team approach was described in all articles (Table 2). Mean duration of the distraction process was 17 days for the external devices, 11 for the internal non-resorbable and 8.5 for the resorbable devices. Mean total amount of distraction was 11.6 mm (external), 17.3 mm (internal non-resorbable) and 18.3 mm (resorbable). Mean consolidation period amounted respectively 5.5 weeks, 7 weeks and 4 weeks. Mean distraction rate varied from 1 mm/day in the external devices up to 2 mm/day for the resorbable devices. Extubation or decannulation data was missing in some articles and ranged respectively from 3-15 days, 4-6 days and 5-7.5 days post-operatively. Drive screws from the resorbable devices were removed ambulatory without sedation, the external devices under sedation but for the internal devices mainly general anesthesia was necessary (Table 3).[46, 50] All reviewed articles described an overall positive outcome; avoiding a tracheostomy or obtaining a successful decannulation in 82%[48], 89%[45] and 94%[5] up to 100%[30, 37, 39, 41, 44, 46, 49-51] of cases. Normal oral feeding after MDO was possible in 86%[49] and 91%[5] up to 100%[28, 37, 41, 46, 47] of cases, and if the growth of the infant was registered there was a normalization in the growth curve seen in almost 100% after one year (Table 4).[30, 44] Cumulative complications described are listed in Table 5.

Table 2 Patient characteristics

Article	Type of MDO	Patients receiving MDO (n)	Diagnosis	Cleft palate (n)	Mean age at MDO (weeks)	Pre-operative investigations	Indication for distraction
Morovic et al. 2004 [44]	External	23/31	- Isolated RS (n= 27) - Stickler's (n= 4)	90% (21)	10 (0.7-36)	genetics evaluation, preoperative team evaluation, feeding observations and nutritional status, lateral cephalogram, nasofiberoptic airway examination, 02 saturation monitoring, polysomnography (on indication)	(1)Micrognatia with severe respiratory difficulty, interruption of the air column on lateral cephalogram, no signs of laryngeal associated pathology on nasofiberoptic examination + frequent desaturations (< 80%) not corrected by conservative measures needing intubation (2) Micrognathia + presence of a tracheotomy (3) Micrognathia + insufficient growth and/or malnutrition and/or great irritability and/or aberrant polisomnography (4) Micrognathia with acute respiratory difficulty after palatoplasty.
Denny et al. 2005 [30]	External	11	- Isolated RS (n=3) - unidentified (n=1) - Stickler's (n= 5) - Freeman Sheldon (n=1) - VCF (n=1)	91% (10)	2.6 (0.5-6.4)	genetics evaluation, preoperative team evaluation, nasopharyngoscopy, CT and 3D CT scan, flexible fiberoptic bronchoscopy, 02 saturation monitoring, length and weight data, polysomnography (only the last 7ptns)	Upper airway obstruction due to tongue posture caused by a small mandible as a primary source of obstruction, as evidenced on radiologic evaluation and nasopharyngoscopy, no tracheo/laryngomalacia or other causes compounding tongue ptosis (e.g. circular pharyngeal collapse) and severe refractory obstruction (desaturations < 70%) otherwise requiring neonatal tracheostomy for airway control. Traditional measures (tongue-lip adhesion/ prone positioning/ nasopharyngeal airway intubation) failed.
Scott et al. 2011 [45]	External	19	- Isolated RS (n= 14) - Stickler's (n=2) - Opitz (n=1), - Arthrogryposis (n=1) - Catel Manzke (n=1)	?	4.8 (0.7-12)	genetics evaluation, preoperative team evaluation, 02 saturation monitoring, airway endoscopies, radiographic imaging, polysomnography (on indication).	Children diagnosed with RS in who should failure to thrive despite conservative measures and tracheotomy and/or G-tube placement was the only other viable alternative.
Monasterio et al. 2004 [43]	External	18	- isolated RS (n=17) - orofacio-digital (n=1)	72% (13)	17 (1.1-21.4)	genetics evaluation, preoperative team evaluation, 02 sat. monitoring for 8 hours, blood gasses, nasopharyngo-scopy, radiographic imaging, esophageal pH studying, polysomnography barium videofluoroscopy	Micrognathia, glossoptosis and upper respiratory obstruction, snoring and respiratory obstruction which were observed in supine position were corrected in the ventral position and cyanosis during feeding requiring >20 minutes for ingestion.

Table 2 Continued

Article	Type of MDO	Patients receiving MDO (n)	Diagnosis	Cleft palate (n)	Mean age at MDO (weeks)	Pre-operative investigations	Indication for distraction
Shen W et al. 2009 [37]	Internal non-resorbable	6	- isolated PRS (n=6)	100% (6)	1.9 (1-3)	genetics evaluation, preoperative team evaluation, 02 saturation monitoring, perinatal feeding history, 3D CT scan and lateral cephalogram, airway endoscopy	Mandibular retrognathia, glossoptosis and cleft palate formation + (1) traditional management (prone positioning, nasopharyngeal airway intubation) failed and the perceived need for long-term respiratory support, result of preoperative 02 saturation of approx. 40% in prone position + (2) distance postpharyngeal wall to lingual root on lateral cephalogram < 3 mm.
Mohamed et al. 2011 [47]	Internal non-resorbable	11	?	100% (11)	18 (8-22)	genetics evaluation, preoperative team evaluation, 02 saturation monitoring, feeding observations, lateral cephalogram, 02 saturation monitoring, polysomnography, CT scan and 3D CT scan	Retromicrognathia, glossoptosis and cleft palate and symptoms of OSAS, unable to control airway during feeding, high respiratory disturbance rates and 02 saturation ranged between 75-85% on polysomnographic, not responding to conservative measures (nasopharyngeal airway or gloosopexia).
Hong et al. 2012 [46]	Internal non-resorbable	5	- isolated RS (n=2) - 4 p deletion (n=1) - Stickler's (n=1) - Otopalatodigit (n=1)	100% (5)	9.1 (4-13.4)	genetics evaluation, preoperative team evaluation, flexible pharyngolaryngoscopie, bronchoscopy, imaging of the craniofacial skeleton, polysomnography videoflueroscopic swallow tests (modified barium swallow) and upper GI series (barium swallow).	Infants who were intuubated at birth and later failed extubation and/or presented with significant 02 desaturation s with signs of respiratory distress despite conservative measures, such as positioning.
Mandell L et al. 2010 [49]	Internal (n=?) external (n=?)	8	- isolated PRS (n=7) - Beal (n=1)	38% (3)	2.5 (1.1 -32)	genetics evaluation, preoperative team evaluation, feeding status and observation, 3D CT scan, flexible nasolaryngoscopy and direct laryngoscopy, polysomnography, bronchoscopy, 02 sat. monitoring	Micrognathia and respiratory obstruction due to tongue base collapse, severe enough to require admission to the NICU and whose airway obstruction could not be controlled with conservative measures (positioning and nasal airway), no presence of a second airway leasion, central sleep apnea and/or severe untreated GERD, and tracheotomy was recommended based on a consensus decision by multidisciplinary team.
Genecov et al. 2009 [5]	Internal (n= 33) external (n=34)	67	- isolated RS (n=64) - Treacher Collins (n= 3)	81% (67)	56 (0.7-288)	genetics evaluation, preoperative team evaluation, 02 saturation monitoring, flexible upper and lower airway endoscopies, lateral X-ray of the neck, pH probe, CT-scan head and cervical spine, polysomnography	Airway obstruction associated with micrognathia, glossoptosis, gastroesophageal reflux, micro-aspiration, swallowing abnormalities and failure to thrive with 02 saturations < 92% on supplemental 02 without improvement by prone positioning and no response on NP tube and/or nasal continues positive airway pressure and no other signs of airway obstruction seen on panendoscopy, neurologic impairment (lack of airway protection) and untreated GERD with (epi)glottic edema.

Wittenborn et al. 2004 [48]	Internal (n=13) external (n=4)	17	- isolated RS (n=14) - Stickler's (n=2) - Treacher Collins (n= 1)	100% (17)	4 (0.7-17.1)	genetics evaluation, preoperative team evaluation, feeding observations and nutritional status, CT scan and 3D CT scan, nasofiberoptic airway examination, polysomnography, polygraphic studies: heart rate, respiratory rate, chest wall impedance, nasal airflow, EMG, 02 saturation monitoring.	Infants with intractable upper airway instability caused by glossoptosis secondary to mandibular micrognathia and cleft palate, in the absence of airway pathology beyond the glossoptosis, not responding to conservative measures (prone positioning, chest rolls and/or nasopharyngeal tubes) and (1) in direct need of a tracheotomy or (2) showing increasing respiratory problems and failure to thrive after observation.
Burstein et al. 2005 [39]	Internal resorbable	15	- isolated RS (n= 12) - Stickler's (n=1) - Opitz (n=1) - bilateral craniofacial microsomia (n=1)	100% (15)	12 (1-44)	genetic s evaluation, preoperative team evaluation, 02 saturation monitoring, lateral and anterior posterior cephalogram, awake flexible fiberoptic airway examination or direct laryngoscopy and bronchoscopy in already intubated patients, polysomnography (when clinically stable enough)	Severe life threatening airway obstruction secondary to retromicrognathia with clinical symptoms.
Breugem et al. 2011 [41]	Internal resorbable	12	- isolated RS (n= 8) - Stickler's (n=2) - suspected Stickler's (n=2)	100% (12)	4.6 (1.6-13.4)	genetic s evaluation, preoperative team evaluation, continous02 saturation monitorin, blood gas evaluation, lateral and anterior posterior cephalogram, 3D CT scan, awake flexible fiberopticairway examination, polysomnography (on indication)	Infants with glossoptosis, micrognathia and airway compromise which could not me treated with conservative measures (prone positioning, nasal contineous positive pressure) and were considered candidates for tracheotomy, with no other causes of airway obstruction seen on endoscopy (tracheomalacy, stenosis) besides the glossoptosis and saturation was < 90% for > 5% of 12 hours observation.

R1 R2 R3 R4 R5 R6 R7 R8 R9 R10 R11 R12 R13 R14 R15 R16 R17 R18 R19 R20 R21 R22 R23 R24 R25 R26 R27 R28 R29 R30 R31 R32 R33 R34 R35 R36 R37 R38 R39

Table 3 Distraction features

Article	Type of MDO	Start (postop day)	Mean duration of distraction (days)	Indicator of end of distraction	Distraction rate (mm)	Mean total amount of distraction (mm)	Consolidation period (weeks)	Removal of MDO	Extubation or decannulation (days)
Morovic CG et al. 2004 [44]	External	3	21	After resolving the obstruction measured by nightly saturation and/or polysomnografy.	1/day	18-25	Age < 6 months: 4 Age > 6 months: 6 controlled by lateral cephalometry.	Ambulatory	15
Denny A et al. 2005 [30]	External	1	14	Observed by correction of the tongue from initial vertical to a physiologically normal horizontal posture.	Day 1-3: 2/day From day 3: 1/day	12.4 (8-15) extracted from Denny AD 2002 62	4	Sedation	3-5
Scott AR et al. 2011 [45]	External	?	?	?	?	?	4-8	?	?
Monasterio FO et al. 2004 [43]	External	3	15	Until overcorrection was evident.	1/day	12 (7-19)	6-8	?	?
Shen W et al. 2009 [37]	Internal non-resorbable	1	15	When max. length of distractor was reached (20mm) or mandibular gum line was 0-2 mm in front of maxillary gum line.	Day 1-5: 1.2/day From day 6: 1/day	16 (9-21)	4	Sedation	4-6
Mohamed AM et al. 2011 [47]	Internal non-resorbable	1	?	?	0.5/twice a day	18 (15-23)	10	General anesthesia	?
Hong et al. 2012 [46]	Internal non-resorbable	1	9-12	Until no maxilla-mandibular discrepancy is left.	1.5 – 2.0/day	18 (15-20)	6-8	General anesthesia	?
Mandell DL et al. 2010 [49]	Internal and external	1-2	12 (8-18)	When airway obstruction was corrected, confirmed with flexible laryngoscopy or conversion of tongue orientation from vertical to horizontal position.	0.6 /three times a day	23 (15-23)	6	Sedation	5.6 (1-8)
Genecov DG et al. 2009 [5]	Internal and external	1	19.4	Once central end-to-end occlusion was achieved.	1/day	22 (10-32)	10.4	- External: often office procedure - Internal: ?	?

Wittenborn W et al. 2004 [48]	Internal and external	1	7.6 (6-15)	When mandibular alveolar arch was 1 mm ventral to the maxillary alveolar arch; maximum activation of the distractor was reached or non-progression of the distractor	1-1.2/twice a day	12-15	4-6	- External: office procedure - Internal: outpatient procedure	7.6 (6-15); After completion of the distraction
Burstein FD et al. 2005 [39]	Internal resorbable	2	9	After maximal technical distraction was achieved (based on length of the drive screws)	2/day	18 (15-20)	4	Ambulatory without sedation	5-7
Breugem C et al. 2011 [41]	Internal resorbable	1.5-2	8 (6-9)	Until mandibular alveolus was in normal position compared to the maxilla or maximal technical distraction was achieved.	1/twice a day	18.5 mm (16-22)	4	Ambulatory without sedation	7.5 (5-11)

R1 R2 R3 R4 R5 R6 R7 R8 R9 R10 R11 R12 R13 R14 R15 R16 R17 R18 R19 R20 R21 R22 R23 R24 R25 R26 R27 R28 R29 R30 R31 R32 R33 R34 R35 R36 R37 R38 R39

Table 4 Outcome of MDO in the reviewed literature

Article	Type of MDO	General outcome	Mean follow up (months)	Complications described
Morovic CG et al. 2004 [44]	External	Complete relieve in respiratory symptomatology in 100%; early decannulation in 100% ; normalization of growth curve in 100% ; proportional mandibular growth at 18 months in 100%.	18	- 13% transient local infection of the skin (n=3) - 9% extrusion of the nails (n=2) - 9% hypertrophic scar (n=2)
Denny A et al. 2005 [30]	External	Normal postoperative polysomnography after 1 week-1 month in 100%, normal oral feeding in 91% after 45 days and in 100% after 1 year. Growth above the 50th percentile in 91%.	60	No complications
Scott AR et al. 2011 [45]	External	Avoidance of a tracheotomy in 89% (n=17); 90% (n=17) outcome score of ≥8/10 ("intermediate-good").	67 (36 – 145)	- 21% long-term tooth loss or malformation(n=4) - 16% hypertrophic scars (n=3) - 16% long-term injury of the marginal mandibular branch of the facial nerve (n=3) - 16% G-tube dependent (n=3) - 5% additional MDO due to failure of mandibular growth and relapsing upper airway obstruction (n=1) - 5% inability to decannulate (n=1) - 5% residual anterior open-bite deformity (n=1)
Monasterio FO et al. 2004 [43]	External	Disappearance of gastroesophageal reflux and sleep apnea in 100%; mean oxygen saturation 93% (range 89-96%); disappearance of abnormal tongue movements and barium stasis in the pharyngeal recess and trachea in 100%; normal pharyngeal transit time in 100%.	2-4	- 28% transient local infection of the skin (n=5) - 6% incomplete osteotomy requiring second operative procedure (n=1)
Shen W et al. 2009 [37]	Internal non-resorbable	No supplemental oxygen after 20 days postop in 100% (n =6), no additional treatment or surgery needed in 100% (n=6), full oral feeding after 1 month in 100% (n=6).	6	No complications
Mohamed AM et al. 2011 [47]	Internal non-resorbable	Uneventful decannulation, removal of tongue stitches or nasopharyngeal airway (100%), mean respiratory index 1 (range 0-2), mean oxygen saturation 97% (range 95%-99%). Normal oral feeding, no breathing problems and normal growth after 6-12 months (100%).	12-24	- 27% transient mild infections of the skin (n= 3) - 9% unilateral incomplete osteotomy (n=1) - 9% transient unilateral mild weakness of marginal branch of facial nerve (n=1)
Hong et al. 2012 [46]	Internal non-resorbable	Avoidance of tracheotomy and other airway interventions (including supplemental oxygen) in 100%. No monitoring or other home care measures on discharge in 100%. Improvement in swallowing function and reflux disease and full oral feeding in 100%	18	- 40% local erythema and tenderness (n=2)

Mandell DL et al. 2010 [49]	Internal and external	Full relieve of upper airway obstruction and discharged home at 7 days (range 2-62 days) after MDO (88%); no regular home monitoring in 100%; Normal oral feeding in 86%.	13 (7-16)	- 12.5% G-tube dependent (n=1)
Genecov DG et al. 2009 [5]	Internal and external	Decannulation for 1 year after MDO or prevention of an eminent tracheotomy in 94% (n=63). Successful swallowing in 91% (n=61). Reduced postop respiratory disturbance index 97% (n=65).	?	- Local infections of the skin; 4.5% in internal MDO (n= 3) and 8.8% in external MDO (n=6) - Replacement related to device failure; 3% in internal MDO (n=2) and 10.2% in external MDO (n=7) - Temporary asymmetric movement of the depressor anguli oris muscle; 4.5% in internal MDO (n=3) and 4.5% in external MDO (n=3) - 3% failed decannulation(n=2)
Wittenborn W et al. 2004 [48]	Internal and external	Successful long term outcome in airway stabilization after extubation in 82% (n=14)	16.5 (8-48)	- Need for tracheotomy; 25% in external MDO (n=1) and 8% in internal MDO (n=1)
Burstein FD et al. 2005 [39]	Internal resorbable	Avoidance of a tracheotomy in 100% (n= 15); early decannulation in 93% (n=14), 7% requirement of fundal plication due to severe gastroesophageal reflux (n=1)	24	- 27% transient local infections of the skin (n=4)
Breugem C et al. 2011 [41]	Internal resorbable	Discharge (mean 17 day post operatively.; range: 11-27) without any nasal continuous pressure in 100% (n=12). Normal oral feeding in 54% (n=6) at discharge and in 36% (n=4) within 4 weeks post operatively.	32 (13-56)	- 8% transient local infections of the skin (n=1) - 8% extrusion of the distraction screw (n=1)

Table 5 Complications

	External device (n=109)	Internal device (n=95)	
		Non-resorbable (n=68)	Resorbable (n=27)
Local infection of the skin	12.8% (14)	11.8% (8)	18.5% (5)
Nerve damage	5.5% (6)	5.9% (4)	-
Device failure needing replacement	6.4% (7)	2.9% (2)	-
Hypertrophic scars	4.6% (5)	-	-
Tooth loss or malformation	3.7% (4)	-	-
G tube independent*	2.8% (3)	-	-
Incomplete osteotomy	1.8% (1)	1.5% (1)	-
Failed decannulation / need for tracheotomy*	1.8% (2)	1.5% (1)	-
Extrusion of the nail	1.8% (2)	-	3.7% (1)
Need for second operative measure	1.8% (2)	-	-
Other	0.9% (1; open bite deformity)	-	-
Total complications	43% (47)	24% (16)	22% (6)
No complications	57% (62)	76% (52)	78% (21)

** 12.5% G-tube dependent (n=1) in Mandell DL et al. 2010 [49] and 3% failed decannulation (n=2) in Genecov DG et al. 2009 [5] are complications which are not included as no difference could be made between external and internal MDO.*

DISCUSSION

Distraction osteogenesis was introduced by lengthening of the femur by Codvilla in 1905 52 and the tibia by Abbott in 1927[53], although it was not until the 1940's that the use in the lower extremities was truly popularized by Illizarov[54] and De Bastiani[55]. Application of the technique in the craniofacial skeleton should be credited to German craniofacial surgeons Wassmund[56] (for clinical advancement of the maxilla in a patient with hypoplasia) as early as 1926 in Berlin, and to Rosenthal[57] (for bone lengthening of the mandible in a micrognathic patient) in 1927. MDO, a term introduced by Rosenthal, seemed to be forgotten worldwide until 1972, when an experimental report in a canine mandible was presented by Sneyder.[58] This was followed by a clinical report of McCarthy et al. in 1992[36], describing a rigid external device for distraction of the mandible in congenital deformities. Since then, numerous reports have been published, demonstrating the feasibility in relieving airway obstruction, preventing tracheotomies or providing a successful decannulation in many cases.[25, 59-62] Currently there are two main type of devices: external and internal distractors. The internal can be subdivided in non-resorbable and resorbable distractors. One of the advantages of the internal distractors is the lack of a cumbersome external device during distraction and the consolidation period. This tends to make the process more acceptable for the parents, offering the possibility for the mother to breastfeed and maintain expander integrity. Also there is a smaller risk of pin-associated infections, compared to external MDO were pin-site hygiene can be challenging. External scars are less notable due to their location under the mandibular ramus, hypertrophic scarring is less

common and there is less risk to damage the marginal mandibular branch of the facial nerve.[63-65] Primary advantage of the external distractor is the ability to use multivector movement performing multiplanar distraction, that can be adjusted during the distraction phase to accommodate to mandibular asymmetries or irregularities.[65] The unidirectional movement of the internal distractors requires a more meticulous planning of osteotomies and vectors and does not allow fine adjustments of mandibular segments to correct any occlusal disharmony that occurs during the distraction process.66 Curvilinear devices have been developed, trying to obviate this problem.[67] Still, both internal and external MDO will require a second operative procedure for removal of the hardware, which is prevented by the use of an internal resorbable distractor. Resorbable distraction has been widely used in craniofacial surgery since several years.[68] The application in infants with RS was first presented in 2002 by Burstein et al.[38] They illustrate the promising outcome and address the benefits of this one stage surgical procedure, and the clinical applicability especially suited for infants. Ow and Cheung present an extended meta-analyses of MDO.[25] However, they do not differentiate between the different types of distractors or describe results for infants in particular. In the present study it was the aim to review the distraction features, results and possible complications per type of distraction and summarize the possible differences.

In all reviewed articles, independent of the type of distractor used, MDO was only performed when conservative measures failed. This was determined by a multidisciplinary team after a range of pre-operative investigations (Table 2). It is an important fact to emphasize, as the usage of nasopharyngeal intubation 69 or intra oral devices such as a palatal plate with pre-epiglottal extension[20, 23] reveal pleasing clinical results, especially in mild forms of respiratory distress. Considering distraction features it was noticed that the duration of the distraction process of the internal resorbable device was twice as short compared to the external device (Table 3). This could be explained by the faster distraction rate, which also led to a quicker discharge from the hospital compared to external MDO.[39, 41] Besides, in external MDO the distraction process sometimes started only at the third post-operative day[44, 51], compared to mainly the first day in internal MDO. Notably, in internal MDO the mean total amount of distraction was also longer (17.3 and 18.3 in internal vs. 11.6 in the external device). Extubation or decannulation time was not much different between the different types of MDO, although not all articles specified this. The consolidation period was also generally corresponding for the different type of distractors. Some authors provoked a slight overcorrection of the mandible compared to the maxilla to indicate the end of the distraction process[37, 48, 51] as others objectified a normal horizontal position of the tongue[30, 49] or an anatomic maxilla-mandibular proportion.[41, 46] The overcorrection is performed to compensate for the regenerative contraction that can occur due to possible decrease in growth capabilities.[37] Morovic et al. saw a disproportional over projection of the mandible during the first year of age, corrected at one year in 70% and at 18 months in the remaining 30%.[44]

Complications encountered consisted mainly of local infection of the skin[37, 39, 41, 44, 46, 48, 50, 51] which did not lead to any delay in the distraction process. Infections of the skin were remarkably more

often seen in the resorbable distractors, which might possibly be due to a reaction caused by the degradation process. All infections healed with topic antibiotic ointment. With regard to the non-internal resorbable devices, Genecov et al. saw an almost twice as high infection rate in external MDO, compared to internal (8.8% vs 4.5%).[5] Secondly, facial nerve problems were encountered in both the external and internal approach and were mainly transient when due to traction on the nerve during the placement of the distractor.[5, 45, 47] Long-term injury of the marginal mandibular branch of the facial nerve leading to asymmetric movement of the lower lip at the corner of the mouth, was associated more often with the external approach as the nerve is not visible during placement of the distractor.[5, 45] No nerve paralysis was seen in the internal resorbable distraction groups.[39, 41] Device failure leading to replacement was the third most common complication, seen both in external and internal non-resorbable MDO, but not in resorbable MDO. Hypertrophic scarring was only seen in the external devices. In two articles no complications were encountered (Table 4,5).[30, 37] An overall smaller amount of complications was seen in internal MDO compared to external MDO (Table 5). Some authors described unsuccessful decannulation or long-term need of a tracheostomy during MDO. Since long-term problems are mainly encountered in the syndromal, more complex cases, MDO should be strongly reconsidered in this patient group, as a variety of underlying potential factors (neurologic dysfunction, persistent supraglottic obstruction or TMJ ankylosis) might not allow decannulation.[45, 49] Up to now, long-term results of only external MDO are described.[30, 45] Especially the size and shape of the distracted mandible and outgrow of the teeth is of great concern.[45] Denny et al. have demonstrated after five years follow up that the mandible was growing appropriately in all patients receiving external MDO.[28] Scott et al. have a medial follow up of 67 months were in 5% of the patients there exists a residual open bite deformity and in 21% a long-term tooth loss or malformation after external MDO.[45] Damaged teeth were first, second and premolars, likely related to the location of the mandibular osteotomy. They prefer an osteotomy posterior to the tooth buds to prevent tooth loss, however not through the mandibular angle, which can be challenging. The same applies for the pins, which preferably are not placed in the tooth buds. Careful planning and modeling may limit complications, although optimal vectors for distraction should be achieved as well, making it sometimes a difficult consideration.[70] 3D CT-scan to locate the foramina of the inferior alveolar nerve and the distal tooth buds in the mandibular bodies[37] or an acrylic model of the skull[40] might be helpful preoperatively. However, in the presence of a life-threatening situation, early intervention is often essential and disadvantages like tooth injury should be weighed against the benefits of preventing an acute tracheostomy.[70, 71] Long-term results of internal distraction, both resorbable or non-resorbable, are not yet available.

The preference for a type of distraction remains questionable as both have their advantages and indications as outlined above. Three articles described the use of both kind of distractors.[5, 48, 49] Wittenborn et al. prefers the internal distractor, due to less chance of device failure and simplified care during the distraction and consolidation process.[48] Genecov et al. depended their choice on availability of the distractors and experience of the team. Indications for the use of external

distractors included the need for large advancements (>20 mm), multidirectional vectors and the presence of adequate bone stock volume. Internal distraction was preferably used in infants younger than one year and a planned single vector distraction. In their series, the internal devices showed minimal scarring, the incidence of pin site infection was lower and breast-feeding was easier 5. Mandell and co-workers also preferred the internal method when feasible, because of less change of device dislodgment, no visible hardware allowing earlier return to school or daycare, reduced parental anxiety and less visible facial scarring.[49] The available small internal resorbable distractors have proven to be very suitable for airway management in infants.[39-41] With the development of curvilinear internal devices[67, 72, 73] and even the preliminary use of BMP's to accelerate bone healing during the distraction process[74, 75] this is a promising and upcoming technique. Current results are pleasing, although long-term data considering outgrow of the mandible is lacking.[39-41]

Even when an additional temporarily tracheostomy or endotracheal intubation is mandatory besides MDO to relieve the acute severe upper airway problem, all reviewed articles illustrated most patients could be decannulated or extubated successfully in before discharge. It is imperative to remember that in our quest to find the appropriate surgical treatment glossopexy and tracheostomy may be lifesaving in the acute phase, but do not correct the micrognathia which is the basic anatomical pathology of RS.[30, 51] After MDO, a quicker rehabilitation associated with less risks and long-term co-morbidities is possible.[27, 30, 32, 34, 76] Moreover, homecare is less cumbersome and the total care is less expensive compared to a tracheostomy.[77, 78] Some authors support the "growth catch up theory" as an argument not to perform MDO.[79, 80] However, when conservative measures fail, a more aggressive approach must be selected at that sudden moment. In contrast to tracheotomies and tongue-lip adhesions which are considered as a transient intervention pending an eventual normal intrinsic normal outgrow of the mandible, MDO is a more definite treatment option and a save fundament for further growth of the mandible.[30, 39] Besides, although some patients may outgrow their micrognathia without intervention, rarely does the mandible reach normal values for size matched with normal infants making a definite treatment option for infants suffering RS more essential.[81] Nevertheless, patients that have received MDO may still need a second operative correction of the mandible later in life, as long-term studies (i.e. longer than five years) are not yet available and some form of relapse has been described in up to 64.8% of cases after MDO in general.[42] With long-term results for MDO in infants with specifically RS being unavailable, certain questions still arise, such as the duration of the distraction and timing of the removal of the device. In the resorbable device, the relation between the speed of degradation of the plate and the presence of a possible (long-term) relapse or outgrow problem still has to be elucidated. Besides, although all articles included in the current study handled mainly the same fundamentals in starting MDO only when conservative measures failed, no strict corresponding protocols suggesting a clear indication were used. Therefore there is potential for bias, both in this study and in other reports.[49] Also the moment when distraction is finished remained somewhat indistinct in some of the reviewed articles. Some used clinical parameters (e.g. optimization of saturation) as others used more technical (e.g. maximal

length of distractor was reached) or anatomic aspects (e.g. overcorrection of mandible compared to the maxilla or normal position of the tongue) as indicator of the end of distraction. This is an important fact as the chance of a relapse might depend on the amount of distraction, but which cannot be well compared now. Finally, as not all articles specified the results for the syndromal and non-syndromal RS patients, it is difficult to find an overall difference in outcome between these groups. It is known that there is a higher mortality rate in children with associated anomalies; 22.8% compared with 5.9% for those with isolated RS.[6] This should be regarded in choosing a treatment strategy for this patient group as a different approach might be necessary. More specific guidance for MDO in infants with RS consisting of standardized indications, patient selection, pre- and postoperative evaluation and distraction processes need to be established.[9, 82] Besides, prospective trials comparing different treatment strategies are necessary and might reveal valuable knowledge for the development of an "ideal approach". [23, 69]

With regard to the reviewed literature and our own experience we would advise a non-surgical approach as primary measure in all cases. When there is a life threatening respiratory obstruction - and any other causes and co-morbidities are thoroughly investigated by before mentioned investigations in a multidisciplinary approach - we suggest to perform MDO. In young infants (i.e. younger than six months) an internal (resorbable) distractor has shown promising results with regard to immediate airway obstruction relieve and also parental acceptance and tolerability in home care. In the older, or multicomplex cases an external distractor might provide benefits over an internal device. Using guided surgery by means of preoperatively planned surgiguides 83 or navigation 84 could eliminate the need for external devices in complex cases and support the utilization of curvilinear internal devices. Additional treatment (for example NG tube feeding) should be started during the distraction process to prevent any further growth retardation. To obviate the lack of comparable data, especially for the amount of distraction needed to resolve the respiratory obstruction, we would also recommend to measure the amount of sagittal discrepancy between the maxillary (point A) and mandibular arch (Pogonion) before and after distraction in all future studies. This will contribute to develop designated treatment algorithms and might provide a fundament for protocols in the near future.

CONCLUSIONS

When conservative measures fail, MDO proves to be an appropriate and save intervention in infants and obviates the side effects seen with tracheostomy and tongue-lip adhesion. This review suggests that the internal device seems very feasible in infants with RS, minimizing side effects such as hypertrophic scarring, nerve damage and extensive care needs, although the indications for usage are more limited compared to the external device. Corresponding protocols and long-term outcome studies are needed to make a comparison between the different types of distraction possible and the use and indication of them more distinct.

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5

Bioresorbable distraction device for the treatment infants with Robin Sequence

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ABSTRACT

Background

Pierre Robin sequence is a well-known craniofacial entity. There are numerous ways to treat the respiratory insufficiency, but sometimes surgical intervention is need- ed. Tracheotomy could be associated with morbidity, and distraction osteogenesis has been established as a stable method to obtain a safe airway. Distraction osteogenesis has traditionally been performed with an external device.

Methods

In this manuscript we describe the feasibility of an internal bioresorbable device. Retrospective descriptive study was performed in a tertiary academic children's hospital. After multidisciplinary team consultation, 12 consecutive patients with Robin sequence were treated with this internal distraction device.

Results

The mean age at surgery was 32 days, and the average amount of mandibular distraction was 18 mm. All patients were extubated after an average of 7.5 days after the surgery. The average length of stay in the hospital was 17 days after surgery. There were no major surgical complications. A tracheotomy was prevented in all our patients, and complications were limited.

Conclusions

Long-term studies are needed to evaluate the influence that internal distraction has on the growth of the mandible and teeth. The internal distraction system seems safe for infants with micrognathia and has certain benefits when compared to the external distractor.

INTRODUCTION

In 1923 Pierre Robin described a constellation of findings that bears his name today.[1] The triad of findings included micrognathia, glossoptosis and respiratory obstruction; however, considerable confusion in the medical literature delineating Robin sequence has been demonstrated.[2, 3] Pediatricians often encounter the entity "Robin sequence"; however, there are still many unanswered questions surrounding this disorder. Robin sequence can still be associated with significant morbidity and even mortality.[4] Glossoptosis associated with airway compromise is most often the culprit instigating respiratory insufficiency (Fig. 1). However, other causes can cause breathing problems, and these patients should be carefully investigat- ed preferably by a multidisciplinary team.[5] Traditionally tracheotomy has been considered the definitive treatment in securing a stable airway when the airway was compro- mised. However, tracheotomy can be associated with significant morbidity and even mortality.[6,7]

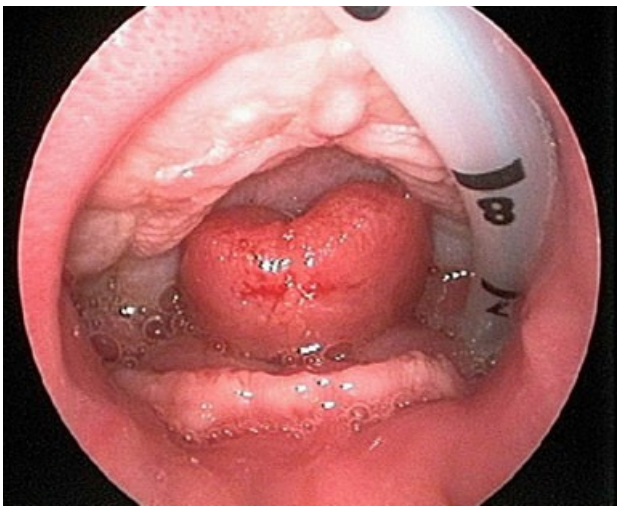

Figure 1 Typical case of glossoptosis. Patient has a cleft of the small palate (not visible on photo). Note retrusion of mandible with regard to maxilla.

Distraction of the mandible has become an accepted method to treat the micrognathia and subsequently the airway compromise.[8-12] Distraction osteogenesis (DO) is a technique in which bone is gradually lengthened after performing an osteotomy. After a short latency period, the bone segments are distracted. The bone segments are separated from each other at a slow, steady rate. Similar to fracture healing new bone will subsequently be formed between these segments. After the acquired bone length is achieved the consolidation period ensues in which the bone segments are held in their advanced positions. This is needed because the newly formed bone has to mature and consolidate. During DO the distraction proceeds at a slow, steady state

ensuing not only bone lengthening but also concomitant soft tissue expansion. Subsequently will not only new bone be formed, but the muscles, blood vessels, nerves and mucosa will also be elongated.

Ilizarov popularized distraction on the lower extremity in the 1940s.[13] Although Codvilla introduced distraction nearly 100 years ago,[14] following in the footsteps of Ilizarov, mandibular distraction was first performed experimentally by Snyder.[15] The first clinical report of mandibular distraction in the English literature was reported by McCarthy et al. in 1992.[16] Like Ilizarov did, mandibular distraction was performed with an external device. Since then, numerous reports have been published demonstrating the feasibility in relieving airway obstruction.[8-12] However, an external distraction system is cumbersome to take care of; it leaves external scars and always needs a second operation to remove the distraction device. In an attempt to alleviate these disadvantages, an internal and resorbable distraction device (located under the skin) was developed.[17]

The goal of this manuscript is to review our results of performing mandibular distraction with a resorbable system in patients with Robin sequence and life-threatening airway compromise.

METHODS

For this study we looked at the patients we treated early, i.e. in the first 3 months after births. Patients were considered for distraction only after a diagnosis of Robin sequence was made (glossoptosis, micrognathia and airway compromise). The medical ethical board approved this study. Patients were seen by a multidisciplinary team consisting of a pediatrician, ENT surgeon, geneticist, dietician and plastic surgeon. Non-invasive treatment options such as prone positioning and nasal continuous positive pressure are sufficient measures for most newborn babies with Robin sequence. Only patients that could not be treated conserva- tively and would traditionally be considered candidates for a tracheotomy were candidates for distraction osteogenesis. Before intervention patients were observed with continuous pulse oximetry and blood gas evaluation (pCO2, HCO 3 etc). Saturation measured over 12 h in all patients was< 90% for>5% of the 12 h.[10] Polysomnography was only used if the aforementioned results were not comparable to the clinical picture. Patients received an endoscopy by the ENT surgeon prior to DO to exclude any other cause of airway obstruction (e.g. tracheomalacia, stenosis etc.) besides the glossoptosis. The first patient treated (Table 1) had already a tracheotomy, while the others were treated primarily for airway compromise. The aim in the first patient was to relieve him of his tracheostoma.

Table 1 Patient characteristics

Patient ID	Date of birth (day.month.year)	Age at surgery (days)	Amount of distraction (mm)	Associated malformations/ syndrome	Outcome	Duration of hospital stay (days)
1	09.19.2006	83	20	COL 11a2 gene mutation (anocular Stickler syndrome)	Admisson with tracheacanule. Minor local symptoms of infection at pint site. Removal 10 months post op.	18
2	10.04.2007	15	18	COL 11a2 gene mutation (anocular Stickler syndrome)	Succesfull detubation on day 9 post op. Minor local symptoms of infection at one pin site.	16
3	10.03.2007	19	16	Non	Successful detubation on day 8 post op.	11
4	11.16.2007	17	20	No mutation on Col2A1 and Col11A1 genes. No definite exclusion of Stickler because of severe myopia	Successful detubation on day 11 post op. Technical failure of one distraction screw 5 weeks after surgery	18
5	01.17.2008	13	18	None	Successful detubation on day 8 post op.	23
6	03.30.2008	94	18	None	Successful detubation on day 5 post op.	14
7	06.26.2008	27	20	Megaencephaly and retardation, no genetic mutation found	Successful detubation on day 8 post op.	27
8	02.08.2010	45	22	None	Successful detubation on day 5 post op.	16
9	06.19.2010	16	20	2.19 Mb deletion in 3q22.2q22.3. Further research is ongoing	Successful detubation on day 7 post op.	15
10	11.03.2009	22	18	None	Successful detubation on day 6 post op.	20
11	07.31.2008	11	18	None	Successful detubation on day 8 post op.	17
12	04.23.2010	24	16	Suspicion of Stickler due to familiar myopia	Successful detubation on day 8 post op.	14

All patients were treated with the Lactosorb internal distractor distributed by W. Lorenz Surgical, a Biomet company. The precise placement has been described previously by Burstein.[17] Briefly, the surgical approach was a submandibular incision (2–2.5 cm) with dissection to the mandibular body and angle while preserving the mandibular branch of the facial nerve. The two dissolvable plates were placed after the vector of distraction was determined from a mandibular X-ray or a CT scan. An osteotomy was performed after the plates were fixated with soluble screws (Fig. 2).

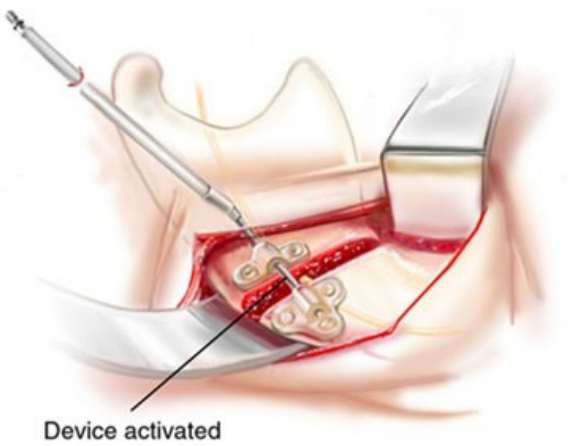

Figure 2 The position of the osteotomy

The distractor wire was subse- quently placed subperiostealy and protruded the skin through an incision placed above the ear (Fig. 3). After the placement of the distractor, we waited for 36–48 h before the distraction was started. A postoperative X-ray was made. Distraction was performed at a rate of 1 mm twice daily (Figs. 4 and 5). After surgery all patients were treated in the pediatric intensive care unit, until the intubation tube could be removed. On average this was performed 5–7 days after the actual distraction was initiated, i.e. when 10–14 mm of bone lengthening was achieved. Distraction was continued until the mandibular alveolus was in a normal position with regard to the maxillary alveolus or until the maximum technical length of distraction with this device (20–25 mm) was achieved (Fig. 6). After a consolidation phase of 4 weeks the distraction screw was removed in the outpatient clinic with patients receiving only paracetamol 30 minutes before removal of the screw. An X-ray was performed before the distraction screw was removed to demonstrate bone consolidation.

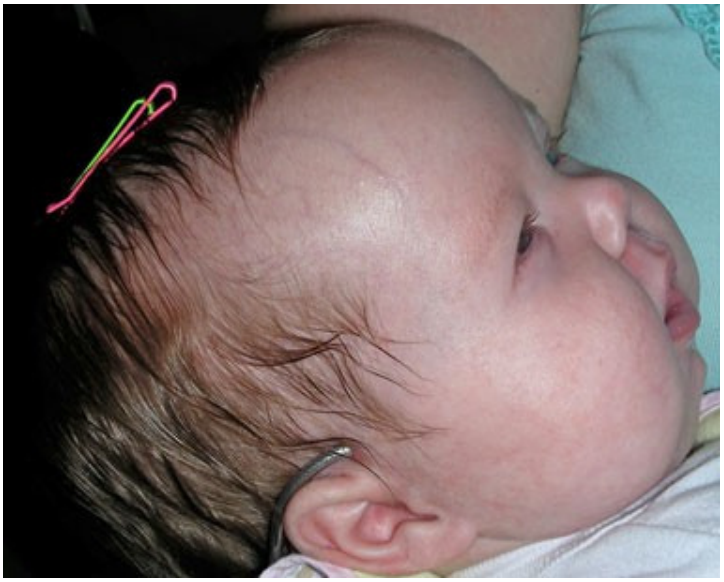

Figure 3 Placement of internal device with distractor wire visible above ear. This could easily be concealed with a baby hat.

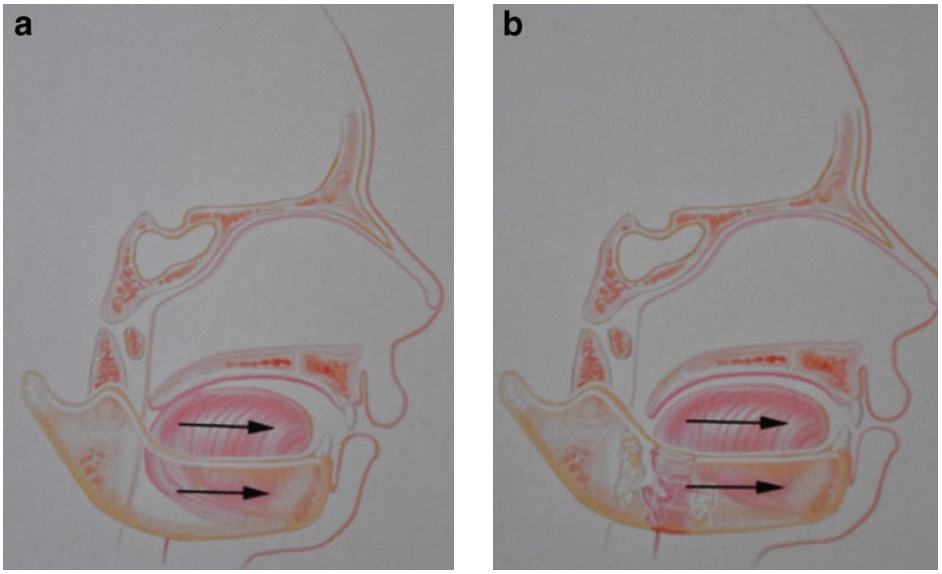

Figure 4 After osteotomy the mandibular is gradually lengthened with the distraction. Prior to distraction (a). This brings the tongue forward (b) and alleviates the respiratory obstruction.

Figure 5 Comparison of resorbable plate size with 2-euro coin.

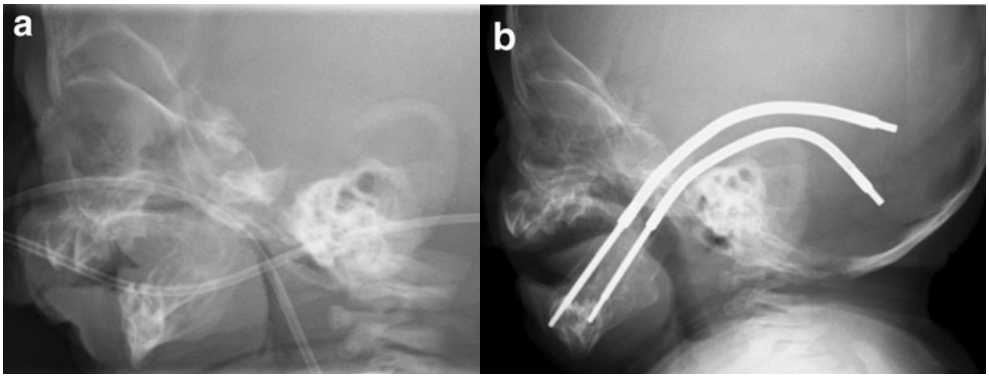

Figure 6 Example of patient before (a) and after (b) surgery. Notice the extra space in the oropharynx after the distraction and that the nasogastric tube has been removed after the distraction process that started at the age of 3 months.

RESULTS

Twelve patients with Robin sequence were included (Table 1). All our patients had an associated cleft palate. Beside our first patient who already had a tracheostoma prior to distraction, a tracheotomy was prevented in all other patients. The mean age at surgery was 32 days (range 11–94 days). The average amount of distraction performed was 18 mm. All patients were extubated after an average of 7.5 days. The average length of stay in the hospital was 17 days after surgery (range 11–27 days). All patients were discharged without any nasal continuous positive pressure. Although feeding issues are not the aim of this manuscript, it should be noted that six of the patients went home without nasogastric feeding and another four patients had the nasogastric feeding discontinued before the distraction screw was removed.

Our first patient treated with internal distraction could not be decannulated. The X-ray showed only about 8–10-mm distraction, despite the expected 20-mm distraction. No surgical re-exploration was performed, but we expect that an incomplete osteotomy or possible mechanical default of the apparatus was the cause. The patient was eventually decannulated at 7 months of age, and it is unknown whether the distraction influenced this in a positive way. In another patient the distraction screw fell out after 95% of the consolidation phase was completed. The patient showed no symptoms, and the technical failure did not lead to any delay or problems. Patient No. 7 in Table 1 developed some redness in the skin around the distraction screw but with antibiotic ointment and oral antibiotics; this resolved without complications.

DISCUSSION

This study demonstrates that the use of an internal bioresorbable distraction system for the treatment of airway compromise in Robin sequence seems a safe procedure with no serious short-term sequelae.

The treatment of patients with airway compromise and associated micrognathia and glossoptosis has been an ongoing research field for many physicians involved in pediatric care. There are numerous ways to address the airway obstruction in newborns ranging from prone positioning to nasopharyngeal airway placement and surgical intervention. Recently the "pre-epiglottic baton plate" (PEBP) has been described as another method to treat sleep apnea in infants with isolated Robin sequence.[18] The aim of our manuscript was not to compare the different treatment methods but to investigate an innovative method. We have previously demonstrated that there is widespread confusion regarding the description of this disorder.[2,3] Moreover, by having different descriptions of Robin sequence, it is not possible to compare various treatment options. Robin sequence affects approximately 1:8000–8500 live births. Additionally it has been demonstrated that many different syndromes could be associated with Robin sequence.[2,3] Some patients have multiple congenital malformations that do not fall within diagnostic criteria for a specific syndrome. It has been demonstrated that syndromic Robin sequence patients are associated with worse outcomes regarding the severity of feeding problems and airway occlusion.[7] For this study we used the definition described originally by Pierre Robin, consisting of micrognathia, glossoptosis and airway compromise. All our patients had an associated cleft palate.

It is well known that most patients with Robin sequence can be treated with positional changes and nasal continuous positive pressure without surgical intervention.[4] However, it is also recognized that a small subgroup needs some form of intervention to maintain an adequate airway.[4, 10-12] Tracheotomies for example can be associated with significant morbidity for the patient and places a huge social burden and responsibility on the family of the patient.[6] Average age at decannulation is 3.1 years, and the long-term sequelae of tracheal stenosis or tracheomalacia may be present in up to 50% to 75% of cases.[6,7,12] Other complications that

could be associated with tracheotomy include sudden airway obstruction from mucous plugging or accidental decannulation. Additional concerns include airway infection, airway bleeding and possible inhibition of proper speech and swallowing development. Tongue–lip adhesion was introduced in 1946 and has long been an alternative to tracheotomies. Success rates have been determined between 50 and 80% although patient characteristics were not always clearly defined in the manuscripts.[19,20] Complications associated with glossopexy include a dehiscence of the adhesion and scarring of the salivary glands. Patients also need a second operation to undo the tongue–lip adhesion.

The feasibility of distraction osteogenesis in the treat- ment of airway problems was recently assessed by a comprehensive meta-analysis performed by Ow and Cheung.[21] This review retrieved 646 patients in which a bilateral distraction was performed to treat upper airway obstruction. Tracheotomy was prevented in 91.3% of neonates. However, distraction osteogenesis is still a relatively new technique and is performed with an external device in most cases.[9-12, 16, 22, 23] External distraction leaves scars on the side of the face and always needs a second operation to remove the pins.[21] The internal device is small (Fig. 6). Patients need only one operation as the material is dissolvable. The inconspicuous scar is located under the border of the mandible and above the ear. The external distraction has the added benefit that multiple vectors of distraction are possible, making it a more suitable distractor in patients with, for example, hemifacial microsomia and an absent condyle of the mandible (class II and III mandibular hypoplasia). However, the external distraction device is cumbersome and could definitely be inconvenient for parents and caretakers. For this reason patients are often admitted to the hospital for extended periods of time.[12] The distractor wire of the internal device above the ear is small, and this could easily be concealed under a baby hat. In this study patients had a distraction at an early age. This obviously was done to prevent a tracheostomy. However, at this age the mandible is also small and soft, and if screws are not adequately fixed they will break out. As the child gets older, the bone will become harder and more stable with subsequent easier fixation of the distractor.

A recent study has demonstrated that the long-term results of distraction osteogenesis are sustained.[11,12] However, the entire process of distraction osteogenesis has multiple steps that each have potential complications and subsequently presents a unique challenge to the surgeon. Potential complications such as open bite deformities, tooth malformations or losses and possible nerve damage should be discussed before every intervention. A recent review has demonstrated that the external distraction device is often associated with the following complications: tooth injury (22.5%), hypertrophic scarring (15.6%), nerve injury (facial and inferior alveolar) (11.4%), infection (9.5%), inappropriate vector (8.8%), device failure (7.9%), fusion error (2.4%) and temporomandibular joint injury (0.7%).[22-24] However, when we compare our study with the only other study population where the same internal resorbable device was used[8,17], it seems that the internal device is associated with less morbidity than the external device. Although it should be mentioned that our study population is small, and long-term follow-up is needed to determine which device is superior.

In our study we had one patient where an "unsuccessful" distraction was achieved. Prior to distraction she had a tracheotomy, as was custom in our hospital at that stage. Objectively we achieved only 10 mm of distraction despite the expected 20 mm. However, we were able to decannulate her at 7 months of age. Since literature demonstrates that the average age of decannulation for children with Robin sequence is 3.1 years, it is possible that the distraction did shorten her tracheotomy time.[25]

It is often stated that the mandible in Robin sequence always has a "catch-up" phase and that patients have a normal mandible in the long-term. However, it is demonstrated in the literature that micrognathia seldom recovers fully and that the previously reported "catch-up growth" often does not occur.[26,27]

Neonates with Robin sequence suffer from two main problems: airway obstruction and feeding difficulties. The main aim of this study was to determine the feasibility of this internal resorbable device to prevent tracheotomies; however, the impact distraction has on feeding was not studied and will be investigated in the future. Still we can address that the majority of our patients were dismissed without the need for a nasogastric tube and were able to be fed with a bottle and a Haberman teat feeder. Many other factors must be taken into consideration before deciding which intervention is best for the patient. In some patients with Robin sequence, mandibular distraction can permanently correct the obstructed airway, and subsequent inconvenience and costs associated with the maintenance of the tracheotomy can be avoided.[8,9,11,12] It has also been demonstrated that some patients need multiple distractions and some patients will only benefit from a tracheotomy because of neurological impairment.[28]

CONCLUSIONS

The internal distraction system seems safe for infants with micrognathia and has certain benefits when compared to the external distractor. A tracheotomy was prevented in all our patients, and complications were limited. Long-term studies are needed to evaluate the influence that internal distraction has on the growth of the mandible and teeth.

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6

Long-term results of mandibular distraction osteogenesis with a resorbable device

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ABSTRACT

Background

Mandibular distraction osteogenesis (MDO) with a unidirectional resorbable device is an effective treatment option for severe upper-airway obstruction in infants with Robin sequence (RS). Long-term effects, especially with regard to teeth development and mandibular outgrowth, are not known.

Methods

RS infants treated at our institution, with a follow-up of ≥5 years, were included. Baseline characteristics were extracted from medical records. Panoramic and lateral cephalometric radiographs were analyzed and patients recalled for physical examination.

Results

Ten infants underwent MDO at a mean age of 3.7 months (median: 19 months; range: 11 days to 27 months). Mean follow-up was 6.8 (5.0–7.9) years. Ten RS infants without MDO (mean follow-up, 7.4 (6.7–8.9) years) were the controls. Shape anomalies, positional changes and root malformations of molars were seen significantly more often than in the control group (p=0.007, p=0.009 and p=0.043, respectively). Mandibular length was shorter (p=0.030), but mandibular ramus height was comparable (p=0.838) with the non-MDO group. Compared with healthy controls, all RS infants had a significantly shorter mandibular length. Acceptable scar formation, lack of nerve injury, a patent airway, and good feeding capacity was seen in 90% of cases.

Conclusions

MDO with a resorbable system reveals overall good short- and long-term results, but the effect on developing molars and mandibular outgrowth likely necessitate secondary procedures. This factor should be considered when deciding on treatment options and counseling of parents.

INTRODUCTION

Robin sequence (RS) is a rare congenital disorder.[1, 2] A concomitant cleft palate may exist, but is not a required feature to define RS.[2] In many cases, associated syndromes or anomalies coincide.[3]

Most RS infants can be treated conservatively but respiratory distress can necessitate surgical measures such as tongue lip adhesion, tracheotomy or mandibular distraction osteogenesis (MDO).[4] Reports have described the feasibility, outcome and differences of external or (resorbable) internal distraction devices in RS treatment.[5-8] Despite good results regarding patency of the upper airway, complications that have been described include hypertrophic scarring, nerve injury, infection, dental injury, inappropriate distraction vector, relapse, device failure, non-union and injury to the temporomandibular joint (TMJ).[7, 9-12] Complications to the molar buds are difficult to predict as these occupy a large proportion of the total infantile mandible volume, nearly approximating the inferior mandibular border.[13] Consequently, they are at potential risk of damage during the procedure. No studies have investigated this matter for RS infants and during a follow-up period of >5 years. Long-term data of the unidirectional resorbable distraction system (RDS) are lacking at all.[14, 15]

We investigated the long-term results of MDO with a RDS in RS infants. Results were compared with those from non-surgically treated controls and healthy controls during a follow-up of ≥5 years. The effect on development of first permanent molars and mandibular outgrowth were addressed. We wished to create awareness of the long-term outcome of this procedure and to facilitate decision-making in this challenging patient group.

PATIENTS AND METHODS

RS infants treated with MDO in the Wilhelmina Children's Hospital in Utrecht (the Netherlands) were the study cohort. Same number of consecutive infants with RS who had not received MDO formed the control group. RS was defined as micrognathia, glossoptosis and respiratory distress. Relevant data had to be retrievable from medical records and a follow-up of ≥5 years was essential. Patients not fulfilling these criteria were excluded.

Distraction osteogenesis was undertaken with an internal unidirectional resorbable device (LactoSorb®; Biomet, Bridgend, UK) according to the method described by Burstein et al.[16] MDO was pursued if infants expressed severe respiratory distress refractory to conservative treatment.[17] Information about the surgical procedure and short-term results are described elsewhere.[14, 17]

Patients were recalled for a physical examination undertaken by a plastic surgeon and pediatric dentist. Baseline characteristics were extracted from medical records. Critical assessment of several predetermined criteria on dental panoramic radiographs with a team comprising a plastic surgeon, pediatric dentist and orthodontist was done. Standardized lateral cephalograms were obtained. Digitization of cephalograms was undertaken with Viewbox v4.0 (dHAL®, Athens, Greece). Measurements of predetermined landmarks on cephalograms were done simultaneously, under

identical circumstances, by two maxillofacial surgeons in a 3-month interval. Bony landmarks are provided in Figure 1. Information on cephalometric parameters reported in a longitudinal follow-up study of healthy Scandinavian children was collected as reference data.[18] The head was fixed into a cephalostat and data digitized (Scriptel®, Columbus, OH, USA).[18]

Data were stored into Microsoft Excel and analyzed further using SPSS v20 (SPSS, IBM, Armonk, NY, USA). Intra-class coefficient (ICC) was used to calculate reliability. ICC >0.75 was termed "excellent", 0.40–0.74 was "fair-to-good" and <0.40 was "poor".[19] Chi-squared tests were used for interactions between categorical variables (e.g., sex). To compare other baseline characteristics and measurements of lateral cephalometric radiographs, Mann–Whitney-U tests and two tailed independent-samples *t*-test were computed.

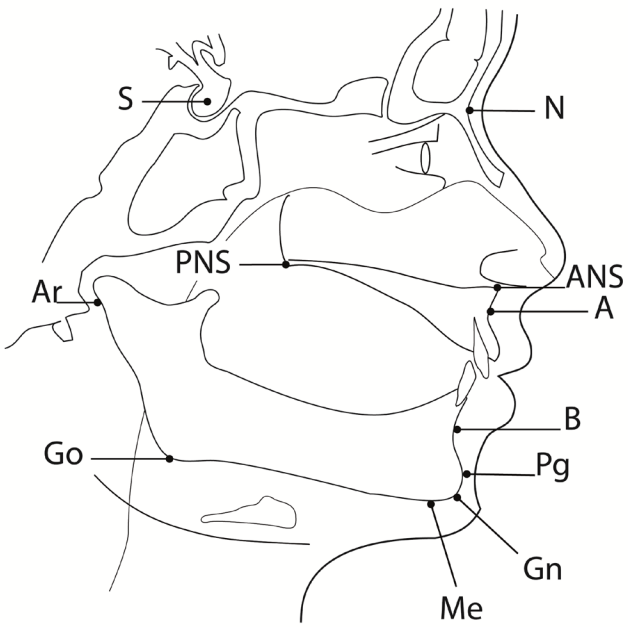

Figure 1 Skeletal reference points used for measurements on lateral cephalometric radiographs. *SNA*, angle between the sella-nasion-A point; *SNB*, angle between the sella-nasion-B-point, *SNPg*, angle between the sella-nasion-pogonion; *Pg-NB*, angle between the pogonion to the nasion - B point; *SN-GoGn*, angle between the sella-nasion and the gonion-gnathion; *SN-GoMe*, angle between sella-nasion and the gonion-menton; *SN-Gn*, angle between sella-nasion to Gonion; *Palatal plane – MP*, angle between palatal plane (i.e., a line between the anterior nasal spine and posterior nasal spine) to the mandibular plane (i.e., a line connecting Go-Me); *Palatal plane – GoGn,* angle between the palatal plane to the gonion-gnathion; *Go-Me*, distance between the gonion and menton; *Ar-Go*, distance between the articulare and gonion (i.e., mandibular ramus height); *Ar-Go-Gn*, distance between the articulare, gonion and gnathion; *S-Ar-Go*, angle between the sella, articulare and gonion (i.e., articular angle); *Ar-Go-Me*, angle between the articulare, gonion and menton (i.e., gonial angle); *Go-Pg*, distance between the gonion and pogonion; *Ar-Pg*, distance between the articulare and pogonion (i.e., mandibular length); *Go-Gn*, distance between the gonion and gnathion; *S-Go*, distance between the sella and gonion (i.e., posterior facial height); *N-Me*, distance between the nasion and menton (i.e., anterior facial height).

RESULTS

Ten consecutive infants who underwent MDO at a mean age of 3.7 months (median: 19 days, range: 11 days to 27 months) were included. Mean follow-up was 6.8 (5.0–7.9) years. Data were compared with those of ten RS infants with a mean follow-up of 7.4 (6.3–8.9) years. All patients had a cleft palate. In 40% of controls, a surgical intervention was necessary due to the severity of airway obstruction. Both infants in whom a tracheostomy was pursued were admitted before 2007, when no MDO was yet performed in our institution. Baseline characteristics are listed in Table 1.

Table 1 Baseline characteristics of the study group and control group

	Mean (SD)		*p**
	MDO	Control	
Number of patients (n)	10	10	NA
Follow-up (years)	6.8 (0.75)	7.5 (0.98)	0.159
Number of females (n)	4	4	1.0
Gestational age (days)	278 (4.75)	275 (6.61)	0.320
Birth weight (g)	3437 (563.99)	3323 (544.88)	0.631
Intervention	100% MDO	30% tracheotomy 10% temporary intubation	NA
Age at intervention (days)	111 (247.4)	21 (18.9)	0.454
Distraction rate (mm)	18.6 (1.35)	NA	NA
Hospital duration (days)	18.7 (4.60)	50.9 (48.50)	0.392
Associated disorders¶	40% iRS, 60% niRS (Stickler, n=2; Osteopathia striata with cranial sclerosis, n=1; Auriculo-condylar syndrome, n=1; other anomalies/ chromosomal defects, n=2)	40% iRS, 60% niRS (Stickler, n=4; other anomalies/chromosomal defects, n=2)	NA

MDO, mandibular distraction osteogenesis; SD, standard deviation; NA, not applicable
**p<0.05 was considered significant*
¶iRS, isolated RS; niRS, non-isolated RS (i.e., presence of a syndrome, or other associated anomalies or chromosomal defects).

Short-term complications after MDO comprised a low-grade skin infection at the entry site of the distraction wire (n=1, 10%), which resolved with antibiotic ointment and oral antibiotics. In another infant, technical failure of one distraction drive screw after 95% of the distraction was completed was noted. Complications did not hamper distraction and all patients were extubated after an average of 7.6 (5–11) days. Distraction drive screws were removed in the outpatient department after 4 weeks of consolidation. Oral feeding was resumed <4 weeks after MDO in all infants.[14] One child suffering from auriculo-condylar syndrome with a normal functioning TMJ had a second distraction at age 5 years caused by recurrence of obstructive sleep apnea syndrome (OSAS). Due to his age and

vertical growth pattern, a curvilinear non-resorbable distractor was used. This distraction yielded a mean length of 23 mm and overcorrected counterclockwise rotation of the chin. The child no longer suffers OSAS but a relative open-bite deformity persists that may require another procedure at the end of adolescence.

Dental panoramic radiographs

Eight missing premolars and/or permanent molars were seen in five patients (50%) of the MDO group compared with five missing premolars and/or permanent molars seen in two cases (20%) of the control group (p=0.170, Table 2). First permanent molars were present in all cases. Second permanent molar was absent in two cases of the MDO group. Six buds of first and second premolars were absent in three cases (30%) of the MDO group compared with five buds in two cases (20%) of the control group.

Table 2 Assessment of dental panoramic radiographs of the study group and control group

		MDO (n=10)		Control (n=10)		p*
		Affected patients (n)	Affected teeth (n)	Affected patients (n)	Affected teeth (n)	
Agenesis		5	8	2	5	0.170
First premolar	0	0	1	2		
Second premolar	3	6	2	3		
First permanent molar	0	0	0	0		
Second permanent molar	2	2	0	0		
Shape anomalies		7	13	1	2	0.007
Second premolar/ deciduous molar		2	4	0	0	
First permanent molar		6	9	1	2	
Positional changes		7	10	1	2	0.009
Second premolar/ deciduous molar		1	3	0	0	
First permanent molar		7	7	1	2	
Root malformations¶						
First permanent molar		4	4	0	0	0.043

MDO, mandibular distraction osteogenesis
**p<0.05 was considered significant*
***Description of teeth according to the International Standards Organization Designation System*
¶Not analyzed for the second premolar because the root was not yet developed in most cases

In seven cases (70%) of the MDO group, shape anomalies of one or more first permanent molars or second premolars/deciduous molars were seen compared with hypoplasia in one case of the control group (p=0.007) (Fig. 2). Positional changes were present in 70% and root malformations in 40% of the MDO group, which was significantly higher compared with the control group (p=0.009 and p=0.043, respectively) (Fig. 3, 4).

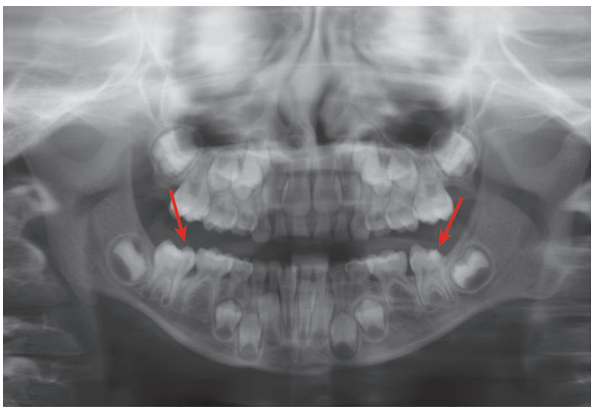

Figure 2 Example of a shape anomaly seen at the mesial surface of the right first molar and the full distal surface of the left first molar. Note the bilateral hypodontia of second pre-permanent molars.

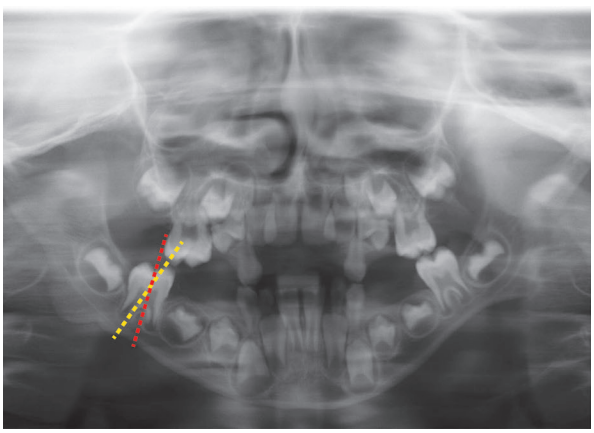

Figure 3 Example of distal inclination of the right first molar.

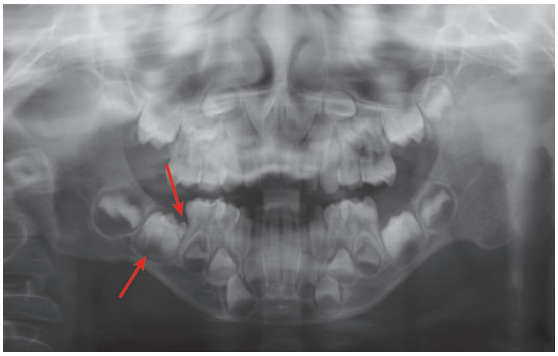

Figure 4 Example of a root malformation at the first molar at the right side. Note the hypoplasia of the mesial surface.

Cephalometric analyses within the RS group

Intra-observer analyses demonstrated good results for all measurements (Table 3). Analyses of lateral cephalograms showed, compared with the RS control group, that the mandible of the MDO group was smaller (Table 4, Fig. 5a) as demonstrated by a significantly smaller mandibular length (Ar-Pg) in the MDO group (77.8 *vs*. 79.5 mm, p=0.030). Size discrepancy was caused by the smaller size of the mandibular body (Go-Gn, Go-Pg, Go-Me) because mandibular ramus height (Ar-Go) was comparable for both groups (p=0.838).

Table 3 Intra-observer reliability of cephalometric measurements

Variable¶	Mean (SD)		ICC*
	First tracing	Second tracing	
SNA (°)	77.1(5.49)	78.2 (5.98)	0.893
SNB (°)	70.8 (5.83)	71.9 (6.43)	0.914
SNPg (°)	70.9 (6.33)	72.6 (6.94)	0.939
Pg-NB (°)	0.13(1.25)	-0.26 (1.55)	0.881
SN-GoGn (°)	43.9 (10.7)	43.1 (11.5)	0.962
SN-GoMe (°)	46.6 (10.7)	45.5 (11.5)	0.958
SN-Gn (°)	73.4 (6.92)	73.0 (7.53)	0.953
Palatal plane – MP (°)	30.0 (10.9)	30.0 (11.52)	0.954
Palatal plane – GoGn (°)	27.9 (9.91)	27.3 (11.10)	0.953
Go-Me (mm)	46.7 (5.83)	44.9 (6.06)	0.841
Ar-Go (mandibular ramus height) (mm)	30.9 (4.46)	30.5 (4.68)	0.806
Ar-Go-Gn (°)	139.7 (12.58)	137.7 (13.01)	0.841
S-Ar-Go (articular angle) (°)	144.8 (9.24)	149.0 (8.81)	0.688
Ar-Go-Me (gonial angle) (°)	142.4 (12.45)	140.1 (12.97)	0.841
Go-Pg (mm)	51.1 (5.66)	50.2 (5.76)	0.887
Ar-Pg (mandibular length) (mm)	75.8 (6.22)	73.99 (6.08)	0.932
Go-Gn (mm)	50.5 (6.69)	49.8 (6.19)	0.871
S-Go (posterior facial height) (mm)	54.5 (6.00)	55.2 (5.65)	0.948
N-Me (anterior facial height) (mm)	94.8 (7.33)	93.8 (7.50)	0.952

¶For abbreviations, *see the legend for Figure 1*
**ICC, Intra-class correlation coefficient*

Table 4 Cephalometric measurements of the study group and control group

Variable¶	Mean (SD)		*p**
	MDO	Control	
SNA (°)	77.0 (6.22)	77.3 (4.66)	0.781
SNB (°)	69.0 (6.19)	72.4 (4.83)	0.149
SNPg (°)	69.0 (6.74)	72.6 (5.27)	0.255
Pg-NB (°)	-0.08 (1.47)	0.30 (0.95)	0.697
SN-GoGn (°)	45.8 (12.58)	42.2 (7.98)	0.699
SN-GoMe (°)	48.6 (12.33)	44.7 (8.30)	0.684
SN-Gn (°)	74.4 (7.39)	72.8 (6.37)	0.645
Palatal plane – MP (°)	33.7 (12.3)	26.8 (7.92)	0.247
Palatal plane – GoGn (°)	30.8 (11.1)	25.4 (7.92)	0.315
Go-Me (mm)	46.4 (11.88)	50.0 (3.66)	0.035
Ar-Go (mandibular ramus height) (mm)	32.1 (10.23)	32.3 (2.31)	0.838
Ar-Go-Gn (°)	143.7 (15.4)	135.9 (6.68)	0.172
S-Ar-Go (articular angle) (°)	142.6 (10.7)	146.1 (7.64)	0.225
Ar-Go-Me (gonial angle) (°)	146.2(14.5)	138.4 (6.99)	0.118
Go-Pg (mm)	51.3 (13.00)	54.2 (3.48)	0.052
Ar-Pg (mandibular length) (mm)	77.8 (19.83)	79.5 (3.30)	0.030
Go-Gn (mm)	50.8 (12.6)	53.5 (3.69)	0.063
S-Go (posterior facial height) (mm)	56.1 (13.67)	56.6 (5.21)	0.481
N-Me (anterior facial height) (mm)	99.2 (22.63)	96.9 (6.30)	0.363

MDO, mandibular distraction osteogenesis; SD, standard deviation
**p<0.05 was considered significant*
¶For abbreviations, *see the legend for Figure 1*

A more vertical growth pattern was seen in the MDO group compared with RS controls (Table 4, Fig. 5b). This was demonstrated by a negative angle between Pg-NB in the MDO group (–0.08° compared with 0.30° in the RS control group, p=0.697), which indicated a more retruded pogonion with respect to the nasion and B-point. A more obtuse gonial angle was seen in the MDO group (146.2° *vs*. 138.4°, p=0.118). More vertical directed growth was also demonstrated by the angles between SN-Go-Gn, SN-GoMe, palatal plane-MP and palatal plane-GoGn: a greater (non-significant) angle in the MDO group was seen compared with RS controls. Anterior facial height (N-Me) was larger for MDO patients than for controls (99.2 *vs*. 96.9 mm, p=0.363) and posterior facial height was smaller (S-Go, 56.1 *vs*. 56.6 mm, p=0.481).

A smaller (non-significant) angle between SNB and SNPg for the MDO group compared with the RS controls was seen (69.0° *vs*. 72.4°, p=0.149 and 69.0° *vs*. 72.6°, p=0.225, Table 4). This could emphasize the difference in mandibular length or a vertical growth pattern. MDO had no influence on maxillary growth as indicated by a similar SNA angle for both groups.

Separate sub-analyses between isolated and non-isolated cases of the control group revealed a significant difference in mandibular length (Ar-Pg), mandibular body (Go-Gn, Go-Pg, Go-Me), the angle between Pg-NB (all p=0.017) and mandibular ramus (Ar-Go, p=0.042). Identical analyses for the MDO group did not demonstrate significant differences among infants even when separate sub-analyses among the various syndromes were undertaken. When comparing cephalometric landmarks only in surgically treated RS infants (n=4 in the control group *vs*. n=10 in the MDO group) no significant differences were found.

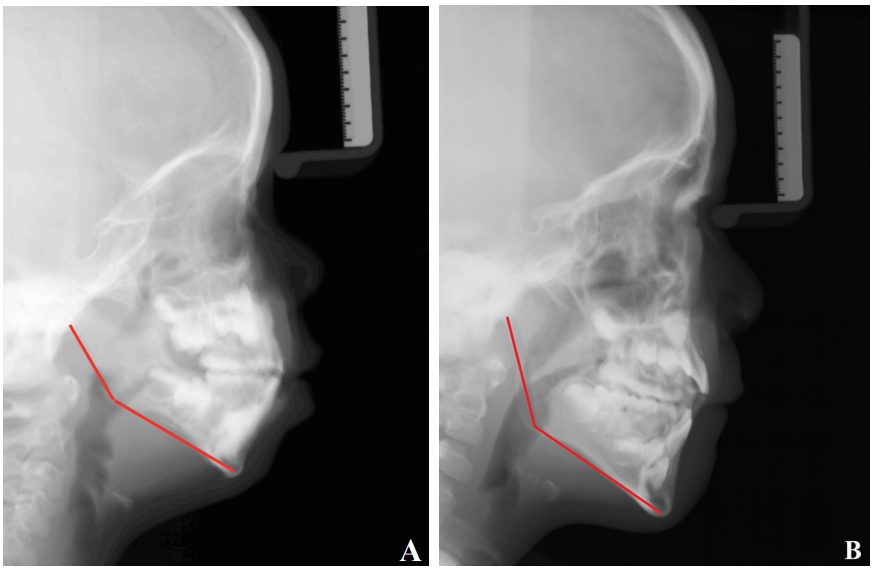

Figure 5 Lateral cephalogram of a 7.3-year-old female with RS after MDO in which the shorter mandibular length and more pronounced vertical growth pattern is seen (**a**), compared with a 7-year-old RS infant of the control group (**b**).

Cephalometric analyses compared with healthy controls

Comparison of the two groups of RS patients with healthy seven-year-old European controls [18] revealed significant differences in all measured points except for the angle between palatal plane and MP (p=0.246) and anterior facial height (N-Me, p=0.073) (Table 5). SNB was significantly smaller in RS groups compared with healthy controls (p=0.002). SNA was significantly smaller in RS groups compared with healthy controls (p=0.043). When comparing both RS groups separately with healthy controls, no other significant differences were demonstrated.

Table 5 Comparison of cephalometric measurements of RS infants with healthy controls

Variable¶	Mean (SD)			*p**
	MDO +	MDO–	Control¥	
SNA (°)	77.0 (6.22)	77.3 (4.66)	81.6 (3.2)	0.043
SNB (°)	69.0 (6.19)	72.4 (4.83)	77.8 (3.1)	0.002
SNPg (°)	69.0 (6.74)	72.6 (5.27)	78.2 (3.3)	0.003
SN-GoGn (°)	45.8 (12.58)	42.2 (7.98)	33.2 (5.3)	0.009
Palatal plane - MP (°)	33.7 (12.3)	26.8 (7.92)	26.3 (4.7)	0.246
Ar-Go-Me (gonial angle) (°)	146.2 (14.5)	138.4 (6.99)	127.9 (4.9)	0.000
Ar-Pg (mandibular length) (mm)	77.8 (19.83)	79.5 (3.30)	94.3 (4.1)	0.000
N-Me (anterior facial height) (mm)	99.2 (22.63)	96.9 (6.30)	101.6 (4.5)	0.073

MDO: mandibular distraction osteogenesis; SD: standard deviation
**p<0.05 was considered significant*
¶For abbreviations, *see the legend for Figure 1*
¥*Cephalometric standards of seven-year-old Swedish children as extracted from Thilander et al.*

Physical examination

A comparable DMFT (Decayed Missing Filled Teeth, in mixed dentition) score of the MDO group with the control group (1.5 *vs.* 2.9, p=0.161) and undisturbed function of the inferior alveolar and marginal mandibular nerve was seen (Table 6). Very acceptable, inconspicuous scar formation was seen (Fig. 6).

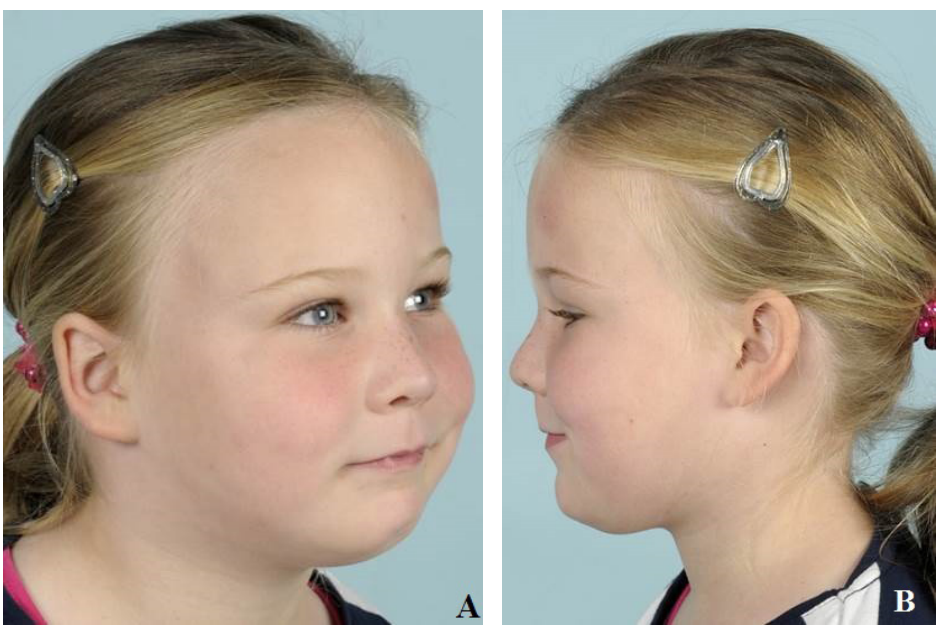

Figure 6 Good scar formation in a 7.3-year-old female after MDO.

Table 6 Outcome of physical examinations of the study group and control group

Variable	MDO	Control	*p**
Mean DMFT¶ score (SD)	1.5 (3.50)	2.9 (2.84)	0.161
Intact sensibility in the inferior alveolar nerve	100%	NA	–
Intact function in the marginal mandibular nerve	100%	NA	–
Acceptable scar formation	100%	NA	–

MDO, mandibular distraction osteogenesis; SD, standard deviation; NA, not applicable
**p<0.05 was considered significant*
¶Decayed Missing Filled Teeth in mixed dentition

DISCUSSION

This is the first report revealing long-term results after MDO with a unidirectional RDS in RS infants. The first permanent molars and second premolars were more affected in the MDO group compared with the control group (Table 2). In 70% (thirteen molars or buds), positional/directional changes were present (Fig. 3). In another 70% of cases a shape anomaly was demonstrated (Fig. 2). Root malformations were seen in 40% of cases (Fig. 4). Despite these results, all first permanent molars erupted in all MDO-group patients. Few studies have addressed dental complications after MDO. Shetye et al. reported a prevalence of 0.67% in 141 patients, treated by MDO at a mean age of 6.3 years, over 16 years.[20] Tibesar et al., reviewing micrognathic infants who underwent distraction with an external device at an average age of 10.7 months, noted teeth damage in 16% of cases.[21] A comprehensive literature review covering all literature on MDO irrespective of age or diagnosis revealed tooth injury in ≤22.5% of cases.[9] Studies that focus on molar teeth injury reveal much higher incidences of tooth damage.[22, 23] Da Silva Freitas et al. reported molar bud/tooth alterations in ≈50% of patients after internal or external MDO (mean age, 8.1 years) after a mean follow-up of 3.7 years, but it was unclear if deciduous- and premolars were included in their analyses.[22] Kleine-Hakala et al. described the effect on molars after MDO with an external bicortical fixed distraction device undertaken at a mean age of 30 days (mean age at analyses: 7.6 years; mean follow-up: 3.6 years).[23] Permanent first, second and third permanent molars were affected in 76% of patients. If external MDO was undertaken in primary dentition, first and second molars were injured most often, whereas MDO in mixed dentition probably caused injury to second and third molars.[23] However, they did not analyze treatment effects on premolars, which hampers comparison with our study.[23] Hong et al. revealed the results of an internal non-resorbable device applied for treatment of RS infants (mean age, 2.3 months; 3–5-year follow-up).[24] Thirty percent of cases developed root malformations and positional chances of deciduous second molars, which is comparable with our findings when looking only at second deciduous molars.[24] However, in that study, the dental developmental stage was primary dentition: information on possible damage to permanent molars was lacking. [24] In preventing damage to molar buds, the position of the osteotomy and screws must be considered. In the present study, an oblique osteotomy was used (Fig. 7). The location is

just slightly proximal to the ramus, which carries a risk of passing directly through the molar buds. Hong et al. used an inverted L-shaped osteotomy, which might facilitate a position just cranial to the molar buds.[24] Whether the buds of permanent molars are safer using this osteotomy is unknown, as the position of them are difficult to assess at birth.[13] Moreover, the chance of damaging the (pre) molar buds after screw placement remains. In the study by Hong et al., all patients underwent CT with three-dimensional reconstructions preoperatively, which aids planning of the exact location of the osteotomy and might prevent damage to buds visible at radiography.[24] However, locating teeth buds in infant mandibles on CT is difficult and requires training/expertise.[25] Monocortical placement of screws is associated with less damage to molar buds compared with bicortically fixed pins/screws.[23, 24]

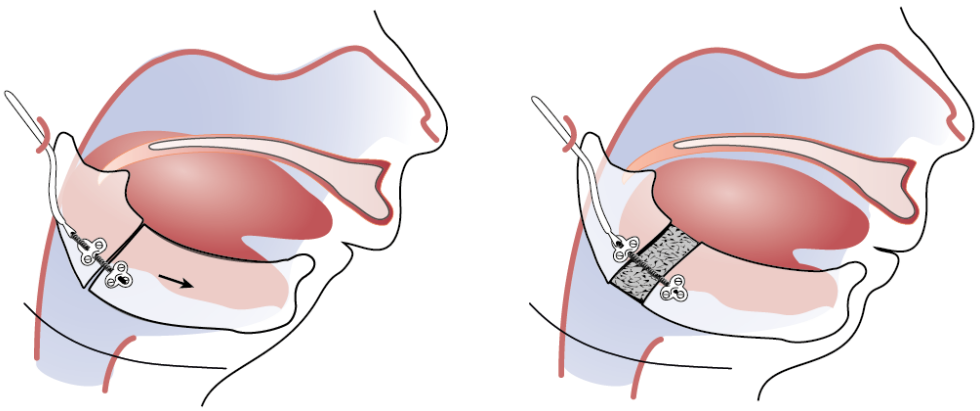

Figure 7 An oblique osteotomy is performed, planned just slightly proximal to the ramus.

Eight missing molars were seen in five patients (50%) of the MDO group compared with five missing molars in two cases (20%) of the control group (Table 2). Future teeth absence might not be due only to the surgical methods used, as permanent tooth agenesis is frequently present in RS infants.[26] Tooth agenesis was found in 20–50% of cases in our study, and usually affected the second premolar. Suri et al. found agenesis in 33% of 146 isolated RS subjects, which also affected the second premolar in most cases.[26] Non-syndromic infants with RS and hypodontia have a significantly smaller mandibular length compared with non-syndromic infants with RS without hypodontia.[26] Suri et al. demonstrated that mandibular growth did not improve during adolescence, suggesting a possible underlying genetic influence in non-syndromic infants with hypodontia.[26]

MDO advances the tongue, resulting in enlargement of the hypopharyngeal space to create a patent airway.[6, 8] Mandibular length and volume increase after MDO.[27, 28] Greatest mandibular growth rates occur at 0.4–1 year of age, and bone growth and remodeling is a complex process characterized by a diverse set of mechanisms and contributions from primary growth centers and functional matrix of surrounding soft tissue.[29, 13] RS infants might lack an intrinsic potential to grow out to values of

healthy counterparts.[30-34] No studies have described the influence of MDO on craniofacial features in RS infants after longer follow-up. We demonstrated that, after a mean follow-up of 6.8 years, RS infants had a significantly shorter mandibular length compared with RS infants who did not undergo MDO. This phenomenon was caused mainly by a smaller mandibular body (Go-Pg, Go-Gn, Go-Me), whereas the mandible ramus height (Ar-Go) was not different between the two groups (Table 4, Fig. 5). The significantly shorter mandibular length in the MDO group could be partly explained by the negative outcome of the distraction, because the intervention is at the moment of the highest growth velocity of the mandibular body.[29] Compromise of vascularization to condylar epiphyses, contractile forces caused by scarification of the periost due to surgery, or compression forces on the mandibular condyle by distraction, might impede mandibular outgrowth and remodeling.[13] However, another explanation might be a preoperative shorter length of the mandibular body in the MDO group compared with RS controls, due to the heterogeneity of RS itself, or presence of a syndrome.[35]

Significant differences in mandibular length were demonstrated between all RS infants and healthy controls (Table 5). SNA and SNB were significantly smaller, which might indicate the poor outgrowth potential of the mandible and maxilla in RS in general, and due to the cleft palate. This observation is in accordance with those of Suri et al., who revealed that isolated RS infants had a significant reduction in mandibular and maxillary lengths, but also mandibular ramus length, compared with normal age- and sex-matched controls.[32] When syndromic RS infants are included, such differences in SNA and mandibular length are also demonstrated.[35] Others also have demonstrated significant reduced length of the mandible in both isolated RS infants and iCPO patients, compared to healthy counterparts, with a more severe reduction in the RS group.[34, 36, 37]

A more, although non-significant, pronounced vertical growth pattern was seen in the MDO group (Fig. 5b). Also others have described a more vertical growth direction in isolated RS subjects who did not undergo MDO.[32, 37] Hence, this pattern might be partly a result of the disorder. It might also be the result of an inappropriate distraction vector in MDO, which potentially leads to malocclusion.[9] It is reported to occur in ≈0.8–28%[7, 11, 21, 38] of cases, but the ideal vector is probably not achieved in a much higher percentage of cases.[10] Distraction is dependent on accurate prediction of desired outcome, and the appropriate vector should be adjusted to it.[39] Preoperative modeling and vector planning with the aid of three-dimensional CT, curvilinear internal/multidirectional external distractors might assist this aim.[40] Another explanation for more severe vertical growth after MDO might be muscle activity on the mandible. These forces might pull the mandible in a more vertical position during distraction. Biodegradable plates/screws might not withstand these forces to the same extent as titanium plates do.[41] Finally, duration of consolidation varies among authors.[6] When the distraction wire that fixates the bone internally is removed after 4 weeks, callus formation might not be sufficient to withstand the ongoing pulling forces of the muscles.

An underlying syndrome can worsen the outgrowth potential of the mandible.[35] Rogers et al. demonstrated a significantly smaller mandibular body and ramus length in syndromic RS infants

compared with non-syndromic RS subjects.[35] This observation is in accordance with our data. In syndromic subgroups, Rogers et al. did not see significant differences at a mean age of 8.6 years, but measurements were closer to normal for Stickler syndrome and velocardiofacial syndrome, and furthest from normal in bilateral microsomia and Treacher Collins syndrome.[35] Most infants suffered an associated syndrome or chromosomal abnormality (Table 1). No significant differences were found in the MDO group between isolated and non-isolated infants but one child suffering auriculo-condylar syndrome needed a secondary distraction due OSAS recurrence. This finding emphasizes that some RS patients (especially in case of an underlying syndrome), lack a normal growth potential and might need a secondary procedure. We agree with Barlett et al., who state that a secondary procedure in a developing facial deformity should not be seen as a negative aspect but instead should be looked upon as optimization of further function and form.[42]

Different types of distractors are available but in our institution we favor a resorbable device because it is a single-stage procedure, elicits minor scar formation, and is well accepted by children and parents (Fig. 6ab).[6, 14, 43] Also, it has been revealed to be a cost-effective surgical option.[44, 45] Drawbacks are the maximum forces that can be applied on fragile plates, which makes it applicable only for those aged <2 years. It would be preferable if curvilinear distractors were available for resorbable devices so that the vector can be optimized.[40]

Our study had limitations. First was its retrospective nature. Second was the size and differences of patient groups. Third, we did not have preoperative radiographs for comparison of outcome. Finally, comparisons with healthy controls were limited to the cephalometric measurements employed in the reference study.[18]

CONCLUSIONS

This is the first study describing the long-term outcome of MDO with an RDS in the treatment of infants with RS, clearly addressing the effect on mandibular outgrowth and teeth, by comparing it to controls. It is an effective treatment option to relieve severe upper airway obstruction in infants with RS, but possible damage to the developing molars and the outgrowth potential and -direction of the mandible, with likely need for subsequent procedures, should not be underestimated. These potential drawbacks should be weighted when deciding on treatment options and counseling of parents. Optimal vector planning and prevention of damage to molar buds could improve results, but longer follow-up studies are required.

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7

Nasopharyngeal airway as conservative treatment option for Robin sequence

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Based on the comment on "The successful use of the nasopharyngeal airway (NPA) in Pierre Robin sequence: an 11 year experience" by Abel F, Bajaj Y, Wyatt M, and Wallis C. Arch Dis Child. 2012 Apr;97(4):331-4

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We want to congratulate Abel et al. on their recent publication, "The successful use of the nasopharyngeal airway in Pierre Robin sequence: an 11 year experience".[1]

Although preceded by earlier reports[2, 3], Heaf et al.[4] confirmed the benefits and demonstrated clinical improvement after usage of a nasoparyngeal airway (NPA) in a series of 12 infants with RS, since its use in 1972. Subsequently, others also demonstrated its beneficial application to feeding and airway problems and reducing the need for surgical intervention.[5-9] Still, possible drawbacks include blockage of the tube, dislodgment, irritation of the larynx by inadequate positioning, aspiration, chest infection, nostril stenosis, long hospital stay or prolonged treatment duration of the NPA, and subsequent parental burden of care.[6, 10, 11]

Abel and co-workers[1] are the first who report on long-term outcomes of a large cohort of infants with RS, treated primarily by NPA, measured by a sleep study. Median follow-up was 12 months (range 2-30 months). Although this is an interesting and well-conducted study, we do want to make some comments that might be of interest for the reader. First, the authors define Robin Sequence (RS) as a triad of micrognathia, glossoptosis, and a cleft palate; there is considerable confusion in the literature regarding the description of RS.[1] Abel et al. state that an obstructed airway "is often present," but do not use it as a required criterion to diagnose RS, despite how all 104 patients with RS suffered some degree of upper airway obstruction (UAO). Before placement of the NPA, patients were admitted for an overnight sleep study and were subsequently divided into three groups, depending on the severity of the UAO: mild UAO (a set of ≥ 3 clusters of desaturations with ≥3 dips in between 85-95%), moderate UAO (a set of ≥3 clusters of desaturations with ≥3 dips in between 80-85%) and severe UAO (a set of ≥ 3 clusters of desaturations with ≥3 at least 3 dips below 80%). Twenty-seven infants suffered mild and 77 suffered moderate/severe UAO. To be able to compare outcome modalities, we suggest using the original description during the initial diagnosis of RS, thus including breathing problems.[12, 13]

Second, we questioned the approach of the initiation of NPA treatment. No comment was made about an endoscopic airway evaluation before initiation of NPA. Fourteen patients ultimately required a tracheotomy, all of whom had undergone a trial with NPA which did not completely overcome their severe respiratory compromise; however, it is unclear whether these 14 patients might have suffered subglottic or tracheal (e.g., tracheomalacia) pathology before NPA treatment was started. After removal of the NPA, 16 patients (25%) still had mild UAO and thus suffered a set of at least three saturation dips between 85-90% during the sleep study. We want to express our concerns regarding the effect of these low saturations, as they could lead to increased energy expenditures by the child and might affect the developing brain, possibly leading to impaired neurocognitive and neurobehavioral development in the long-term.[14-19]

Third, Abel et al. demonstrated that 82 patients (79%) needed a nasogastric (NG) tube for a few weeks to months. During NPA treatment, there is a high risk of aspiration and persistent malnutrition;[20-22] in contrast, after mandibular distraction osteogenesis (MDO), an improvement in feeding and swallowing function is seen and the duration for NG tube placement is much lower.[23-29] Abel et al.

report that only two patients (1.9%) in their study had undergone MDO, which is still tracheotomy-dependent. However, these two patients already belonged to the subgroup of "undecannulated patients" (n=5), which makes a clear comparison to the "normal" NPA group impossible. Moreover, it remains unclear if this subgroup consisted of patients with an associated syndrome which might affect the airway problems. We suggest that in the syndromal cases the usage of MDO should always be reconsidered, as the outcome can be poor due to underlying malformations.

Mean duration until final removal of the NPA was eight months, and in 11.1%, even longer than 12 months. In these seven patients, the duration of NPA treatment was 14, 17, 18, 22, 23, and 60 months. Once the parents were deemed competent to manage the NPA, the infants were discharged home with replacement NPAs and suction apparatuses. Still, there rests a relatively long social burden on the parents and caregivers of the patient. In the case of MDO, the average time before removal of the hardware is usually 4-10 weeks, which limits the period that parents are confronted with the associated care and possible anxieties of an external, visible "device" and chance for dislodgement.

In conclusion, some infants can be successfully treated with an NPA and it has shown to be a feasible, relatively minor invasive treatment option, which should be incorporated in a treatment algorithm for infants with RS as a primary measure; however, we want to stress that each case should be individually analyzed and that MDO should be considered a possible alternative in the treatment regime, due to the relatively quick process, less cumbersome home care situation, and good results regarding respiratory and feeding problems.

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Cost analyses of tracheotomy and mandibular distraction osteogenesis

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ABSTRACT

Background

Many treatments have been described for infants with Robin sequence and severe respiratory distress, but there have not been many comparative studies of outcome and cost-effectiveness. The aim of this study was to compare the cost and complications of two common interventions – mandibular distraction osteogenesis and tracheostomy.

Methods

Nine patients with isolated Robin sequence (mandibular distraction osteogenesis, n = 5, and tracheostomy, n = 4) were included in the analyses. Predetermined costs and complications were obtained retrospectively from medical records and by questionnaires to the parents over a 12-month period.

Results

Overall direct costs (admission to hospital, diagnostics, surgery, and homecare) were 3 times higher for tracheostomy (€105.523 compared with €33.482, p = 0.02). Overall indirect costs (absence from work) were almost 5 times higher (€2.543 compared with €543, p = 0.02). There was a threefold increase in overall total cost/patient (both direct and indirect) for tracheostomy (€108.057 compared with 34.016, p = 0.02) and 4 times more complications were encountered.

Conclusions

This study shows that mandibular distraction osteogenesis in infants diagnosed with Robin sequence costs significantly less and results in fewer complications than tracheostomy, and this contributes to our current knowledge about the ideal approach for infants with Robin sequence and might provide a basis for institutional protocols in the future.

INTRODUCTION

Mandibular micrognathia leading to glossoptosis and obstruction of the airway are the findings originally described by Pierre Robin in 1923.[1] The sometimes severe obstruction of the upper airway can lead to obstructive apnoea and feeding problems.[2] Non-surgical interventions such as placing the child prone can be applied as a primary treatment and can be useful, particularly in mild cases.[3] However, surgical measures are required in up to 23% of infants with serious respiratory obstruction, which can be challenging.[3] For a long time tracheostomy was considered to be the gold standard. However, the incidence of complications was high and the mean age of decannulation in children with Robin sequence was 28 months, thereby exposing both child and parents to a medical and social burden.[4–7]

The principle of mandibular distraction osteogenesis in infants with Robin sequence is based on lengthening the mandible, so that the base of the tongue is advanced away from the airway, which corrects the supraglottal airway obstruction.[3] Numerous reports have been published that illustrate the feasibility of relieving the obstruction, which removes the need for tracheostomy or provides successful decannulation in many cases.[8]

The medical system is in need of treatments that not only provide a good functional outcome, but are also cost- effective. We know of 2 published studies that have compared the costs of tracheostomy and mandibular distraction osteogenesis in infants, yet no distinction was made between infants with isolated or syndromal Robin sequence, and only direct healthcare costs were included.[9,10] The purpose of the present study was to present a comparative cost analysis, including both direct healthcare and indirect (productivity losses) costs for tracheostomy and distraction osteogenesis in infants with isolated Robin sequence treated in a tertiary referral children's hospital in the Netherlands.

METHODS

We retrospectively surveyed the medical records from our hospital from 1 January 1998 to 1 July 2012, and included patients younger than 6 months who had isolated Robin sequence with a supraglottal obstruction that led to respiratory obstruction that could not be treated conservatively, and who were treated by either tracheostomy or mandibular distraction osteogenesis. Until 2007 tracheostomy was routine, but nowadays we prefer mandibular distraction as it causes fewer respiratory complications. Before the intervention all children had a genetic evaluation, monitoring of continuous pulse oximetry for 12 h or more, measurement of blood gases, and flexible fibreoptic airway examination when awake, evaluated by a multidisciplinary team.[11] They were followed up for 12 months, starting on the day the patient started treatment. Ethics committee approval was obtained.

We have listed variables that were of concern. These included direct costs as a result of hospital admission (ward, intensive care unit (ICU) and outpatient clinic, diagnostics (radiology, haematology, microbiology, and virology), surgery (surgical team and devices), and home care (hours of care from a specialised nurse). Other indirect costs related to the parents' absence from work were included. The variables were multiplied with standard reference prices obtained from the Dutch manual for costing research in health care,[12] tariffs from the National Health Authority of the Netherlands[13] or internal cost prices (Table 1). The components of each variable were retrieved by a thorough search of each patient's medical record (Table 2 A and 2B). The amount of homecare needed and the time the parents spent away from work were obtained retrospectively from a questionnaire (Table 3).

Table 1 Cost parameters

Parameter	Reference price (€) per unit
Direct costs	
Hospital	
Academic hospital ward	575.00/day
Intensive Care Unit (ICU)	2183.00/day
Outpatient clinic	72.00/visit
Diagnostic tests	
X-ray	50.00/image
Blood	2.15/test
Microbiology	31.31/test
Virology	26.80/test
Operation	
Surgeon	135.50/hour
Surgeon registrar	29.45/hour
Anaesthesiologist	135.50/hour
Anaesthesiologist registrar	29.45/hour
Instrument assistant	30.50/hour
Nurse	30.50/hour
Mandibular distraction (bilateral)	1237.26/operation
Tracheostoma	108.26/operation
Tracheostoma change*	41.58/change
Home care	35.00/hour
Indirect costs	
Work absenteeism	30.02/hour

** The mean of both tracheostomy tubes was calculated*

Table 2A Distribution of variables studied: patients treated by tracheostomy.

Variable	Case 1	Case 2	Case 3	Case 4	Mean (SD)
In hospital					
Ward (days)	63	69	100	66	75 (17)
Intensive care unit (days)	8	9	14	7	8 (5)
Outpatient visits	19	15	16	16	17 (2)
Diagnostic tests					
Radiology (No. of films)	7	5	2	3	4 (2)
Haematology (No. of variables investigated in each sample)	150	195	118	249	178 (57)
Microbiology (No. of tests)	2	5	30	3	10 (13)
Virology (No. of tests)	2	9	5	1	4 (4)
Surgery					
Duration (min)	71	28	30	37	42 (20)
Home care Hours*	92.5	1259	1488	1640	1120 (703)
Absence from work					
Days	10	18	14	15	14 (3)

**Over a period of 36 weeks.*

Table 2B Distribution of variables studied: patients treated by mandibular distraction osteogenesis.

Variable	Case 1	Case 2	Case 3	Case 4	Case 5	Mean (SD)
In hospital						
Ward (days)	15	11	44	17	6	19 (15)
Intensive care unit (days)	7	10	8	7	10	8 (2)
Outpatient visits	14	22	19	21	21	19 (3)
Diagnostic tests						
Radiology (No. of films)	12	18	12	9	17	14 (4)
Haematology (No. of variables investigated in each sample)	87	260	96	138	116	139 (70)
Microbiology (No. of tests)	0	3	1	0	1	1 (1)
Virology (No. of tests)	0	0	2	0	0	<1 (<1)
Surgery						
Duration (min)	86	86	108	118	147	109 (25)
Home care Hours*	0	0	0	12	0	2 (5)
Absence from work						
Days	4	5	0	3	3	3 (2)

**Over a period of 2.5 weeks.*

Table 3 Short questionnaire to the parents.

The following questions refer to the period of the dismissal of the child out of the hospital up to one year after surgery and need to be answered conscientiously and truthfully.
1. Did you or any other direct caretaker (e.g.(grand)parents, friends, neighbors) have to reduce or completely stop their working activities after the discharge of the child out of the hospital, in order to undertake certain care for the purposes of the care for the child?
2. If yes: how many days/hours during which period?
3. Were you (additionally) in need of (extra) homecare?
4. If yes: what kind of homecare and during which period?

When we calculated duration of absence from work, we assumed that there are 1540 working hours/year.[12,13] The total costs of surgery consisted of the general costs of the team and theatre and the specific costs related to the intervention (equipment). The tracheostomy tubes that we used were Tracoe® 350 neonatology (Tracoe medical GmbH, Frankfurt, Germany) and ShileyTM PED paediatric (Covi- dien Respiratory and Monitoring Solutions, Boulder, USA). A mean of 4 exchanges/year was used.14 As this was an outpatient procedure, only the predetermined price for a new tracheostomy tube was calculated. We used a LactoSorb resorbable internal distractor (Walter Lorenz, Inc., Jacksonville, FL) for mandibular distraction osteogenesis.[11] Complications during hospital admission and at home were recorded retrospectively. The component that could not be included in the analysis because of lack of data was the number of consultations. Finally the number of visits to the general practitioner, costs of travel to the hospital, ambulance transport, and psychological support were not considered, as they could be prone to recall bias.

Microsoft Excel (Microsoft Inc., Redmond, WA, USA) was used to organise the data, and the significance of differences was assessed with the help of the Mann–Whitney U test (IBM SPSS Statistics for Windows 20.0, Amonk, NY, USA, IBM Corp.). Probabilities of less than 0.05 were accepted as significant.

RESULTS

Sixteen patients required mandibular distraction because of severe respiratory distress caused by a supraglottal obstruction that did not respond to conservative measures. Thirteen met the selection criteria for the present study, but 6 were excluded because they also had additional syndromes and two because of incomplete data, which resulted in the inclusion of 5 patients (mean (range) age 39.0 (11–94) days). Eight patients had a tracheostomy for the same indications, of whom one was excluded because of insufficient data and 3 because of an additional syndrome, resulting in 4 cases (age 29.5 (5–45) days) being included.

Cumulative costs/patient using the predetermined refer- ence prices are shown in Table 4. Overall direct costs (for admission to hospital, diagnostics, surgery, and homecare) were 3 times higher for tracheostomy (€105.523 compared with €33.482, $p = 0.02$). Overall indirect costs (absence from work)

were almost five times higher (€2.543 compared with €543, p=0.02). There was a threefold increase in overall total costs/patient (both direct and indirect) if patients were treated by tracheostomy (€108.057 compared with €34.016, p = 0.02). Cumulative costs for homecare and absence from work accounted for the largest share in difference of the total cost (€41.725 for tracheostomy compared with €618 for distraction) (Fig. 1). Four times more complications occurred after tracheostomy than after mandibular distraction (Table 5).

Table 4 Mean (range) cumulative costs (€)

Variable	Tracheostomy	Mandibular distraction	Mean difference	*p* value
Direct costs				
Hospital				
Ward	42.838 (36.225–57.500)	10.695 (3450–25.300)	32.143	0.02
Intensive care unit	20.739 (15.281–30.562)	18.337 (15.281–21.830)	2402	0.73
Outpatient visits	1.188 (1080–1368)	1397 (1008–1584)	209	0.19
Diagnostics	1.022 (789–1427)	1022 (747–1553)	0	0.91
Operation				
General	270 (182–463)	710 (560–958)	440	0.02
Intervention-specific	275 (0–275)	1237 (0–1237)	962	0.02
Home care	39.191 (3220–57.400)	84 (0–420)	39.107	0.02
Indirect cost				
Absence from work	2534 (1788–3200)	534 (0–889)	2000	0.02
Total cost	108.057 (109.192–119.606)	34.016 (28.210–46.964)	74.041	0.02

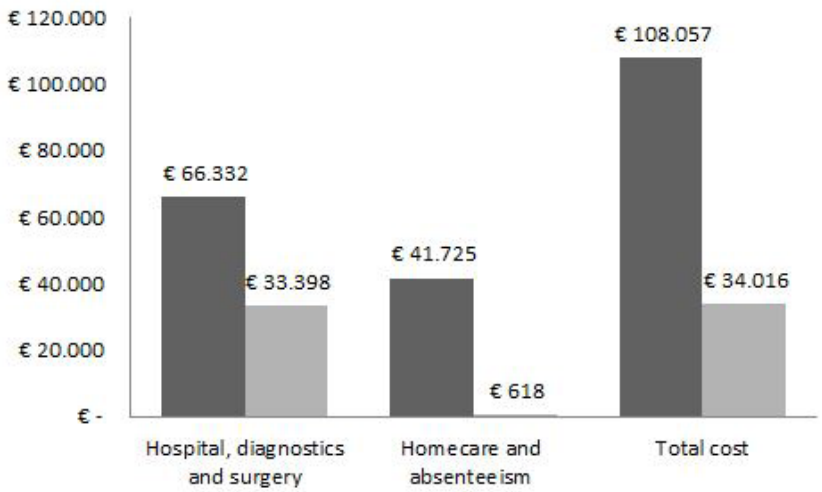

Figure 1 Estimated differences in cost. Blue = tracheostomy, and red = mandibular distraction osteogenesis

Table 5 Complications during admission to hospital.

Case No.	No. of complications	Complications
Tracheostomy		
1	4	Upper airway infection; respiratory syncitial (RS) virus infection; reduced oxygen
		saturation; and RS virus infection
2	6	Reduced oxygen saturation with bradycardia; upper airway infection; reduced oxygen
		saturation; lower airway infection; peritracheal eczema; and tracheal stenosis
3	4	Accidental decannulation × 2; bronchiolitis; and upper airway infection
4	3	Upper airway infection; airway infection (undefined); and upper airway infection
Mean (SD)	4 (1.3)	
Mandibular distraction		
1	0	–
2	1	Wound infection
3	4	Reduced oxygen saturation; impaired growth because of low nutritional intake; luxated
		right distractor; and RS virus infection
4	0	–
5	0	–
Mean (SD)	1 (1.5)	

DISCUSSION

We organised the current study to gain insight into the differences in cost between 2 conventional treatments for infants with Robin sequence in a European tertiary referral children's hospital. Indirect costs were also included, which to our knowledge have not been included in previous costings.

The duration of stay in hospital was 3 times longer for tracheostomy than for mandibular distraction, which induced a twofold increase in total hospital cost/patient (€64.765 com- pared with €30.429, p = 0.02). The stay on the ward was 4 times longer after a tracheostomy, as the duration of ICU stay was roughly comparable (Table 2A and 2B). The lengthy post- operative stay on the ward was probably because a child may be discharged only when the parents and caregivers are fully familiar with tracheostomy care. Kohan et al.[10] described a threefold increase in cost/patient after tracheostomy because the hospital stay was longer. Hong et al.[9] found similar results in their cost analysis and associated most of the high total cost for the tracheostomy group with prolonged postoperative hospital stay. Both also included infants with other craniofacial syndromes, who were excluded from our series. Such coexisting conditions might have led to the difference in cost being even greater.

The cost of diagnostics and visits to the outpatient clinic were comparable for the 2 interventions.

Overall cumulative costs of surgery were 3.6 times higher for mandibular distraction than for tracheostomy (€1.947compared with €545), as the duration of mandibular distraction was 2.6 times longer (109 compared with 42 min) and the equipment used was more expensive (Tables 2A, 2B and 3). The cumulative hospital costs (ward, ICU, outpatients, diagnostics, and surgery) were still twice as high for tracheostomy as for mandibular distraction (€66.632 compared with €33.398) (Fig. 1). Hong et al.[9] allocated 29% of the total cost in the mandibular distraction group to the cost of the intervention. They also charged for removal of the distractor, which was not necessary in our series as we used a resorbable one.

An important consequence of tracheostomy is the need for the infant to be constantly surrounded by people familiar with tracheostomy care, which leads to a substantial social burden on the (grand) parents or those caring for the child at home or in day-care centres. The prolonged duration of tracheostomy care is a serious parental concern.4 Besides the social aspects, it is also likely to lead to adjustments in employment. In both cost analyses that have been published to date, those related to absence from work and home care were not calculated, but were expected to be high.[9,10] In the current study, parents of patients with tracheostomies reported more days absent from work than parents of babies who had had mandibular distraction, which resulted in an almost fivefold increase in costs (€2.543 compared with €534, $p = 0.02$). It has been shown that after tracheostomy patients need a mean of 31 h of home care each week for 36 weeks, and this amounts to costs of €39.191/ patient. Only one child needed a total of 12 h of homecare during just over 2 weeks after mandibular distraction, which cost €84.

Overall, the total costs (direct and indirect) of tracheostomy were 3 times higher than those of mandibular distraction (€108.057 compared with €34.016, $p = 0.02$). Homecare and absence from work made up 46% of the total cost in the tracheostomy group, compared with only 2% after mandibular distraction. Hospital-related costs accounted for 53% of the total cost in the tracheostomy group, whereas for mandibular distraction these made up most of it (89%). Differences between the total cost of treatments were more obvious than have been described in other cost studies, where there were differences of 1.69 or 2.0.10 However, as mentioned before, only the direct hospital costs were calculated in these studies, while we have shown that the amount of home care needed makes up a large additional difference in cost between the groups.

Tracheostomy is known to have a large percentage (51–77%) of both early and late complications such as (air- way) infections, granulation, or fistulas, and difficulties with feeding and swallowing.[6,15] Mortality, usually as a result of accidental decannulation and obstruction to the cannula, can be up to 6%.[16] However, these numbers have declined with improved perioperative management, and now vary between 0.7–1.6%.[6,17] In our series, there were 4 times more complications after tracheostomy than after mandibular distraction (4 compared with 1). Airway infections were seen in all the patients in the tracheostomy group and in none after mandibular distraction, probably because of the less optimal barrier function of the airway (Table 5). Kohan et al.[10] found a 14.7-fold increase in costs, related only to pneumonia, when they compared tracheostomy with mandibular distraction.

Numerous reports have been published about the feasibility of mandibular distraction. The main advantage of resorbable distractors is that no second operation is necessary to remove the distraction wires.[18] A common complication is local infection of the skin, which we found in one patient. This might have been the result of degradation of the plate, and could easily be treated with local antibiotic ointment. The presence of an airway infection has not often been described after mandibular distraction, nor was it encountered in the current study.[19,20] A recent meta-analysis by Ow and Cheung[21] reported that mandibular distraction prevented the need for a tracheostomy in 91.3% and 78.4% successful decannulations after distraction.

Limitations of the current study include the size of the groups studied and the duration of follow up. However, as the data from our patients were homogeneous, we do not expect a bigger study group to add any additional value to the already large differences currently present. Patients with Robin sequence together with other syndromes were excluded to create a more homogeneous group and to prevent inclusion of possible extra costs from syndrome-related conditions, as this was not the aim of the current study. As our data were not normally distributed, we used a Mann–Whitney U test to assess the significance of differences.

Our follow-up period was one year, as the financial impact is expected to be the greatest during the first year, but we still do not know what the long term results of mandibular distraction are, and what costs they will incur (for example, dental implant after possible loss of a tooth bud). It might be possible that analysis over a longer period would show less distinct differences between the interventions because of these effects. However, patients with tracheostomy also incur potential long-term costs for home care, and for treatment of speech abnormalities and feeding difficulties.

As this was a retrospective study, recall bias has limited the availability of all costs during hospital admissions and the period at home. Finally, we should be aware that there may be other feasible options for treatment for infants with Robin sequence, which were disregarded in the current study as they are not used regularly at our centre.

Mandibular distraction seems an appropriate treatment for infants with Robin sequence both in terms of postoperative results and costs. Since 2007 this has been the first choice when a surgical approach was needed in our institution. Previously most such patients were treated by tracheostomy, and as indications were identical an optimal comparison could be made. However, sometimes mandibular distraction does not offer a permanent solution to the obstructed airway, for example when a (sub)glottal stenosis is present. We strongly recommend proper investigations using a multidisciplinary approach, and including nasoendoscopic airway investigations and observation, and saturation monitoring, before starting any intervention. We are currently working on a structured treatment algorithm, as it is clear that many practice patterns exist, which makes it difficult to judge the outcome.[22] In conclusion, this is to our knowledge the first comparative cost analysis of tracheostomy and mandibular distraction osteogenesis for the treatment of airways obstruction in infants with Robin sequence. It includes both direct and indirect costs during one year's follow-up. The profound differences contribute to our current knowledge and under- standing in the search to the ideal intervention and approach, and aid a more conscious treatment strategy.

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9

Feeding difficulties in children with Robin sequence

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ABSTRACT

Objectives

In addition to breathing problems, patients with Robin sequence (RS) often encounter feeding difficulties (FD). Data regarding the occurrence of FD and possible influencing factors are scarce. The study aim was to elucidate these factors to improve treatment strategies.

Methods

A retrospective comparative cohort study was conducted, consisting of 69 infants diagnosed with both RS and a cleft palate, and 64 isolated cleft palate only (iCPO) infants. Data regarding FD, growth and airway intervention were collected during the first 2 years of life. A systematic review of the literature was conducted to identify reported FD in RS patients.

Results

RS patients had more FD (91%) than iCPO patients (72%; p=0.004). In RS patients, nasogastric-tube feeding was necessary more frequently and for a longer period than in iCPO infants (both p<0.001). Growth was lower in RS than iCPO infants (p=0.008), and was not affected by the kind of airway management (conservative/surgical; p=0.178), cleft palate grade (p=0.308) or associated disorders (p=0.785). By contrast, surgical intervention subtype did significantly affect growth, with highest weights for infants treated with tracheostomy. Mean reported FD for RS in the literature is 80% (range: 47–100%), and 55% (range: 11–100%) of infants need nasogastric-tube feeding.

Conclusions

FD is present in a large proportion of infants with RS, which indicates the need for early recognition and proper treatment to ensure optimal growth. Growth during the first 2 years of life is significantly lower in RS patients than iCPO patients, which indicates the need for careful attention and long-term follow-up.

INTRODUCTION

Although preceded by several earlier reports,[1, 2] the French stomatologist Pierre Robin is credited as the first to draw attention to a symptom triad of breathing problems, glossoptosis and micrognathia, known as Robin sequence (RS). RS occurs in 1 in 8,000[3, 4] to 14,000,[5] depending on geography and ethnicity. Associated syndromes or anomalies coincide with RS in the majority of cases,[6] and a concomitant cleft palate (CP) may exist, but is not a required feature of RS.[7-13]

Besides the varying degrees of respiratory problems, infants with RS frequently have feeding difficulties (FD).[14] Swallowing difficulties directly related to the glossoptosis[14] and oroesophageal motor disorders caused by primary brainstem dysfunction[15] have been described as causes. FD is also a common feature in infants with a CP.[16, 17] These physiological abnormalities impede successful coordination of breathing, sucking and swallowing. In infants with RS and a concomitant CP, these features can negatively affect the feeding process and there is a considerable risk of failure to thrive.[18] Consequently, these patients are often in need of nasogastric (NG)-tube feeding.[19]

Although the majority of infants with RS and airway obstruction can be treated conservatively,[20-24] surgical measures such as tongue lip adhesion (TLA),[25, 26] tracheotomy[27, 28] or mandibular distraction osteogenesis (MDO)[29-31] may be necessary. While the effect of these interventions on the obstructed airway has been frequently reported, information regarding the influence on FD is limited.[14, 32]

To the best of our knowledge, this study is the first to identify factors that influence feeding and growth in RS and describe weight gain in the first 2 years of life. By obtaining a better understanding of all the facets of this condition, the treatment of these infants can be further optimized.

PATIENTS AND METHODS

Retrospective Cohort Study

Baseline Characteristics

All infants diagnosed with RS (defined as the presence of micrognathia, glossoptosis and signs of airway obstruction) and a concomitant CP treated at the Wilhelmina Children's Hospital Utrecht, the Netherlands between 1996 and 2012 were included in the study group. All infants diagnosed with an isolated CP only (iCPO), without associated anomalies, were included in the control group. A retrospective analysis of the medical records during the first 2 years of life was conducted. Ethics committee approval was obtained to conduct this study (reference number: WAG/th/14/020120). The following variables were extracted from the medical files: sex, gestational age (GA), birth weight, grade of CP (grade 1–4)[33] and airway and nutritional treatment. In the study group, a subdivision was made between non-isolated RS infants (i.e., diagnosis of an additional syndrome, associated anomalies or chromosomal defects) and isolated RS infants. Airway intervention was either conservative (i.e., prone/side positioning and possible use of supplemental oxygen, nasopharyngeal airway, oropharyngeal airway (mayotube) or continuous positive airway pressure) or surgical. The

surgical intervention group was further divided into five subtypes: MDO, TLA, tracheotomy (Tr), TLA+Tr, and MDO+Tr.

Feeding and Growth

FD were defined as (parentally) reported feeding problems, such as choking, regurgitation, gagging, distress, long-lasting feedings (≥30 minutes), impaired intake and/or nasal regurgitation.[34] FD can lead to insufficient weight gain, failure to thrive, need for NG-tube feeding, and can potentiate airway or respiratory compromise.[12] Medical records and growth charts were thoroughly analyzed. In addition, parents received a phone call requesting participation in a short questionnaire about FD.

The following variables were collected: presence of FD, need and duration of NG-tube feeding, and weight at birth and at 1, 3, 6, 9, 11, 14, 17 and 24 months of age (if available). Growth was measured as a change between the consecutive measurements at these nine time points. In addition, normal weight standard deviation scores of healthy controls were collected.[35] In the surgical intervention subtypes, besides total NG-tube duration, the postoperative (i.e., after the airway intervention) NG-tube duration was also collected.

Statistical Analysis

Data were analyzed using SPSS 20.0 (IBM SPSS, NY, USA). For interactions between nominal variables, chi-squared tests were used. To compare interactions between nominal and interval variables, t-tests and one-way ANOVA were computed. For two interval variables, two-way Pearson correlations were calculated. To compare growth, linear mixed model analysis was performed to model the repeated measurements data. In non-normally distributed data, non-parametric tests were used: Mann-Whitney U and Kruskal-Wallis H.

Systematic Literature Review

A systematic review of the literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines to assess current data on the combination of RS and FD.[36] Electronic databases were searched using specific keywords (Table 1) for articles published between July 1967 and August 2014, according to the search and inclusion processes as illustrated in Figure 1. All relevant Level I to Level IV[37] articles were included for further analysis (Table 2).

Table 1 Search Strategy of the Systematic Literature Reviews in the Databases Used

Database	Search query
PubMed	((("Pierre Robin Syndrome"[Mesh]) OR (pierre robin syndrome[tiab] OR pierre robin sequence[tiab] OR PRS[tiab] OR pierre robin[tiab] OR robin sequence*[tiab]))) AND ((("Feeding Behavior"[Mesh]) OR "Eating Disorders"[Mesh]) OR (feeding behavior*[tiab] OR feeding behaviour*[tiab] OR feed*[tiab] OR nutrition*[tiab] OR feeding difficult*[tiab] OR eating difficult*[tiab] OR feeding problem*[tiab] OR eating problem*[tiab] OR eating disorder*[tiab]))
Embase	((('pierre robin syndrome':ab,ti OR 'pierre robin sequence':ab,ti OR 'prs':ab,ti OR 'pierre robin syndromes':ab,ti OR 'pierre robin sequences':ab,ti) OR 'pierre robin syndrome'/exp) AND (('feeding behaviour':ab,ti OR 'feeding behaviours':ab,ti OR 'feeding behavior':ab,ti OR 'feed':ab,ti OR 'feeding':ab,ti OR 'nutrition':ab,ti OR 'nutritions':ab,ti OR 'feeding difficulty':ab,ti OR 'feeding difficulties':ab,ti OR 'feeding problem':ab,ti OR 'feeding problems':ab,ti OR'eating problem':ab,ti OR'eating problems':ab,ti OR'eating difficulty':ab,ti OR'eating difficulties':ab,ti OR'eating disorder':ab,ti OR'eating disorders':ab,ti) OR'feeding behavior'/exp OR'child nutrition'/exp OR'nutritional disorder'/exp OR'feeding disorder'/exp)) AND [embase]/lim NOT [medline]/lim
Cochrane library	Feeding behaviour* OR feeding behavior* OR feed* OR nutrition* OR feeding difficult* OR eating difficult* OR feeding problem* OR eating problem* OR eating disorder*:ti OR feeding behavior* OR feeding behavior* OR feed* OR nutrition* OR feeding difficult* OR eating difficult* OR feeding problem* OR eating problem* OR eating disorder*:ab AND pierre robin syndrome OR pierre robin sequence OR PRS OR pierre robin OR robin sequence*:ti OR pierre robin syndrome OR pierre robin sequence OR PRS OR pierre robin OR robin sequence*:ab
CINAHL	(TI pierre robin syndrome OR pierre robin sequence OR PRS OR pierre robin OR robin sequence* OR AB pierre robin syndrome OR pierre robin sequence OR PRS OR pierre robin OR robin sequence*) AND (S1 AND S2) TI (pierre robin syndrome OR pierre robin sequence OR PRS OR pierre robin OR robin sequence*) OR AB (pierre robin syndrome OR pierre robin sequence OR PRS OR pierre robin OR robin sequence*) TI (Feeding behaviour* OR feeding behavior* OR feed* OR nutrition* OR feeding difficult* OR eating difficult* OR feeding problem* OR eating problem* OR eating disorder) OR AB (Feeding behaviour* OR feeding behavior* OR feed* OR nutrition* OR feeding difficult* OR eating difficult* OR feeding problem* OR eating problem* OR eating disorder)
Google Scholar	pierre robin sequence OR pierre robin syndrome OR PRS AND feeding difficulties OR feeding problems OR nutrition

CINAHL, Cumulative Index to Nursing and Allied Health Literature.

Table 2 Comprehensive Results of the Systematic Literature Review

Article	Population	Reported FD	Treatment n (%)			Duration	Growth/weight gain	Intervention	Effect on FD
			NG-tube	Gastrostomy	Other				
Abadie et al. 2002[39]	- N: 66 - GI, RG, CP -iRS	98%	34 (52%)	-	-	3 months	Normal in 97%	Tr	26% (n=5) bottle feeding after Tr
Anderson et al. 2007[40]	- N: 12 - GI, MG, CP, ORD -iRS, sRS	100%	12 (100%)	-	-	nm	Mean of 28 g/day	NPA	nm
Baujat et al. 2001[15]	- N: 35 - GI, RG, CP - iRS, sRS	100%	30 (86%)	-	-	8.6 months (+/- 1.7 months)	nm	nm	nm
Bütow et al. 2009	- N: 143 - GI, MG/RG, CP - iRS, sRS	52%	27 (19%)	2 (6%)	Suction and drinking plate (n=134, 94%)	nm	nm	Suction and drinking plate	26% (n=35) NG-tube feeding or gastrostomy needed
Cruz et al. 1999[41]	- N: 43 - GI, MG, CP - iRS, sRS	nm	5 (11%)	12 (26%)	-	NG-tube ≥3 months	nm	Tr/TLA	nm
Daniel et al. 2013[42]	- N: 39 - GI, MG, ORD - iRS, sRS	82%	32 (82%)	-	-	nm	3230 +/- 590 g (birth) 8890 +/- 1290 g (12 months)	MDO, NPA, CPAP	nm
Evans et al. 2006[43]	- N: 115 - GI, RG/MG, CP, ORD - iRS, sRS	95%	27 (23%)	49 (43%)	Nipple (n=40, 35%)	nm	nm	NPA, Tr, TLA	nm
Glynn et al. 2011[27]	- N: 69 - GI, MG, CP - iRS, sRS	70%	48 (70%)	2 (3%)	-	3 months (3 weeks–6 months)	nm	NPA, Tr, TLA	nm
Gozu et al. 2010[44]	- N: 20 - GI, MG, CP - iRS, sRS	60%	12 (60%)	-	-	nm	nm	MDO	nm
Hamdi et al. 2004[45]	- N: 30 - CP, ORD, FD - iRS, sRS	100%	30 (100%)	-	-	57 days (1–120 days)	nm	TLA, Tr, removable palatal appliance	nm
Li et al. 2002[46]	- N: 82 - GI, MG, CP - iRS, sRS	nm	46 (42%)	-	Obturator plate/ CP bottles (n=36, 44%)	nm	nm	NPA,TLA, Tr	nm

Lidsky et al. 2008[47]	- N: 82 - GI, MG, CP - iRS, sRS	nm	-	17 (25%)	-	nm	nm	Tr, MDO	Reduction of need for feeding intervention in iRS
Maas et al. 2014[54]	- N: 151 - MG/RG and ORD/ GI/FD/snoring/ hypoxaemia/failure to thrive/syndrome or CP - iRS, sRS	89%	76 (55%); data only provided at time of discharge, after a mean of 19 (11–38) days	-	Feeding plate (n=56, 37%)	nm	Decrease of 0.59 (1.08–0.11) in SD score for weight, during admission	Orthodontic plate therapy, CPAP, Tr, TLA, mandibular traction, functional therapy (e.g. Castillo Morales)	Infants with pre-epiglottic baton plate demonstrated better weight gain during admission
Meyer et al. 2008[48]	- N: 74 - GI, MG, CP - iRS, sRS	50%	19 (26%)	18 (24%)	-	nm	nm	Tr, MDO, NPA	nm
Smith et al. 2006[49]	- N: 60 - GI, MG/RG, CP and/ or ORD - iRS, sRS	62%	17 (28%)	20 (33%)	-	26% 0–3 months, 31% 4–18 months, 43% >18 months	Successful oral diet in 89% of patients after 3 years FU	Tr or MDO	nm
Stubenitsky et al. 2010[50]	- N: 44 - GI, MG/RG, CP, ORD - iRS	100%	30 (68%)	1 (2%)	Reflux therapy (n=27, 61%)	nm	Mean weight gain 722 g in 4 weeks	NPA	nm
van den Elzen et al. 2001[51]	- N: 74 - MG, CP and/or GI - iRS, sRS	68%	30 (41%)	2 (3%)	Central venous line (n=1, 1%)	nm	Significant number of infants (24%, p=0.002) with body weight <P10 at age 6–24 months compared with healthy controls	Tr	nm
van Lieshout et al. 2013[52]	- N: 59 - MG/RG and ORD - iRS, sRS	47%	25 (34%)	3 (4%)	-	nm	nm	Tr, MDO	nm
Vatlach et al. 2014[3]	- N: 82 - MG/RG with at least: ORD, GI, FD or CP - iRS, sRS	83%	40 (49%)	-	Haberman feeder (n=16, 20%); regular nipple (n=21, 26%)	nm	SDS of weight decreased from −0,72 at admission to −1,46 at discharge (p <0.05)	Tr, MDO, CPAP, NPA, orthodontic plate therapy, TLA, functional therapy (e.g. Castillo Morales)	nm
Wagener et al. 2003[53]	- N: 22 - MG, GI, ORD, CP - iRS, sRS	100%	22 (100%)	-	-	4 months (1 week–11 months)	56% ↑ weight; 44% ↓ weight	NPA	nm

FD, feeding difficulties; NG-tube, nasogastric tube; MG/RG, micrognathia/retrognathia; GI, glossoptosis; ORD, obstructive respiratory distress; CP, cleft palate; iRS, isolated Robin sequence; sRS, syndromic Robin sequence; Tr, tracheotomy; TLA, tongue lip adhesion; MDO, mandibular distraction osteogenesis; NPA, nasopharyngeal airway; CPAP, continuous positive airway pressure; nm: not mentioned.

R1 R2 R3 R4 R5 R6 R7 R8 R9 R10 R11 R12 R13 R14 R15 R16 R17 R18 R19 R20 R21 R22 R23 R24 R25 R26 R27 R28 R29 R30 R31 R32 R33 R34 R35 R36 R37 R38 R39

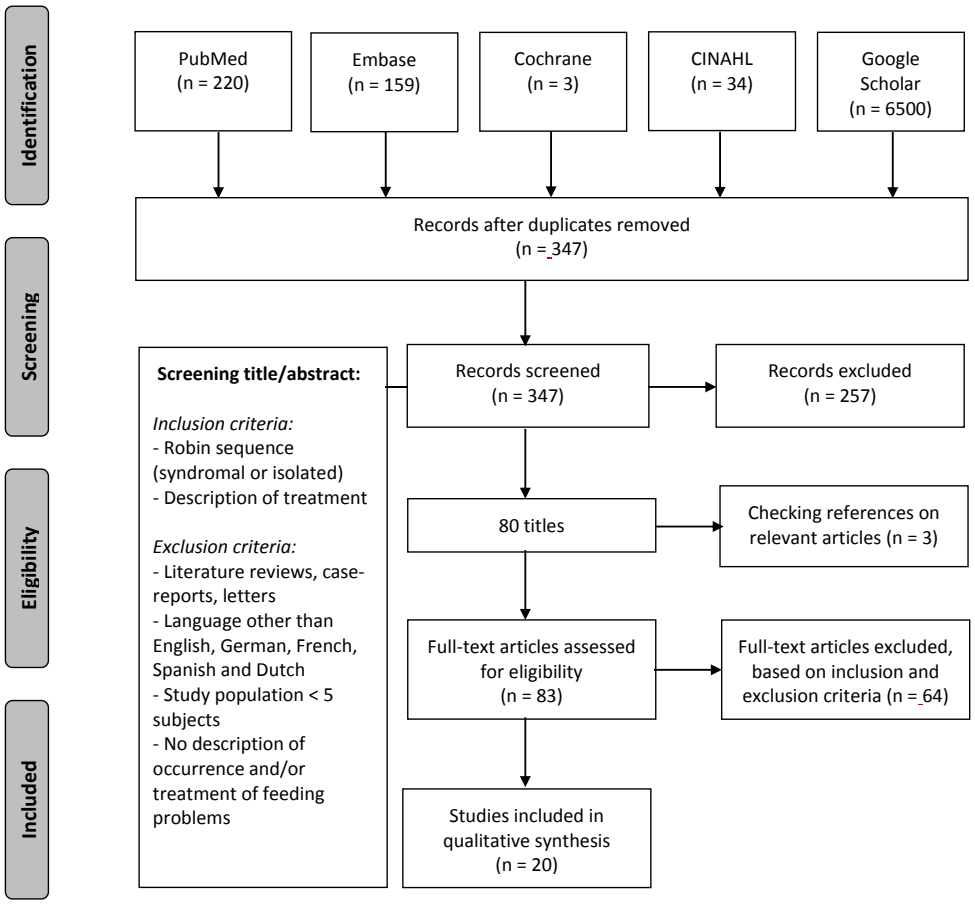

Figure 1 PRISMA Flow Diagram of the Literature Search

RESULTS

Baseline Characteristics

Sixty-nine RS patients (study group) and 64 consecutive iCPO patients (control group) were included. The study group included significantly more patients with a grade 3/4 CP than the control group (p<0.001). The majority of the study group (54%; n=37) was made up of non-isolated RS patients. Of these, more than half had an associated syndrome (51%, n=19), Stickler syndrome (n=9) being the most common (Table 3).

Table 3 Baseline Characteristics of the Patients in the Study and Control Groups Treated in the Wilhelmina Children's Hospital between 1996 and 2012

Variable		Study group (RS) n (%)	Control group (iCPO) n (%)	*p*-value*
Total number of patients		69	64	
Sex	Male	32 (46%)	23 (36%)	0.22
	Female	37 (54%)	41 (64%)	
Gestational age	<37 weeks	8 (12%)	7 (11%)	0.91
	≥37 weeks	61 (88%)	57 (89%)	
Birth weight (g)		Mean: 3217 SD: 669	Mean: 3302 SD: 556	0.44
Grade of CP¶	1: Submucous cleft or bifid uvula	3 (4%)	9 (14%)	<0.001
	2: Soft palate only	10 (15%)	27 (42%)	
	3: Soft palate and segment of hard palate	38 (56%)	18 (28%)	
	4: Total palate up to incisive foramen	17 (25%)	10 (16%)	
Associated disorders	Isolated RS	32 (46%)		0.06
	Non-isolated RS	37 (54%)		
	Stickler syndrome	9		
	Treacher Collins syndrome	2		
	Spondyloepiphyseal dysplasia	1		
	4q deletion syndrome	1		
	Van der Woude syndrome	1		
	Osteopathia striata with cranial sclerosis	1		
	Goldberg–Shprintzen syndrome	1		
	Yunis–Varon syndrome	1		
	Auriculo–Condylar syndrome	1		
	Hemifacial microsomia	1		
	Other	18		

RS, Robin sequence; iCPO, isolated cleft palate only; SD, standard deviation; CP, cleft palate.
**p-value <0.05 was considered statistically significant*
¶Modified from Jensen et al. cleft palate classification (1988),[34] according to the division made in the Dutch Cleft Registry database

FD and NG-tube Feeding

RS patients expressed FD (91%; n=63) more than iCPO patients (72%; n=38, p=0.004). In RS and iCPO patients with FD, a highly significant association was found in CP grade between the two groups (p<0.001); while a grade 3 and 4 CP was most common in RS patients with FD (grade 3: 60%, n=37; grade 4: 23%, n=14), a grade 2 CP was most common in iCPO patients with FD (50%; n=19; Table 4). In a logistic regression analysis controlled for CP grade, presence of FD was still significantly associated with the RS patient group (p=0.005).

Table 4 Association of Feeding Difficulties and NG-tube Feeding between the Study and the Control groups

Variable		Study group (RS)	Control group (iCPO)	*p*-value*
Total number of patients		69	64	
With feeding difficulties		63 (91%)	38 (72%)	0.004
Sex	Male	27 (43%)	15 (40%)	0.74
	Female	36 (57%)	23 (61%)	
Gestational age	<37 weeks	7 (11%)	5 (13%)	0.76
	≥37 weeks	56 (89%)	33 (87%)	
Birth weight (g)		Mean: 3237 SD: 644	Mean: 3289 SD: 586	0.68
Grade of CP	1: Submucous cleft or bifid uvula	2 (3%)	3 (8%)	<0.001
	2: Soft palate only	9 (15%)	19 (50%)	
	3: Soft palate and segment of hard palate	37 (60%)	10 (26%)	
	4: Total palate up to incisive foramen	14 (23%)	6 (16%)	
Associated disorders	Non-isolated RS[£]	36 (57%)	NA	NA
	Isolated RS	27 (43%)		
With NG-tube feeding		55 (80%)	12 (19%)	<0.001
NG-tube feeding duration (days)		Median: 59.00 Mean rank: 33.13	Median: 9.56 Mean rank: 9.72	<0.001
Sex	Male	24 (44%)	7 (58%)	0.36
	Female	31 (56%)	5 (42%)	
Gestational age	<37 weeks	7 (13%)	4 (33%)	0.08
	≥37 weeks	48 (87%)	8 (67%)	
Birth weight (g)		Mean: 3217 SD: 661	Mean: 3039 SD: 733	0.41
Grade of CP[¶]	1: Submucous cleft or bifid uvula	1 (2%)	0 (0%)	0.23
	2: Soft palate only	9 (17%)	5 (42%)	
	3: Soft palate and segment of hard palate	32 (59%)	4 (33%)	
	4: Total palate up to incisive foramen	12 (22%)	3 (25%)	
Associated disorders	Non-isolated RS[£]	32 (58%)	NA	NA
	Isolated RS	16 (42%)		

Due to missing values, the results for certain variables presented in this table do not correspond with the total participants per investigated variable

RS: Robin sequence; iCPO, isolated cleft palate only; SD, standard deviation; NG-tube, nasogastric tube, NA, not applicable

**p-value <0.05 was considered statistically significant*

[¶]Modified from Jensen et al. cleft palate classification (1988),[34] according to the division made in the Dutch Cleft Registry database

[£]Presence of a syndrome or other associated anomalies or chromosomal defects

NG-tube feeding was more often necessary in RS patients (80%; n=55) than iCPO patients (19%; n=12, $p<0.001$). Furthermore, NG-tube feeding lasted longer in RS patients (median 59.0 days in study group vs. median 9.6 days in control group, $p<0.001$). There was no significant association between the grade of CP (1–4) and the incidence of FD ($p=0.23$; Table 4). NG-tube duration of the isolated (125 days; SD 203) and non-isolated (125 days; SD 171) RS patients did not differ significantly ($p=0.996$).

Growth

Birth weights of the two groups were comparable (iCPO group 3302 g vs. RS group 3217 g, $p=0.41$). However, the iCPO group showed a significantly higher overall growth over the time points 1–9 (birth to 24 months of age) than the RS group ($p=0.008$). This increased growth in the iCPO group was also visible when separately analyzing time points 1–4 (birth to 6 months of age) and 5–9 (9–24 months of age; Table 5, Fig 2). When additionally controlling for grade of CP over time points 1–9, this difference remained significant ($p=0.030$).

Taken into consideration all nine time points, in the following analysis both sex and group (iCPO vs. RS) were controlled for. Neither presence of FD nor the need for NG-tube feeding revealed significant effects on growth ($p=0.893$ and $p=0.467$, respectively). Furthermore, the grade of CP (1–4) did not significantly affect growth ($p=0.308$; Table 5). Since a clinical interaction between the CP grade and group type could exist, this was also separately tested, showing that the interaction between the grade of CP (1–4) and group did not significantly affect growth ($p=0.112$).

Within the RS group, neither the presence of associated disorders (isolated/non-isolated) nor intervention type (surgical/conservative) had a significant effect on growth ($p=0.517$ and $p=0.052$, respectively; Table 5).

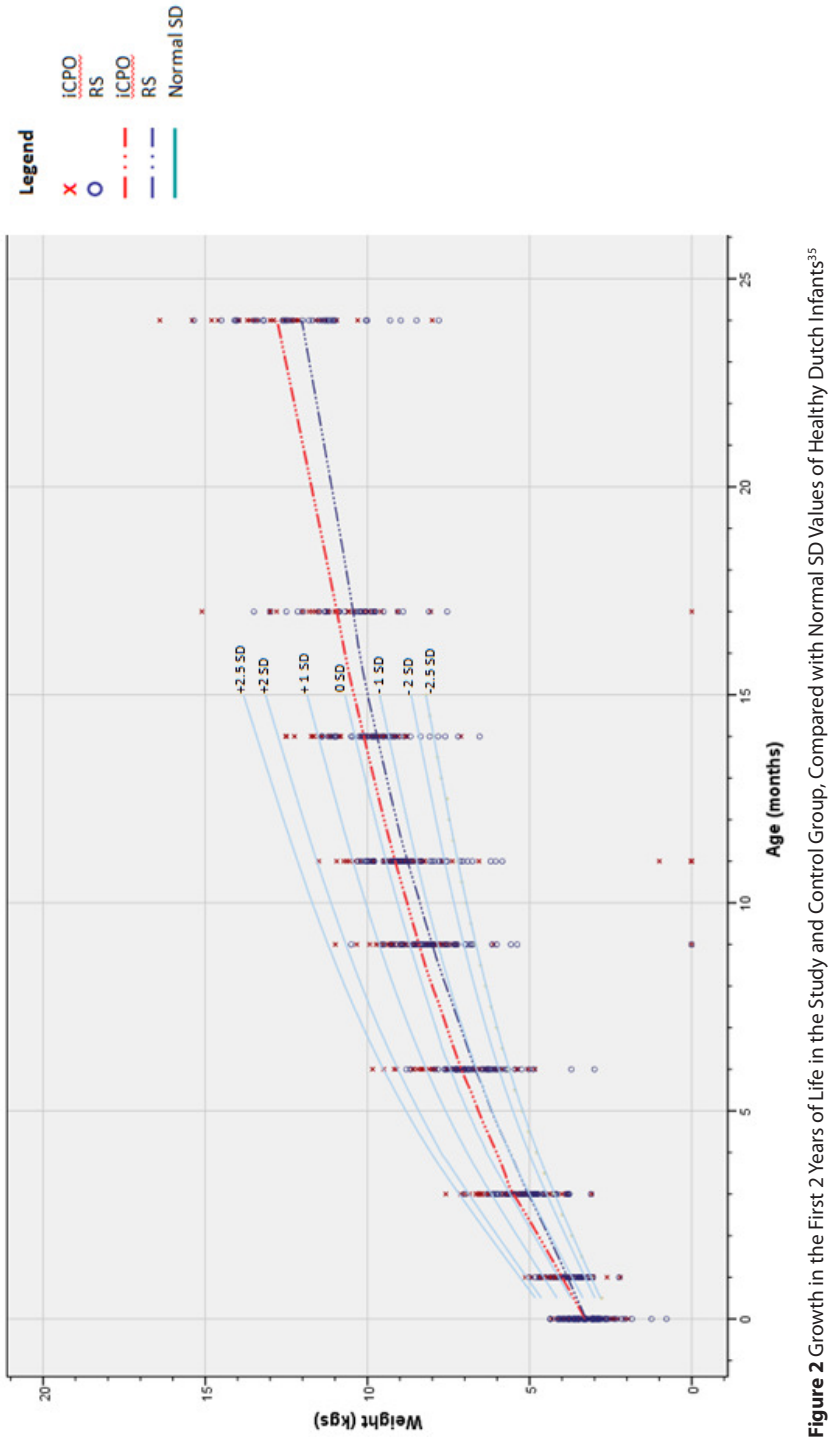

Figure 2 Growth in the First 2 Years of Life in the Study and Control Group, Compared with Normal SD Values of Healthy Dutch Infants[35]

Table 5 Variable Effects on Growth Measured by Weight (in grams) over the Nine Measured Time Point**s**

Variable effects on growth¶		EMM (g)	SE	95% CI (upper bound–lower bound)	*p*-value*
Time points 1–9 (birth to 24 months of age)	iCPO	5620	96	5263–5678	0.008
	RS	5261	95	5240–5581	
Time points 1–4 (birth to 6 months of age)	iCPO	3805	65	3676–3934	0.044
	RS	3619	65	3471–3746	
Time points 5–9 (9 to 24 months of age	iCPO	9833	143	9551–10114	0.026
	RS	9390	138	9119–9661	
Time points 1–9¥ (birth to 24 months of age)	iCPO	5588	106	5380–5796	0.030
	RS	5268	112	5047–5490	5268
Feeding difficulties**,µ	Yes	6902	87	6147–6488	0.467
	No	6767	192	6094–6849	
NG-tube feeding**,µ	Yes	6584	189	–396–346	0.893
	No	6559	189	–346–396	
Grade of CP**,µ	1: Submucous cleft or bifid uvula	5468	237	5019–5953	0.308
	2: Soft palate only	5540	130	5283–5797	
	3: Soft palate and segment of hard palate	5489	107	5278–5699	
	4: Total palate up to incisive foramen	5198	146	4911–5486	
Associated disorders§,µ	Isolated RS	6479	151	6181–6777	0.517
	Non-isolated RS£	6621	154	6317–6825	
Intervention type§,µ	Surgical	6902	203	6504–7301	0.052
	Conservative	6484	179	6132–6836	
Surgical intervention subtype§,µ	MDO	7965	188	7587–8344	0.007
	TLA	7720	336	7049–8391	
	Tr	8765	223	8317–9213	
	TLA+Tr	6423	752	4920–7927	
	MDO+ Tr	8383	412	7555–9210	

EMM: estimated marginal means; SE: standard error; CI: confidence interval; MDO: mandibular distraction osteogenesis; TLA: tongue lip adhesion; Tr: tracheotomy; NG-tube: nasogastric tube; RS: Robin sequence; iCPO, isolated cleft palate only; CP, cleft palate
Time points: weight at birth, 1, 3, 6, 9, 11, 14, 17 and 24 months of age
¶All measurements were controlled for gender
**p-value <0.05 was considered statistically significant*
¥ Also controlled for grade of CP
***Also controlled for group*
§Only analyzed within the RS group
£Presence of a syndrome or other associated anomalies or chromosomal defects
µFor time points 1–9 (birth to 24 months of age)

Interventions in the Study Group

While 40 (60%) RS patients could be treated with conservative measures, in 27 infants (40%) a surgical intervention was performed because of severe respiratory distress. MDO was pursued at a mean age of 36 days (SD 32) in 14 (52%) of these cases, TLA (mean age: 77 days, SD 49) in 3 cases (11%) and a tracheotomy was performed (mean age: 45, SD 27) in 7 cases (26%). Finally, in one case after TLA, a tracheotomy was performed due to an unstable airway. In two other cases, MDO was performed after tracheotomy (Table 6). Background information on the decisional process can be found in earlier work.[38]

FD showed a significant association with intervention (surgical/conservative; p=0.04); while all surgically treated patients had FD (100%), in the conservatively treated group 85% expressed FD. Surgical or conservative intervention did not show a significant association with sex (p=0.96), GA (p=0.50) birth weight (p=0.10) grade of CP (p=0.45) or associated disorders (p=0.35). Since 100% of the surgically treated patients showed FD, further investigation of presence of FD within the type of surgical treatment was not possible (Table 6).

Surgically treated RS patients were significantly more often in need of NG-tube feeding than conservatively treated patients (93% vs. 63%, p=0.03). NG-tube feeding lasted significantly longer in surgically-treated RS patients (median: 72.0 days; mean rank 29.4; p=0.011) compared to conservatively-treated patients (median: 21.0 days; mean rank 19.2). Surgical intervention subtype had a significant effect on postoperative duration of NG-tube feeding (p=0.003), with a median of 36.5 days for MDO, 183.0 days for TLA, 461.5 days for tracheotomy and 38.0 days for MDO+Tr. A post-hoc test revealed significant differences between all these group interactions (p<0.05), except for TLA vs. Tr (p=0.302), TLA vs. MDO+Tr (p=0.083) and MDO vs. MDO+Tr (p=0.874; Table 6).

The subtype of surgical intervention (MDO, TLA, Tr, TLA+Tr or MDO+Tr) also demonstrated a significant effect on growth from birth to 24 months of age (p=0.007); a post-hoc test showed significant differences between MDO vs. Tr (p=0.008), TLA vs. Tr (p=0.012), Tr vs. TLA+Tr (p=0.004), TLA+Tr vs. MDO (p=0.05) and TLA+Tr vs. MDO+Tr (p=0.029; Table 5).

Table 6 Associations for the Different Interventions in the Study Group

		Conservative	Surgical	*p*-value*	Surgical intervention subtype					
					MDO	TLA	Tr	TLA+Tr	MDO+Tr	*p*-value*
Total number of patients		40 (60%)	27 (40%)		14 (52%)	3 (11%)	7 (26%)	1 (4%)	2 (7%)	
Feeding difficulties	Yes	34 (85%)	27 (100%)	0.04	14 (100%)	3 (100%)	7 (100.0%)	1 (100.0%)	2 (100%)	n.a.
NG-tube feeding	Yes	28 (63%)	25 (93%)	0.03	14 (100%)	3 (100%)	6 (86%)	0 (0%)	2 (100%)	0.006
NG-tube duration (days)[&]		Median: 21.0	Mean: 72.0	0.011	Median: 36.5	Median: 183.0	Median: 461.5	NC	Median: 38.0	0.003
		Mean rank:19.2	Mean rank: 29.4		Mean rank: 8.9	Mean rank:18.3	Mean rank: 21.2	NC	Mean rank: 9.0	
Sex	Male	18 (45%)	12 (44%)	0.96	6 (43%)	1 (33%)	3 (43%)	0 (0%)	2 (100%)	0.48
	Female	22 (55%)	15 (56%)		8 (59%)	2 (67%)	4 (57%)	1 (100%)	0 (0%)	
Gestational age	<37 weeks	5 (13%)	2 (7%)	0.50	0 (0%)	0 (0%)	1 (14%)	1 (100%)	0 (0%)	0.006
	≥37 weeks	35 (88%)	25 (93%)		14 (100%)	3 (100%)	6 (86%)	0 (0%)	2 (100%)	
Birth weight (g)		Mean: 3139	Mean: 3409	0.10	Median: 3205	Median: 3785	Median: 3920	Median: 2680	Median: 3287	0.19
		SD: 713	SD: 521		Mean rank: 12.11	Mean rank: 16.33	Mean rank: 19.07	Mean rank: 2.5	Mean rank: 11.75	
Grade of CP**	1: Submucous cleft or bifid uvula	3 (8%)	0 (0%)	0.45	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.13
	2: Soft palate only	5 (13%)	5 (19%)		4 (31%)	1 (33%)	0 (0%)	0 (0%)	0 (0%)	
	3: Soft palate and segment of hard palate	21 (53%)	15 (58%)		5 (39%)	2 (67%)	7 (100%)	0 (0%)	1 (50%)	
	4: Total palate up to incisive foramen	11 (28%)	6 (23%)		4 (31%)	0 (0%)	0 (0%)	1 (100%)	1 (50%)	
Associated disorders	Isolated	21 (53%)	11 (41%)	0.35	4 (29%)	0 (0%)	4 (57%)	1 (100%)	2 (100%)	0.089
	Non-isolated¶	19 (48%)	16 (59%)		10 (71%)	3 (100%)	3 (43%)	0 (0%)	0 (0%)	

MDO: mandibular distraction osteogenesis; TLA: tongue lip adhesion; Tr: tracheotomy; NG-tube: nasogastric tube; SD: standard deviation; n.a.: not applicable
xNo calculation possible because of too few cases
**P-value <0.05 was considered statistically significant*
[&]In the surgical intervention subtypes only the postoperative NG-tube duration was included.
***Modified from Jensen et al. cleft palate classification (1988),[34] according to the division made in the Dutch Cleft Registry database*
¶Presence of a syndrome or other associated anomalies or chromosomal defects

Systematic Literature Review

The literature search resulted in 347 unique titles. After initial screening, the full text of 80 potentially relevant articles was retrieved. References of these were checked, which provided three additional papers. These 83 texts were then analyzed by selection criteria and validity, yielding 20 articles (Table 2).[3, 15, 23, 27, 39-54]

The selected reports included a mean of 65 patients (range: 22[53]–151[54]) with mixed isolated and non-isolated RS cases. In the majority, RS was defined as infants expressing micrognathia, glossoptosis and a CP, while in the others obstructive respiratory distress or FD were (optionally) included in the features of RS. An average of 80% of cases expressed FD (range: 47[52]–100[15, 40, 45, 50]). On average, NG-tube feeding was given to 55% of the infants (range: 11[41]–100[40, 45, 53]), and a gastrostomy in 17% (range: 2[23]–43[43]). Other feeding interventions described were special plates[23, 46, 54] or functional therapy (such as Castillo Morales).[3] When mentioned, mean duration of NG-tube feeding varied between several weeks[27, 53] and 18 months.[49]

DISCUSSION

The current study reports on FD in 69 infants with RS, in which significantly more FD and lower growth were demonstrated in the first 2 years of life than in 64 infants with iCPO. This report is the first to present long-term data on FD, weight and influencing factors in a relatively large cohort of RS infants, compared with iCPO infants. By gaining insight about this challenging patient group, treatment strategies can be optimized and expectations of caretakers and parents better managed.

FD and Growth

FD is an important and common symptom in RS, possibly leading to failure to thrive and developmental problems, if not recognized and treated in time.[39] Successful feeding depends on a chain of complex, rhythmically coordinated, successive movements.[55] Due to anatomical changes this chain is disrupted in infants with RS, and can be aggravated because of concomitant CP or neuromotor disabilities related to a possible underlying syndrome or other anomalies.[56] Spriestersbach et al.[57] reported FD in 73% of infants with a CPO, which is comparable to our findings. In our study, significantly more feeding difficulties were seen in infants with RS (91%) than iCPO (72%), after controlling for CP grade (p=0.005). Consequently, in RS patients, NG-tube feeding was needed more frequently and for a longer period of time.

RS patients had significantly lower growth than iCPO patients and during the first 2 years of life. This difference continued to be present amongst the two groups when controlled for CP (p=0.030). As Fig. 2 illustrates, in the iCPO group, growth was higher than that in the RS group during the first 3 months and the resulting difference between the two groups remained up to 24 months of age. Yet, growth curves of both groups remained within the 0SD (P50) and -1SD (P16) line of healthy counterparts. Becker et al. also found that RS patients were lighter and shorter at birth than healthy

controls and iCPO patients.[58] In a follow-up study, van den Elzen et al. demonstrated that almost a quarter of infants with RS had a body weight <P10 after 6–24 months.[51] Moreover, Marques et al. revealed a significant difference between the mean weight curves of infants with RS and healthy controls, finding the infants weight <P10 during almost the follow-up period of six months.[59] In contrast to the current study, Wan and co-authors[60] reported no differences between the weights of iCPO and RS patients after a follow-up of twelve months. However, only mild cases of RS were included, which might explain the discrepancy.[60]

A possible explanation for the lower growth in RS than iCPO patients proposed by Becker et al.[58] is that the occurrence of a CP and growth retardation are associated with the same factor (such as smoking). However, this explanation has been demonstrated in all cleft types, except for RS.[61] Another hypothesis is the presence of morphological characteristics as primary predisposing factors, which is supported by the finding that infants with a cleft have a tendency towards smaller cranial circumference.[62] Genetic factors are of interest, especially the role of growth factors that might influence growth retardation in RS.[58] In addition, airway infections during 0–3 months of age negatively affect growth.[63] Finally, arguments for other origins of feeding disorders and subsequent growth retardation in patients with RS exist, such as primary brainstem dysfunction or neuromotor disabilities, which might be more prevalent in RS than iCPO patients.[15, 39]

Although CP patients have a lower weight than healthy controls,[58] they tend to "catch up" later in childhood.[58, 63] To date, no studies exist that describe growth patterns in patients with RS until adolescence. Glossoptosis and severity of micrognathia progressively improves in the majority of infants within 2–6 years of age.[19, 39] Thouvenin et al. demonstrated that severe functional feeding and respiratory disorders did not affect long-term developmental outcomes.[19] However, only isolated RS infants or RS with Stickler syndrome were included in this study.[19] Longer follow-up studies of both isolated and non-isolated RS infant are needed to evaluate a possible catch-up in growth and the effect of the lower weight on further (cognitive) development.

As expected, the presence of NG-tube feeding did not influence growth for the RS and iCPO patients. Interestingly, FD also did not significantly affect growth. This finding could emphasize the somewhat subjective nature of FD, especially when reported by parents. Another explanation is that infants with FD are more likely to receive NG-tube feeding. When NG-tube feeding was adequately started, no differences in growth were seen between infants with reported FD and those without FD.

Airway Interventions

In the majority (58%) of RS cases, airway problems could be managed conservatively. In our institution, surgical options are only considered after nasopharyngeal airway NPA treatment failure.[38] Until 2006, either TLA or tracheotomy were performed. After 2006, MDO has become our surgical procedure of preference in a supraglottic airway obstruction.[29, 38] Significantly more infants with RS who underwent surgical airway interventions expressed FD (p=0.03), which is comparable

to the data of Daniel and co-workers[42] and might illustrate the relation of FD to the severity of airway problems. Growth was not affected by the type of airway intervention (conservative vs. surgical, p=0.178); therefore, we hypothesize that adequate relief of airway obstruction is important to maintain adequate growth.[60] This finding is substantiated by the similar findings of Daniel et al.[42], in which the degree of adequately treated OSA did not influence growth infants with RS.[42]

After MDO, NG-tube feeding duration was significantly shorter than that after other interventions, which corresponds with the results of another study.[32] Moreover, disappearance of gastroesophageal reflux has been demonstrated after MDO.[14] This positive effect of MDO on feeding capacity and growth has also been confirmed by others.[44, 47, 64-67] In addition, Lidksy and co-authors[47] show that timing of surgery (i.e., MDO within 3 months) dramatically reduces the need for feeding interventions in isolated RS patients. The findings of Spring et al. indicate that MDO performed at a young age might increase the risk of transient FD and growth decline. However, 70% of the infants in this study were fed orally post operatively, which just might not be sufficient for these children to grow adequately.[68]

In the present study, the subtype of surgical intervention influenced growth; infants <2-yr-old receiving MDO or TLA had significantly lower weight than the tracheotomy subgroup. This growth difference might result from a disproportionate presence of comorbidities or syndromes in the various surgical subtype groups, differing ages at surgery or longer NG-tube durations in infants treated with tracheotomy. Despite some evidence of the beneficial effects of airway interventions on feeding performance, the primary goal of a surgical procedure is to alleviate respiratory problems.[47, 56]

Associated Anomalies

Infants with syndromes such as those in non-isolated RS often have FD.[69] In the current study, a higher, although nonsignificant, presence of FD and NG-tube feeding frequency was seen in the non-isolated RS patients, compared with the isolated RS group. No significant effect of the presence of an associated disorders or syndrome was illustrated on growth, a finding which is in agreement with other studies.[23, 42, 51, 70, 71] In addition, the duration of NG-tube feeding in isolated vs. syndromic RS patients was not different. However, other underlying problems (e.g. neuromotor dysfunction) might persist longer, having a negative effect on feeding capacity despite relief of airway problems.[15, 47, 51] In some studies, a higher rate of gastrostomy placement has been found in syndromic than isolated RS patients.[41, 72] In conclusion, infants with a syndromic diagnosis need closer follow-up to monitor growth and feeding capacity.[68]

Analysis and Treatment of FD

FD and failure to thrive in RS patients is most commonly related to upper airway obstruction. However, other causes of FD exist.[42, 73] Therefore, it is important to distinguish between respiratory-related FD and neuromotor disabilities that affect sucking and swallowing coordination.[56] Although

numerous papers mention FD, there is still no scientific agreement about what they exactly encompass.[34] Consequently, these difficulties are regularly manifested in objectified measures, such as weight or the incidence of NG-tube feeding.[34] Several interventions are proposed to confirm the presence of FD, such as dysphagia or gastroesophageal reflux (GER) [15,15, 39, 74-76] However, there is no consensus about which investigations should be performed, and their validity is sometimes questionable.[75] We strongly believe it is important to define feeding issues together with parents and feeding therapists as early as possible. If GER is clinically suspected, a trial of reflux therapy can be started, as the incidence of GER is known to be higher in RS.[56] Moreover, NG-tube feeding should be started when there is insufficient weight gain.[12] Marquis et al.[77] stress the importance of hypercaloric feeding and demonstrate a quicker improvement in weight gain and relief of respiratory problems, compared with controls. In addition, many authors advise feeding-facilitating techniques, stimulating the orofacial and tongue musculature and encouraging sucking to improve neuromuscular coordination by introducing small amounts of bottle feeding as soon as possible.[3, 27, 53, 78] Finally, monitoring of urinary sodium has been suggested, as oral sodium supplementation in cases with a low urine sodium, significantly improved weight gain in infants with RS.[79] Besides growth, maternal bonding,[80] psychological well-being[81] and even (social and cognitive) development[16, 17, 82] can be negatively influenced by FD in the long term, which therefore need to be monitored during follow-up.

Strengths and Limitations

The first limitation is the study's retrospective nature. Hence, some data, such as the infant's length, were difficult to retrieve and thus excluded. We did not examine nutritional status by using other anthropometric measurements, such as mid upper arm circumference and skin fold thickness.[83, 84] FD remains difficult to define. Consequently, differences in severity of FD amongst the included infants existed, but no subdivision could be made. Secondly, other forms of therapy not used in our institution, such as Castillo Morales[3] or palatal plate therapy,[45, 85, 86] have been described. Moreover, in our clinic, it is uncommon to perform a gastrostomy in children under 1 year of age; hence, we only provide data on usage of NG-tube. Thirdly, in our data analysis, we did not include information of deceased patients. Fourthly, we did not provide separate outcomes of the conservative treatment subtypes (such as NPA) on feeding issues. In addition, the effect on the airway of the performed interventions was not separately described, as this is beyond the scope of this report. Finally, RS is a heterogenic disorder, thus the distribution of syndromes or associated anomalies might influence the results. Strengths include that this is the first comparative study to report in detail on feeding issues and growth in two large cohorts over a relative long study period, using weight at nine measuring moments as objective parameters and analyzing the influence of various parameters.

CONCLUSIONS

In this retrospective study, the prevalence of FD was significantly higher and NG-tube feeding was more frequent and for a longer period in infants with RS than iCPO. In addition, growth in the first 2 years of life was significantly lower in RS than iCPO infants, although following a steady curve between the 0 and -1 SD line compared with healthy counterparts. Neither presence of associated syndromes or malformations nor the type of intervention negatively affected growth, which might be explained by early recognition and treatment of FD in our cohort. The subtypes of surgical intervention did reveal a significant effect on growth which might be caused by the heterogeneity of the treated infants. The cause of and long-term effect for the lower growth in RS needs further investigation.

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10

A pragmatic approach to infants with Robin sequence: A retrospective cohort study and presence of a treatment algorithm

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ABSTRACT

Background

Initial approaches to and treatments of infants with Robin sequence (RS) is diverse and inconsistent. The care of these sometimes critically-ill infants involves many different medical specialties, which can make the decision process complex and difficult. To optimize the care of infants with RS, we present our institution's approach and a review of the current literature. We provide a comprehensive and pragmatic approach to the analysis and treatment of infants with RS which could serve as useful guidance in other clinics.

Methods

A retrospective cohort study was conducted among 75 infants diagnosed with RS and managed at our institution in the 1996-2012 period. Additionally, the conducted treatment regimen in this paper was discussed with recent literature describing the approach of infants with RS.

Results

Forty-four infants (59%) were found to have been treated conservatively. A significant larger proportion of nonisolated RS infants than isolated RS infants needed surgical intervention (53% vs. 25%, *p*=.014). A mandibular distraction was conducted in 24% (n=18) of cases, a tracheotomy in 9% (n=7), and a tongue-lip-adhesion in 8% (n=6). Seventy-seven percent of all infants had received temporary nasogastric tube feeding. The literature review of 31 studies showed that initial examinations and the indications to perform a surgical intervention varied and were often not clearly described.

Conclusions

RS is a heterogenic group with a wide spectrum of associated anomalies. As a result, the decisional process is challenging and a multidisciplinary approach to treatment is desirable. Current treatment options in literature vary and a more uniform approach is recommended.

INTRODUCTION

Mandibular micrognathia, glossoptosis with subsequent airway obstruction, is the original triad of symptoms described by Pierre Robin in 1923.[1] By 1934 the frequent association of a cleft palate was noted by him.[2] These features combined are currently known as Robin sequence (RS). RS may be an isolated condition, but an associated syndrome is present in about 45-80% of cases.[3] Reported incidences are estimated to be 1:8,000 to 1: 14,000 births.[4-6] Symptoms of the condition include varying degrees of upper airway obstruction (UAO) and feeding problems, leading to failure to thrive.[7, 8] Mortality rates vary from 0-26% and are most usually caused by severe UAO leading to obstructive apnea and secondary cardiac problems.[8]

Infants born with RS have been treated with numerous different methods.[9] Most airway management strategies initiate treatment with positional change.[7] With an inadequate response, non-surgical interventions, such as the use of a nasopharyngeal airway[10, 11] or a palatal plate[12-15] are commonly pursued. Still, in some cases there can be more severe respiratory obstruction or failure to thrive, necessitating some other form of intervention.[16] This decision-making process can be challenging for caregivers. To date, many authors have described their preferred surgical techniques, such as tongue lip adhesion (TLA)[17, 18], tracheotomy[19, 20], subperiosteal release of the floor of the mouth[21, 22] or mandibular distraction osteogenesis (MDO)[23, 24].

Currently, guidelines are lacking, and there is a paucity and discrepancy of information in the medical literature on how specific decisions are made. The rationale for the choice of a specific approach is often not or only scantily addressed. It is known that physicians often utilize a treatment method that was learned during their residency period and often continue with this approach.[25] Also, the surgeon's preference varies between different specialties.[25] Especially in the treatment regimen of this heterogenic disorder, were a multidisciplinary approach is inevitable, all of this may lead to unnecessary interventions and a potential delay in definitive treatment.[7, 26]

The objective of this study is to present a treatment algorithm based on our experience of airway management in infants with RS. The rationale of specific decisions will be covered. This will provide a comprehensive guidance for a designated treatment strategy and contributes in optimizing the care of infants with RS.

MATERIAL AND METHODS

All infants < 1 year old diagnosed with RS, who have been treated at the Wilhelmina Children's Hospital Utrecht the Netherlands over sixteen years (1996-2012), were included in this retrospective cohort study. Ethics committee approval was obtained. RS was defined as signs of airway obstruction and presence of micrognathia. Information about duration of admission and treatment outcome with a follow up of at least one year was extracted from medical records. Moreover demographic characteristics, performed diagnostics, interventions and treatment approach were critically

analysed. A subdivision between the nonisolated RS infants (i.e. diagnosis of an additional syndrome related to RS or of other associated anomalies or chromosomal defects not directly related to the features of RS) and isolated RS infants (i.e. only the features of RS without any additional anomaly) was made. Independent samples t-test and Mann-Whitney U test were performed (IBM SPSS Statistics 20.0, IBM Inc., NY, USA).

Subsequently a literature search to find existing algorithms covering the approach to infants with RS was performed. The search was performed in January 2014 without time limits. Similar keywords were used in the Embase, Medline, CINAHL, Cochrane Library and Google Scholar databases ("(pierre) robin syndrome/sequence" and "algorithm(s)", "approach", "(airway) management", "intervention", "regimen" or "treatment"). Only articles that included a clear description of the patient group, performed examinations, decisional factors and performed interventions were included. Moreover, concise, state of the art reviews suggesting a treatment approach, were included. The bibliographies of the selected studies were hand searched for any additional articles. The search and inclusion process was performed by two authors (E.P. and B.S.). Finally, the pragmatic approach from our institution is presented in a schematic way.

RESULTS

Retrospective cohort analyses

From 1996-2012, 75 infants diagnosed with RS were treated in our institution. Baseline characteristics are summarized in Table 1. Mean follow up was 7.4 years (range: 1-17). Fifty-two percent (n=39) were female. Seventy-two patients (97%) had a cleft palate. The minority of cases (43%, n=32), had an isolated form of RS. In one third of the cohort (31%, n=23) an associated syndrome was present, Stickler (n=11, 48%) being the most common. In a quarter (26%, n=20), additional anomalies or chromosomal defects were identified, which were not directly related to a syndrome associated with the features of RS.

Table 1 Baseline characteristics of infants with RS patients treated in the Wilhelmina Children's Hospital 1996-2012

Patients	Number of patients (%)	Female	Male	Median age of presentation in days (IQR*)	Gestational age in days	Mean birth weight in grams (SD)	Presence of CP (%)	CP type¥ (%)
Isolated RS	32 (43)	20	12	10.0 (5-17.75)	275(median), 270(p25), 282 (p75)	3135 (789)	97	I (0); II (16); III (58); IV (26)
Nonisolated RS	43 (57)	19	24	8.0 (1.25-32.75)	277(median), 273 (p25), 282 (p75)	3237 (553)	98	I (3); II (24); III (56); IV (17)
Syndromic RS	23	10	13	7.5 (1-17.75)	279 (median), 273 (p25), 281 (p75)	3314 (512)	100	I (4); II (13); III (61); IV (22)
Stickler syndrome	11							
Treacher Collins syndrome	2							
Spondyloepiphyseal dysplasia	2							
4q deletion syndrome	1							
Van der Woude syndrome	1							
Osteopathia striata with cranial sclerosis	1							
EEC syndrome¶	1							
Goldberg-Shprintzen syndrome	1							
Yunis-Varon syndrome	1							
Auriculo-Condylar syndrome	1							
Hemifacial microsomia	1							
RS with other associated anomalies or chromosomal defects	20	9	11	10.5 (2-62.75)	275 (median), 272 (p25), 282 (p75)	3149 (597)	95	I (0); II (37); III (53); IV (10)

RS, Robin sequence; SD, standard deviation; CP, Cleft Palate

** IQR: interquartile range*

¥ CP type: I, submucous cleft or bifid uvula; II, soft palate; III, soft palate and segment of the hard palatte; IV, soft palate and hard palate up to incisive foramen

¶ EEC Syndrome, Ectrodactyly – ectodermal dysplasia – cleft syndrome

The majority, (59%, n= 44) of the infants admitted to our hospital could be successfully managed conservatively (Table 2). This consisted of side/prone positioning, temporary supplemental oxygen or usage of CPAP, a mayotube or nasopharyngeal airway (NPA) (Fig. 1). In 41% (n=31) a surgical intervention was pursued, at a mean age of 50 days (SD 55). Until 2006 this consisted of TLA whenever possible. If TLA failed, or there was a (sub)glottic pathology, a tracheotomy was performed. Since 2006 the primary surgical intervention for UAO caused by a supraglottic obstruction is MDO. During the study period, in more than half of the surgically treated cases (58%, n= 18) MDO was pursued, in 19% (n=6) TLA and in 23% (n=7) a tracheotomy. Average duration until decannulation after a tracheotomy was 13.4 months (range: 4.1-36.5). More than half of the nonisolated RS infants, compared to only a quarter of the isolated RS infants needed surgical intervention (53% vs. 25%, *p*=.014) (Table 2). Moreover, mean duration of admission was significantly shorter in the isolated group than in the nonisolated group (33 days vs. 58 days, *p*=.018). Two infants with syndromic RS received two interventions: one patient had a tracheotomy prior to MDO, another needed a tracheotomy directly after release of the TLA. Both were successfully decannulated afterwards.

Seventy-seven percent of all infants received temporary nasogastric (NG)-tube feeding during an average of 247 days. Average duration of NG-tube feeding was significantly longer in the surgically treated group than in the conservative treated group (resp. median: 72 days, mean rank: 30.5 vs. median: 21 days mean rank: 19.7, *p*=.008). Presence of NG-tube feeding showed a highly significant relation with mean duration of admission (*p*=.000); patients who had received NG-tube feeding were longer admitted in the hospital (44.2 days; SD 39.1) as compared to patients who had not received NG-tube feeding (4.1 days; SD 3.6).

Fourteen infants needed temporarily endotracheal intubation prior to surgical intervention, due to severe respiratory distress. Eleven were successfully extubated after surgery. Six infants (8%), all syndromic RS, ultimately died due to cardiac or pulmonary pathology at a mean age of 416 days (44 days – 3 years). All had been immediately intubated within several days after birth. One child was diagnosed with 4q deletion syndrome and received a TLA 23 days after birth and subsequently a tracheostomy 52 days after birth. He died due to a cardiac arrhythmia ten months after the surgery. An infant with Yunis-Varon syndrome underwent TLA after 20 days but could not be extubated, and ultimately died after 41 days due to severe respiratory obstruction. Another infant with Treacher Collins who was primarily treated successfully with MDO two weeks after birth, died at almost two years of age due to aspiration pneumonia. A child with spondyloepiphyseal dysplasia died 44 days after a tracheotomy due to cardiac failure. Another child with psychomotor retardation, recurrent feeding difficulties and an atrial and ventricle septum defect, died possibly due to a cardiac problem at the age of nine months. At the request of the parents no autopsy was performed. Finally, a patient with severe psychomotor retardation, blindness, epilepsia, gastro-esophageal reflux and recurrent pneumonias died at three years of age due to sepsis en respiratory insufficiency after an aspiration pneumonia.

Table 2 Approach to infants with RS treated in the Wilhelmina Children's Hospital 1996-2012

	Total study group	Isolated RS	Nonisolated RS	*p*-value*
Number of patients	75	32 (43%)	43 (57%)	
Conservative treatment¶	44 (59%)	24 (75%)	20 (47%)	0.014
Surgical treatment¥	31 (41%)	8 (25%)	23 (53%)	0.014
MDO	18	6	12	
TLA	6	1	5	
Tracheotomy	7	1	6	
Mean age at surgical intervention in days (SD)	50 (55)	57 (42)	47 (60)	0.620
Mean duration of admission in days (SD) ±	48 (43)	33 (35)	58 (45)	0.018
Conservatively treated group (SD)	30 (30)	24 (32)	35 (27)	0.285
Surgically treated group (SD)	73 (46)	55 (35)	80 (48)	0.163
Nasogastric tube	58	20 (63%)	38 (88%)	0.009

MDO, mandibular distraction osteogenesis; TLA, tongue lip adhesion; SD, standard deviation
** p-value <0.05 was considered statistically significant*
¶ Side- or prone positioning, supplemental oxygen, mayotube or nasopharyngeal airway
¥ The first surgical intervention was counted
± Total duration of all hospital admissions related to airway- or feeding problems in the first year of age

Figure 1 Use of a nasopharyngeal airway as conservative treatment option in a one month old infant with RS

Literature review

The literature search yielded a total of 393 articles. Duplicates were excluded and abstracts were further analysed for relevance. Five literature studies[7, 9, 16, 27, 28] 25 retrospective case studies[8, 10, 14, 19, 20, 29-48] and one prospective cohort study 49 fulfilled our selection criteria and were included for further analysis. There was final agreement between the two authors regarding the inclusion process. A summary of the approach described in these articles is listed in Table 3.

Table 3 Approaches described in current literature until January 2014

Study	Population*	Performed examination**	Indication for (surgical) intervention	Type of intervention***	(%)
Abel et al. 2012[10]	- N: 104 - MG, GI, CP - iRS, sRS	- Overnight sleep study - Microlaryngobronchoscopy when Tr was considered	Moderate (≥3 clusters ≥3 sPO2 80-85%) or severe ORD (≥3clusters ≥3 sPO2 <80%) not responding on positioning and NPA	Tr	19%
Augarten et al. 1990[43]	- N: 8 - MG, GI, CP	- Monitoring of vital parameters, blood gases and weight gains - Lateral neck radiographs	Respiratory rates ≥60/min, requirement of ≥60% 02, Pa02 ≤65mmHg and PaCO2 ≥60 mmHg or acidaemia, despite positioning	TLA Tr if no improvement after TLA	38%
Benjamin et al. 1991[19]	- N: 26 - MG/RG, GI - iRS, sRS	- Pulse oximetry - Laryngoscopy before endotracheal intubation	Oxygen saturation <90% for > 10% of the time not improving by position or NPA	Endotracheal intubation Tr if this fails, to bypass obstruction	23%
Bull MJ et al. 1990[30]	- N: 21 - RS (not specified) - iRS, sRS	- Modified PSG during 2 hours - When indicated: Nasoendoscopy, airway fluoroscopy, upper GI radiographs and scintiscan and head CT - Suggestive/gastroesophageal reflux but normal radiographic studies: pH probe during PSG	- ↑ End tidal CO2 or uncorrectable desaturation (<90% in >5% of the sleep time or <80% in 1% of the sleep time) with 2L nasal 02 - Continued failure to thrive despite nutritional and oxygen supplementation	TLA or Tr	48%
de Buys Roessingh et al. 2007[29]	- N: 48 - MG/RG, GI, ORD, CP - iRS, sRS	- Pulse oximetry - Serial blood gas (every 2 days). - Nasoendoscopy, bronchoscopy, pH-probe - PSG if monitoring shows bad results	Desaturation < 90% with clinical evidence of respiratory distress or chronic CO2 retention (BE>6.5) despite CPAP followed by NPA and palatal plate	TLA, Tr	0%
Caoutte Laberge et al. 1994[31]	- N: 125 - MG/RG, GI, ORD - iRS, sRS	- Serial blood gas measurement - Oxygen saturation monitoring - Modified PSG (according to Freed et al. 1988)	PO2 <60mmHg or PCO2 >50 mmHg	Subperiosteal release of the floor of the mouth musculature or TLA; Tr if no relieve of UAO	18%
Cheng et al. 2010[32]	- N: 20 - MG, GI, ORD	- Continuous oxygen saturation measurement - Laryngoscopy and bronchoscopy before MDO - Preoperative PSG	Extensive periods of desaturations < 90% not responding on CPAP	MDO + TLA	30%
Cole et al. 2008[33]	- N: 39 - MG, GI, CP	Weight gain and saturation monitoring	Moderate to severe respiratory distress when nursed side to side or with NPA	No surgical intervention performed	0%
Cruz et al.1999[34]	- N: 47 - MG, GI, CP - iRS, sRS	- PSG, nasoendoscopy - Laryngoscopy,and consideration of flexible and or rigid bronchoscopy before invasive treatment. - Speech/ swallow team evaluation using oropharyngeal motility studies	No resolve of the "airway difficulty" with positioning or short-term use of an NPA	TLA Tr in (sub)glottic pathology or other swallowing or neuromuscular difficulties	43%
Dauria et al. 2008[35]	- N: 9 - MG, ORD - iRS	- Laryngoscopy and bronchoscopy - 3D CT before distraction	Failure of positioning or NPA	Tr MDO if no compounding pathology and /or gestational age >39 weeks	44%

Evans et al. 2011[7]	Literature study	- Modified PSG is important in early infancy for CO2 retention in addition to hypoxemia or desaturation, overnight full PSG may have a role when clinical picture is not clear. - Laryngoscopy and bronchoscopy	No airway stability (abnormal oxygen saturations, carbon dioxide levels, presence of work of breathing and signs of airway obstruction) maintained by positioning or NPA.	Temporarily endotracheal intubation TLA/MDO: Single level tongue base obstruction Tr: >1 level of obstruction or not a candidate for TLA/MDO	-
van den Elzen et al. 2001[8]	- N: 74 - MG, CP, GI - iRS, sRS	- Continuous pulseoximetry - PSG on indication, not routinely performed	Hypoxia (continuous and persistent SpO2 levels <90%) not responding on positioning or NPA.	Endotracheal intubation Tr (if no successful extubation within 4-6 weeks or after repeated intubations)	15%
Freed et al.1988[36]	- N: 6 - MG, CP, GI, ORD - iRS, sRS	- Transcutaneous oxygen and transcutaneous carbon dioxide levels during a minimum of 8 hours (range 8 to 18hrs) - Modified PSG - Studied in lateral, prone and supine position for ≥45min.	- Average oxygen levels <60mmHg and CO2 levels >60mmHg during ≥8 hours - Any O2 level <80% - Obstructive episodes on PSG	TLA	67%
Gangopadhyay et al. 2012[44]	Not mentioned	- Continuous pulse oximetry - PSG can be a useful tool	Inadequate results on sleep studies and poor weight gain despite positioning, supplemental O2 and NPA	TLA or MDO (both options discussed with parents and team)	Not mentioned
Gilhooly et al.1992[37]	- N: 15 - MG, GI, ORD - iRS, sRS	4- channel PSG including ECG	"Event of obstruction" of ≥15 seconds during sleep or quiet activity or shorter episodes associated with ↓ HR < 80 BPM or sPO2 < 85% despite positioning.	TLA	40%
Glynn et al. 2011[20]	- N: 69 - MG, GI, CP - iRS, sRS	- Nasoendoscopy - Continuous oxygen saturation monitoring for 24-36 hours - Hearing assessment with otoscopy, tympanometry, visual response and pure audiometry. - Microlaryngobronchoscopy before Tr	Sp02 <90% >5% of the time, despite positioning and NPA	Endotracheal intubation Tr if attempts to extubate fail	14%
Hoffman et al. 2003[46]	- N: 72 - MG, GI, ORD, CP - iRS, sRS	- Clinical examination - PSG - Bronchoscopy	Average transcutaneous O2 <60 mmHg/CO2> 50 mmHg, SpO2 < 880%, and/or obstructive episodes on sleep study despite positioning and supplemental oxygen	TLA Tr for (sub)glottic pathology	35%
Jarrahy et al. 2012[27]	Literature study	- CT-scan, manometry, electromyography, 24 hours pH monitoring, and nuclear medicine imaging to evaluate presence of reflux - Nasoendoscopy pre- and postoperative, "sleep – evaluation".	Failure of positioning/NPA or unsuitable airway for a trial of nonsurgical management	Subperiostal floor of mouth release TLA, MDO, Tr	-

Kochel et al. 2010[14]	- N: 7 - MG, GI, ORD +/ CP - iRS, sRS	- Nasoendoscopy - Continuous pulse oximetry - Blood gas analyses	Clinical signs of respiratory distress (i.e. agitation, dyspnea, tachypnea, intercostal recession etc.) or oxygen desaturation or respiratory acidosis in blood gas analyses	Orthopedic oral appliance with/ without extension (posterior, extra oral or pharyngeal tube)	100%
Van Lieshout et al. 2013[38]	- N: 59 - MG/RG, ORD - iRS, sRS	- PSG (in all infants with ORD despite prone positioning or with persistent feeding difficulties) - Nasoendoscopy on indication	Failure of prone positioning and respiratory support (NPA, CPAP and/or oxygen supplementation)	Tr and/or MDO	7%
Mackay et al. 2011[16]	Literature study	- Evaluation of desaturation occurring spontaneously, during feeding and sleep - Nasoendoscopy, bronchoscopy - PSG, pH monitoring, CT scan and cephalometrics	Persistent obstruction despite positioning or NPA	TLA MDO (if TLA fails) Tr (if MDO fails)	-
Marques et al. 2000[49]	- N: 62 - RG, GI, ORD - iRS, sRS	- Nasoendoscopy - Continuous pulse oxymetry	Sp02< 90%, increasing respiratory effort and/or no removal of NG tube possible despite NPA within 15 days.	TLA (type 1 obstruction) Tr (type 3 or 4 obstruction, or no improvement after TLA/NPA)	35%
Poets and Bacher 2011[9]	Literature study	- Clinical observation - PSG	Significant UAO during sleep, defined as a mixed-obstructive apnea index (MAOI) > 3 in a sleepstudy	Pre-epiglottic baton plate	-
Schaefer et al. 2003[41] Schaefer et al. 2004[42]	- N: 21 - max-man. discrepancy of > 3mm, GI, +/- CP.	- Pulse oximetry for ≥12 hours, PSG (continuous monitoring oxygen saturation, end-tidal CO2 and EEG during sleep), nasoendoscopy and bronchoscopy before invasive intervention	Any single saturation below the 80% orPO2 <90% for >5% of the monitored time despite positioning	TLA MDO (if TLA fails) Tr if no response to TLA/MDO or (infra)glottic problem present	57%
Scott et al. 2012[28]	Literature study	- Nasoendoscopy - PSG if no life threatening airway compromise is present - Serial capillary blood gases (to document a trend of elevated or increasing carbon dioxide levels), - continuous-pulse oximetry and cardiac monitoring	Signs of upper airway obstruction despite prone- or side positioning or NPA	TLA, Tr, MDO	-
Thouvenin et al. 2013[48]	- N: 141 - RG, GI, CP - iRS, sRS	- Continuous monitoring of cardiac and respiratory rhythms, regularly check of transcutaneous PO2 and PCO2 levels. PSG on indication - Karyotype assay, echocardiography, skeletal radiography, ophthalmologic examination	Oxygen saturation < 90% for >5% of the time or saturations < 80% not responding on positional changes or NPA	Tr	Not mentioned
Tomaski et al. 1995[47]	- N: 90 - MG, GI, CP - iRS, sRS	- Flexible fiberoptic nasopharyngolaryngoscopy, cardiac and pulmonary evaluation, chest radiogram, electrocardiogram, ophthalmologic and genetics consultation - PSG, continuous pulse oximetry and apnea monitoring - Pre-op: lateral X-ray, rigid direct laryngoscopy and bronchoscopy	Positioning and NPA are not successful in relieving airway obstruction	Tr	12%

Wagener et al. 2003[39]	- N: 22 - MG, ORD, GI, CP - iRS, sRS	Continuous oxygen saturation monitoring	Severe UAO (cyanotic attack, transcutaneous oxygenation > 90%, PCO2 < 50 mmHg) not responding on positioning or NPA	No surgical intervention necessary	0%
Vyas et al. 200840 Kohan et al. 2010[45]	- N: 149 - MG, ORD - iRS, sRS	-PSG -Radionuclide milk scan (severity of gastroesophogeal reflux and gastric emptying) with 24-hours pH probe (in indeterminate results) and laryngobronchoscopy	Intubation at birth necessary, failed extubation or failed conservative treatment (prone positioning or NPA)	MDO Tr if: 1. Central apnea 2. Severe gastroesophageal reflux 3. Other airway lesions	78%

** MG/RG: micrognathia/retrognathia, GI: glossoptosis, ORD: obstructive respiratory distress, CP: cleft palate, iRS: isolated Robin sequence, sRS: syndromal Robin sequence*
*** PSG: polysomnography*
**** Tr: tracheotomy, TLA: tongue lip adhesion, MDO: mandibular distraction osteogenesis*

Wilhelmina Children's Hospital approach

Our treatment algorithm is presented in Figure 2. Infants diagnosed with RS are initially treated in prone or side position when their condition allows it. Prior to any decision making, the patient is observed for at least 24 hours. Monitoring of vital parameters, measurements of oxygen saturation by continuous pulse oximetry, capillary blood gas analysis and more recently transcutaneous carbon dioxide measurements (Tosca®) are performed.[50-52] Observation of clinical signs of respiratory distress during sleep and awake, as well as feeding ability are documented by experienced nursing and medical staff. We consider oxygen saturations of < 90% for >5% of the monitored time and/or any single desaturation < 80% as a sign of UAO.[39, 41, 42] Blood gas analysis revealing respiratory acidosis (pCO2 > 50 mmHg, HCO3 > 30 mmHg) or transcutaneous CO2 > 50 mmHg during >25% of the total sleep time is indicative of hypoventilation.[53] Results are discussed in a multidisciplinary setting consisting of at least a pediatrician, plastic surgeon, otolaryngologist and a pediatric intensive care specialist after 24-48 hours of monitoring. A clinical geneticist is always consulted. Based on the observations and measurements, patients are divided into mild UAO or moderate/severe UAO. These characteristics are described in Figure 2.

Patients with RS with *mild UAO* remain closely monitored in prone or side position (Fig. 2). Depending on the clinical condition, measurements are repeated and reassessed. Poor weight gain is defined as < 150 grams/week.[41] In these cases further analysis by a pediatrician is indicated and NG-tube feeding may be necessary.[37, 54] If the before mentioned measurements remain normal, patients will be discharged after the parents are sufficiently instructed. Pulse oximetry is continued at home for an average of three months, and at least once a month the pediatric outpatient department is visited.

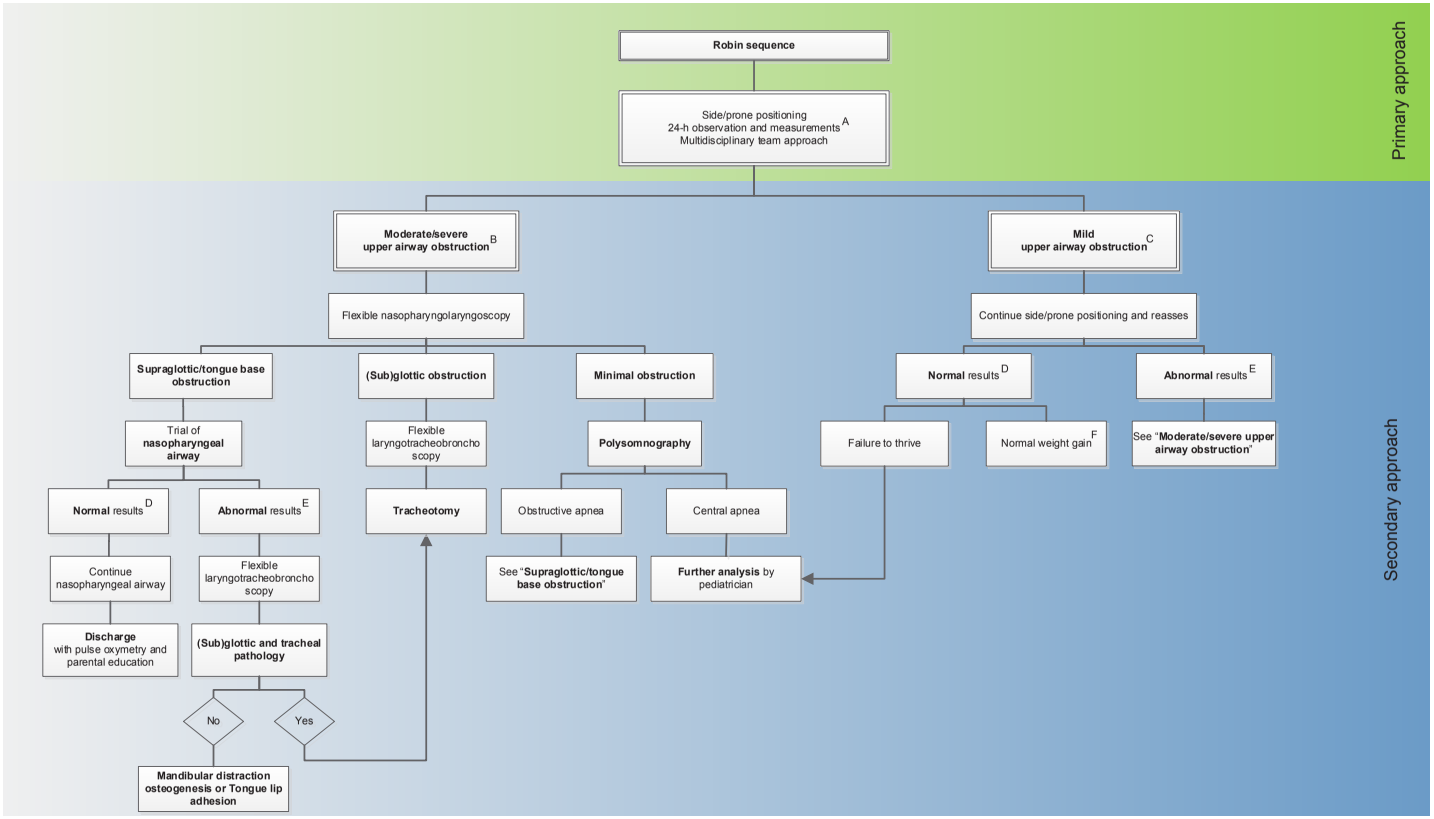

Figure legend

A: Observation and measurements
* Vital parameters (heart rate, respiratory rate, blood pressure), oxygen saturation by continuous pulse oximetry, capillary blood gas analysis or transcutaneous carbon dioxide measurement
* Clinical signs of respiratory distress (i.e. agitation or altered conscious level, dyspnea, use of accessory respiratory muscles, tachypnea, snoring, stridor, position dependent airway obstruction) during sleep and awake and feeding ability

B: Moderate/severe upper airway obstruction
* Clinical signs of respiratory distress
* SaO2 < 90% for > 5% of the monitored time and/or any single desaturation < 80%
* Respiratory acidosis: pCO2 > 50 mmHg, HCO3 > 30 mmHg or transcutaneous CO2 > 50 mmHg during > 25% of the total sleep time

C: Mild upper airway obstruction
* No or minor clinical signs of respiratory distress
* SaO2 < 90% for ≤ 5% of the monitored time and no single desaturation < 80%
* No respiratory acidosis

D: Normal results: no/mild upper airway obstruction and normal weight gain after regular reassessment
E: Abnormal results: Moderate/severe upper airway Obstruction and/or failure to thrive
F: Normal weight gain: ≥ 150 grams/week

Figure 2 Algorithm of the institutional approach to infants with Robin sequence

In *moderate to severe UAO*, the location of the airway obstruction should be investigated by direct flexible laryngoscopy to localize the site of obstruction and to identify possible other airway comorbidities that would influence the decision making process (Fig. 2).[55] True glossoptosis or other supraglottic obstruction can be diagnosed by this measure (Fig. 3). If the clinical symptoms cannot or only partially be explained by the visible airway obstruction, an overnight polysomnography (PSG) is warranted. Hereby central apneas, mixed apneas or episodes of obstructive apnea can be diagnosed, as the glossoptosis tends to be a dynamic problem and could not be identified with laryngoscopy. If substantial central or mixed apnea is detected, a specialist in pulmonary or sleep medicine is consulted. Once the diagnosis of a supraglottic/tongue base obstruction is made, an NPA or mayotube is inserted to maintain a patent airway, and the infant is closely monitored. It is important to mention that other options for conservative treatment, such as orthopedic appliances (like palatal plates or the pre-epiglottic baton plate), have been described to date.[12-14] However, these are not implemented in our algorithm as we are currently not familiar with the use of it in our institution. In the most *severe cases of UAO* (i.e. micrognathia with severe clinical signs of respiratory obstruction, any single desaturation < 80% or severe respiratory acidosis despite positioning) immediate MDO or TLA could be anticipated. However, in our institution we advocate a trial period of NPA prior to any surgical measure. Depending on the clinical condition of the infant, the case is then reassessed in our team after several days of continuous and cautious monitoring. If earlier mentioned measurements and observations are normal and the infant shows sufficient weight gain, NPA treatment will be continued. If the infant shows deterioration despite NPA, the surgical options will be discussed with the parents. Until 2006, either TLA or tracheotomy were performed. However, after 2006, MDO has become our surgical procedure of preference when a supraglottic obstruction and a true micrognathia together with a normal functioning temporomandibular joint is present.[56] Before surgery is pursued, other pathology should be ruled out by flexible laryngotracheobronchoscopy. Moreover, radiological assessment of the mandible with a lateral X-ray or CT-scan is obtained (Fig. 4). Our performed technique with a resorbable internal distraction apparatus has been described previously.[23, 24] Occasionally, when patients do not have a very small mandible but evident glossoptosis is present, TLA is performed. Still, as it is difficult to accurately assess the mandibular size in infants, often both procedures and their (dis)advantages are discussed in our team and with the parents. After surgery vital parameters and blood gasses with pulse oximetry should be regular reassessed.

In our cohort 29 infants (39%) suffered *mild* RS according to our classification. Of these, four (14%) had to be subsequently treated according the *moderate/severe* limb of the algorithm, of whom one patient ultimately received a tracheostomy. Forty-six (61%) of the admitted infants were initially classified as *moderate/severe* RS and treated accordingly. Of these, 30 infants (47%) were treated surgically.

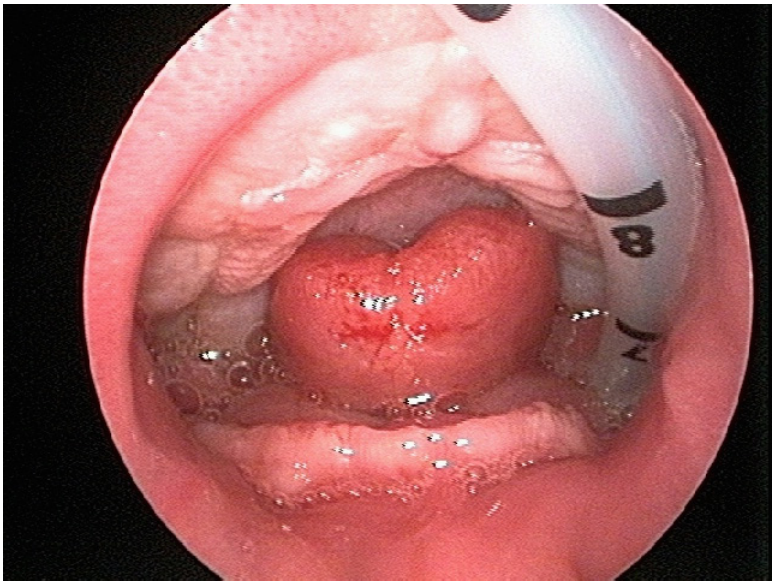

Figure 3 Example of glossoptosis evaluated by direct flexible laryngoscopy

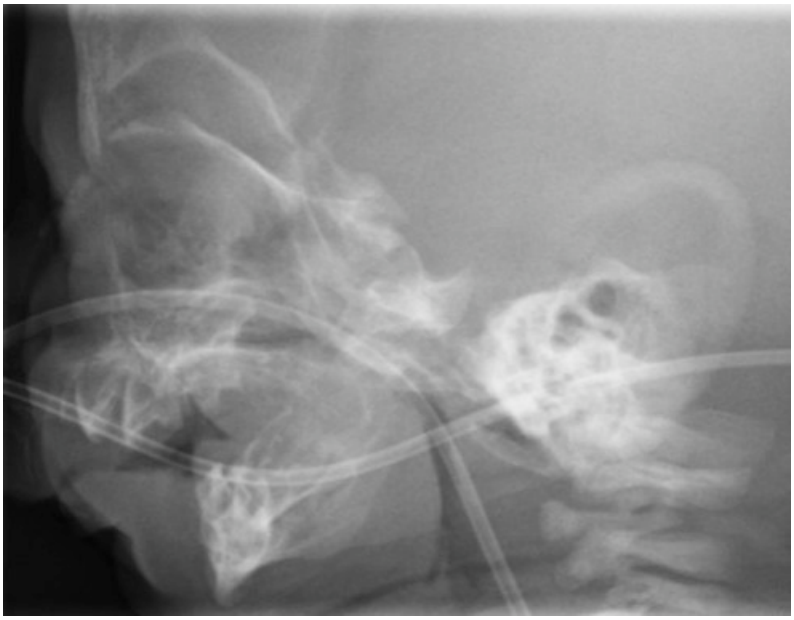

Figure 4 Example of micrognathia seen on lateral X-ray

DISCUSSION

The current study was performed due to the paucity of treatment algorithms for infants with RS in the literature. A plethora of different treatment modalities is suggested, but decisions and rational on which the interventions are based are variable and often ambiguous. A more standardized approach to this challenging clinical entity should be used. An efficient strategy with a multidisciplinary approach might decrease mortality and morbidity, as possible respiratory and feeding problems may be more quickly recognized and treated more efficient.[31] By a thorough retrospective analysis of the treatment regime in our institution and a review of the current literature, we have developed recommendations in the form of an algorithm, that could be applied as a guidance for other centers involved in the care for infants with RS.

The understanding of RS is amongst others hampered by the numerous different definitions that are used to describe this condition.[26, 57-59] Most authors of the analysed studies use the criteria described by Pierre Robin in 1934, thus presence of micrognathia, glossoptosis, respiratory distress and a cleft palate (Table 3).[2] According to others, in our institution we define the disorder as presence of micrognathia combined with signs of UAO.[38] Sometimes we encounter difficulty in determining glossoptosis, possibly due to the fact that intra-oral inspection does not immediately have to reveal its presence and no easy applicable scale of measurement exists. Glossoptosis can be a dynamic problem in which the degree of "ptosis" of the tongue, and subsequent upper airway obstruction, varies, depending on the position and state of the infant (for example asleep, during feeding or tired). Moreover, UAO in patients with micrognathia does not necessarily indicate glossoptosis, since other or additional causes for airway obstruction might be present (e.g. neurologic abnormalities, pharyngeal hypotonia or choanal atresia) in RS.[3, 55] Therefore, we advise to perform a flexible laryngoscopy in cases with moderate/severe UAO to quickly obtain more information about this matter (Fig. 3). Endoscopic findings in RS have been clearly described and graded.[55] Finally, the presence of a cleft palate is not obligatory for the diagnosis, although it was encountered in 97% of our patients.[9, 44]

A common understanding in literature is to start every treatment of an RS patient with conservative measures. In our series more than half of the infants (59%, n=44) could be treated conservatively, which is comparable to others.[30, 32, 34, 35, 37, 49] Conservative treatment usually starts with prone or side positioning, which will reduce airway obstruction at tongue base level by allowing the mandible and tongue to fall forward. Some do advocate side positioning, since prone positioning might obscure signs of respiratory distress and makes it difficult for the parents to interact with their baby.[33] Supplemental oxygen can be provided when necessary by a nasal cannula. When positioning fails, use of an NPA, mayo tube or CPAP are frequently described secondary measures (Table 3). NPA has obtained a lot of interest, and revealed good results (Fig. 1).[10, 29, 33, 39] According to our approach, the majority of the authors starts using an NPA when positioning fails. [8, 10, 16, 19, 20, 27-29, 33-35, 38-40, 44, 45, 47-49] As we have obtained feasible results, we currently use NPA in every infant with significant UAO before

a surgical measure is initiated, and no longer apply a mayotube or CPAP. Yet, the exact place of CPAP still needs to be defined in the treatment of RS. Certain drawbacks of NPA are known. Duration of treatment, obstruction or luxation of the tube, the burden of care for the parents when the child is discharged with NPA and persistent feeding problems during the treatment, have been described.[10, 60] Finally, also other conservative options, such as the custom made palatal plate or pre-epiglottic baton plate (PEBP) have been described to date.[12, 14, 15] The promising results of a velar extension in the PEBP have been demonstrated in a randomized clinical trial regarding isolated RS infants.[15] It has also revealed positive effects on feeding issues.[61] The PEBP might completely obviate the necessity of a surgical intervention, by non-invasively moving the base of the tongue forward and subsequently widening the oropharynx. It is speculated that this protrusion of the tongue might also stimulate mandibular growth, although this has not yet been proven.[13] Still, when using these orthopedic appliances it is necessary to have an experience team, including skilled nurses who can guide and train parents in handling the PEBP.[9] As demonstrated in literature, the training during residency is of paramount importance regarding what technique will be utilized in the institution.[25] However, the country and the supporting medical system will also influence the decision-making in what the most useful conservative treatment option will be.

The percentage of infants that need invasive treatment differs from 0%[14, 29, 33, 39] – 78%[40, 45] in medical literature (Table 3). These varying percentages are illustrative of the difficulty to accurately define at which exact point the infant fails to respond to conservative treatment and a surgical intervention is anticipated. Many authors tend to use cut-off values derived from specific tests such as PSG or blood measurements to determine candidacy for surgery (Table 3).[10, 19, 20, 29-32, 36, 37, 39, 41, 42, 44, 46, 47] While we also take account of oxygen saturations and CO2 levels, we strongly recommend that the multidisciplinary team considers all available results including clinical observation and feeding status, when deciding about escalating care (Fig. 2). Standard usage of PSG in the management of RS remains a point of discussion.[7, 28, 29, 37, 62] In accordance to others and as demonstrated in the flowchart, in our institution PSG is only performed on indication, to exclude central apneas or to quantify more subtle airway obstruction if the clinical symptoms cannot or only partially be explained by the visible airway obstruction (Fig. 2).[7, 19, 20, 29, 37, 39] In the majority of the studies that used PSG routinely, a so-called "modified PSG" is performed by using only certain components of PSG.[31, 32, 36, 37, 41, 42, 46] It is mandatory that important matters such as the exact indication, frequency, and the extensiveness of the conducted tests on PSG are clarified in further studies, and strict recommendations for its use can be made.

Forty-one percent of the infants of our cohort needed a surgical intervention, comparable to findings described by others.[29, 30, 34, 35, 37, 43, 46] In the analysed literature surgical interventions consist mainly of TLA[20, 20, 28-31, 34, 36, 37, 41-43, 46, 49] or MDO when TLA failed[16, 41, 42] (Table 3). Some recommended MDO as primary measure[35, 40, 45] or a combination of MDO and TLA[32]. Generally, tracheotomy was considered as final option when there was no improvement after TLA and/or MDO.[7, 16, 27, 28, 31, 34, 35, 41-43, 46, 49] Other indications were the presence of a central neurological impairment or coinciding upper airway (i.e.

(sub)glottic obstruction or tracheo- or laryngomalacia), cardiac, pulmonary or gastro-esophageal pathology, contributing to the respiratory distress.[7, 27, 28, 30, 34, 35, 40-42, 44, 46] Still, some authors choose tracheotomy as the primary surgical strategy after conservative treatment has failed.[10, 19, 20, 47, 48, 63] In our series MDO was the primary choice in more than half of the surgically treated cases (Table 2). Until 2006, TLA was our surgical procedure of preference with subsequent tracheotomy if TLA failed or could not be performed due to (sub)glottic pathology. At this moment we only perform TLA in the rare cases where patients have an obvious glossoptosis without clear micrognathia. Objectively assessing the size of micrognathia is not easy and currently the (dis)advantages of both MDO and TLA are discussed in a multidisciplinary team meeting and with the parents. It is important to emphasize the risk of glossoptosis recurring after TLA release.[64] MDO also proves to be more effective than TLA in resumption of normal oral feeding.[65] In our series all children could bottle feed within four weeks after distraction and NG-tube feeding could be stopped.[24] Additionally, since we use a resorbable distracting system, there is no need for a second intervention, while patients with TLA need secondary surgery to release the adhesion.[24] Finally, there is less scar formation after MDO.[66] However, long term follow up studies after MDO in RS patients are still scarce. Also possible damage to the permanent molars in the osteotomy region and mandibular outgrow after MDO remains a point of investigation and discussion. In order to clarify these matters, analyses are currently undertaken at our institution.

Six infants (8%) of our cohort, all nonisolated RS patients, died after a mean of 416 days (44 days – 3 years). Reported mortality rates in literature vary from 0% up to 26%.[8] It is important to realize that RS is a heterogenic disorder with numerous causes and also possible co-morbidities, which can aggravate the already present symptoms.[44] An additional syndrome or malformation makes the treatment regime especially challenging and a multidisciplinary approach indispensable. In 75% of the infants with isolated RS, conservative measures revealed to be sufficient to maintain an adequate airway. In contrast, of the nonisolated infants, only 47% could be treated conservatively (Table 2). This important, significant finding (p= 0.014), demonstrates the relevance of adequate and early genetic analysis. Less favorable airway outcomes are more common in nonisolated RS, potentially attributed to airway and swallowing problems independent of glossoptosis.[28, 31, 47, 67] In addition, mandibular size and morphology vary significantly in syndromic RS.[68] Although we are aware that an associated syndrome could have important consequences for the long term mandibular outgrowth, this does not influence our initial treatment approach, as the respiratory distress still needs to be treated and will be alleviated by advancing the mandible. However, MDO or other surgical interventions, should only be considered after other or additional etiologies of respiratory compromise (such as tracheo-or laryngeomalacia), are ruled out. Also, it needs to be addressed that conservative measures can obtain good results and should always be performed in first instance, also in syndromic RS infants.[14]

It is still not fully elucidated what risk factors exist and which infants have an absolute contraindication to receive surgery. Murage and co-workers reviewed the results of fifty infants who were treated

with MDO and concluded that the absence of a CP, presence of gastro-esophageal reflux and need for Nissen fundoplication might be associated with failure of MDO.[69] Prematurity, low birth weight, late operation, preoperative intubation, diagnosis of a syndrome and cardiac and pulmonary abnormalities did not preclude success in appropriately selected patients.[69] On the contrary, others demonstrated that besides gastro-esophageal reflux, also preoperative intubation, late operation (older than two weeks), low birth weight and diagnosis of a syndrome were significant predictive markers of failure of TLA and necessity of a tracheotomy.[67, 70] The cited studies are retrospective and may contain substantial bias. Prospective studies, systematically collecting data are needed to understand risk factors for failure and success of interventions, and to develop evidenced based clinical guidelines to facilitate treatment planning.

Besides the airway problems, feeding difficulties are also a common finding in infants with RS and should be adequately supported.[7, 71] Seventy-seven percent (n= 58) of the infants in our series needed NG-tube feeding during an average of 247 days. This comprised of significantly more infants of the nonisolated group (88%), compared to 63% of the isolated RS patients (p=.009). Duration of NG-tube feeding was also significantly shorter in the conservative treated group (p=.008). However, in all cases after MDO, NG-tube feeding could be successfully stopped within four weeks post operatively, independent of the syndromic or nonsyndromic status. Feeding difficulties in RS can have multiple causes.[61] For the one hand attributed to the micrognathia, glossoptosis or the possible concomitant cleft palate, but also to possible additional upper digestive tract motor dysfunction, leading to oesophageal motility disorders or reflux disease. Associated cardiac or other complex abnormalities can also lead to compromised growth.[7] In persistent feeding problems we advise consulting a pediatrician or pediatric neurologist to rule out other pathology.

One of the strengths of the current study is that it gives a clear insight of the treatment in a relatively large cohort of infants with RS, and a structured and pragmatic algorithmic approach including the rationale of the decisions taken. This could be used as a guidance in other institutions. Moreover it provides a clear overview of approaches described in literature. Limitations include a possible selection bias as this is a tertiary centre. Also the retrospective nature of the study and the relatively short follow up period should be emphasized. Finally, we are fully aware that our approach could differ from the supporting medical system and regional habits of other institutions. Other treatment options, such as orthopedic appliances, have been described in current literature yielding very good results.[9, 13, 14] Yet, in our institution we don't have experience in using them. However, this does not preclude their beneficial use in infants with RS in other practices.

It should be addressed that many different treatment options could probably be performed on a patient. Each intervention has known (dis)advantages and the outcome depends on multiple factors. Burden of care, treatment duration, long term complications and financial implications should be considered.[65, 66, 72, 73] Furthermore, surgical skills and preferences will influence the approach of the treatment center.[25] It is demonstrated that mortality and morbidity is significantly lower in infants treated by the use of a decisional model.[40, 45] However, the choice of a specific treatment for an infant

with RS is a continuous and dynamic process, with multiple factors to be regarded and with many caretakers involved. The algorithm as presented in the current study should be used as a guideline, and not as a rigid decision tree since every patient is unique. Still, by using an algorithm, we hope to prevent possible unnecessary proceedings and a potential delay in treatment by helping involved caretakers in decision-making. Prospective studies will give us more insight in the outcome of the different strategies, which unfortunately do not exist to date. By using an algorithm it might be easier to compare the outcome of the different modalities in the nearby future.

CONCLUSIONS

RS is a heterogeneous disorder with numerous different treatment strategies described to date. A pragmatic approach is presented in this manuscript. The management of RS involves a multidisciplinary team approach to achieve a safe airway and adequate growth. We hope this manuscript will serve as a guidance for caretakers involved in the care for infants with RS and as an impetus for conducting future (preferably prospective) studies.

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11

Discussion

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Robin sequence (RS) is a heterogenic disorder, whose treatment involves different caregivers from various disciplines, with different views on the approach, diagnosis, and treatment of RS. Subsequently, this makes the treatment of these patients, sometimes critically ill infants, very challenging.

In this thesis, we aim to provide insight into several aspects of RS, mainly regarding diagnostics and treatment, and to facilitate decision-making, counselling of involved caretakers, and managing the expectations of parents, to optimize the care of infants with RS.

EPIDEMIOLOGY

RS generally occurs in 1 in 8,500 to 14,000 live births, depending on geography and ethnicity.[1, 2] Recently, two studies provided a more detailed insight into the Robin sequence population of the USA and Germany.[3, 4] The essential characteristics of RS are undefined, which may partially explain the lack of knowledge regarding RS epidemiology;[5-7] however, knowing the prevalence of RS will greatly aid in optimizing care and counselling parents and caregivers. The incidence of RS in the Netherlands is unknown; subsequently, our retrospective study in chapter 2 was conducted to clarify this. When adhering to the registration of RS in the Dutch Cleft Registry, managed by the Dutch Association for Cleft Palate and Craniofacial Anomalies (NVSCA), 246 CP patients were diagnosed with RS in the Netherlands during 2000-2010, yielding a birth incidence of 1:8,593 (11.6 per 100,000). As the agreement on associated anomalies between the Dutch Cleft Registry and the patient's medical charts has proven to be moderate to poor, a second data source was used.[8] Strict criteria were used to define RS: CP, micrognathia, and upper airway obstruction. A cohort of 376 infants with a cleft palate (CP), from three academic centres (Wilhelmina Children's Hospital (WCH) in Utrecht, the Academic Medical Centre/Emma Pediatric Hospital (AMC) in Amsterdam, and the VU Medical Centre (VUMC) in Amsterdam) were critically analysed. One-third of the CP population of the WCH/AMC/VUMC cohort suffered from RS. A birth prevalence of 1:5,641 (round off 1:5,600), or 17.7 per 100,000, was subsequently calculated for 2000-2010 in the Netherlands. On average, a more severe cleft grade was present in the RS population than in the CP population. The least registered feature of RS in both the Dutch Cleft Registry and regional patient medical records was glossoptosis, possibly explained by the absence of a dedicated field or text box for glossoptosis on the registration form of the Dutch Cleft Registry and uncertainty about what constitutes glossoptosis and the difficulty of establishing its presence. This study addressed the ongoing debate about the definition and diagnostic criteria of RS and the lack of a national database that accurately records the clinical characteristics of patients suspected of RS. A systematic review of the literature revealed that the prevalence of RS varied between 1:3,900 and 1:122,400 (0.8-32.0 per 100,000), with a mean prevalence of 1:24,500 (8.0 per 100,000). These varying numbers could be caused by differences in method, accuracy of the registration, or the criteria used to diagnose RS. Moreover, other factors, such as genetic, environmental, and socio-economic factors, may obviously influence the variance, which needs further prospective studying.[9-14]

PATHOGENESIS

RS is a causal heterogeneous disorder and a thorough investigation of the underlying pathogenesis is advisable. More than half of the infants born with RS will have an associated syndrome, chromosomal abnormality, or other additional anomalies.[15, 16] Stickler syndrome is the most common condition that features RS;[15] Stickler syndrome is an autosomal dominant connective tissue disorder with characteristic ocular, orofacial, auditory, and articular manifestation, most often caused by mutations in *COL2A1, COL11A, COL9A1* (recessive variant) or *COL11A2* (in the non-ocular type). Other associations with RS include chromosomal abnormalities (such as chromosome 22q11.2 deletion syndrome) or skeletal dysplasias (for instance, campomelic dysplasia spectrum).[17] In the same multicentre cohort (WCH/AMC/VUMC), retrospective analyses of all consecutive RS patients (defined as CP, micrognathia, and upper airway obstruction) born between 1995 and 2013 was performed (chapter3). The initial diagnoses of 191 patients were re-evaluated with a team of clinical geneticists. Seventy-two patients (37.7%) had an isolated form of RS; of the 119 (%) non-isolated patients, 14.3% (n=17) had a proven chromosome abnormality that likely explained the phenotype. A Mendelian disorder was diagnosed in 47.1% (n=56) of the non-isolated patients, of which Stickler syndrome (n=27) was the most frequently diagnosed; in 38.7% (n=46) there was an unknown cause. RS is not only causally heterogeneous, but also phenotypically and pathogenically variable.[18] In the patients with a reliably diagnosed etiology (n=73), the mechanism was a connective tissue dysplasia in 43.9% of the non-isolated patients, neuromuscular disorders in 5.5%, a multisystem disorder in 47.9%, and unknown or uncertain in 2.7% (chapter 3). The symptoms seen in RS can originate from multiple mechanisms, besides micrognathia and glossoptosis.[19] Consequently, under some circumstances, such as when the mandible is restricted from growth due to external factors, it might be better to wait and treat the infant with conservative measures, such as an NPA. In contrast, in tissue dysplasia, it might be better to consider surgery at an earlier stage, as it is not likely that the mandible will 'catch up' later in infancy. With improved understanding of the pathogenesis and subsequent expectation of the mandibular outgrowth potential, one could stratify the treatment according to the etiology and pathogenesis of RS. A longitudinal, multidisciplinary follow-up of the infants is therefore recommended, including a clinical geneticist.[20] Moreover, standardized recommendations regarding the kind of genetic diagnostics to be performed should be made in the future. Re-evaluation in our institution changed the diagnosis in 48 of the 191 patients (25.1%). This is also demonstrated in literature and again emphasizes standard follow-up of all RS patients over a prolonged period of time.[15] Several studies have investigated the genetic bases of RS and found some candidate gene loci, supporting a genetic basis for RS;[17, 21, 22] this emphasizes the importance of collecting a full family history of three generations to provide a clue about an underlying diagnosis. The present limited knowledge and insight into RS's pathogenic mechanisms suggests a need for additional pathogenetic studies, as optimal patient care will depend on such studies.

SYMPTOMS, APPROACH, AND ANALYSES

Respiratory distress and feeding problems are the two major problems for infants with RS. Neonates with RS present with respiratory obstruction varying from mild to severe, which generally begins directly after birth or during the first weeks of life.[23] Early recognition is of major importance, since respiratory obstruction is associated with considerable morbidity and even mortality. Hypoxemia can lead to pulmonary, haemodynamic, and cerebral problems, insufficient growth, and possibly affects normal neurocognitive and neurobehavioral development in the long term;[24-26] however, adequate (invasive) treatment, in cases of severe feeding and respiratory disorders, seems to protect the cognitive potential of RS children in the long-term.[27] Therefore, appropriate treatment strategy should be quickly anticipated.[23, 28] Published norms for arterial oxygen saturation levels range from 89% to 100%, depending on age.[24, 29-32] Different criteria to judge the severity of respiratory distress are described in the literature (chapter 10); some only use the number and depth of desaturations, obtained by continuous pulse oximetry, while others rely on measurements of polysomnography (PSG). Different cut-off values for mild, moderate, and severe respiratory distress are used and most studies are retrospective with a limited follow–up (see also Table 3, chapter 10). Although PSG is regarded as the 'gold standard' to diagnose obstructive or central sleep apnoea, PSG usage in the management of RS remains controversial and may not be needed in all cases.[33, 34] When severe obstructive episodes are present at the initial presentation, sometimes a quick surgical intervention is pursued, and there is no time for sleep studies. The value of the integration of the outcome of different obtained investigations, such as blood gas analyses, saturation levels, and flexible nasopharyngolaryngoscopy and subsequent clinical evaluation in a multidisciplinary team, should not be underestimated. In accordance with others, in our institution, PSG is only performed on indication, to exclude central apnoeas or to quantify more subtle airway obstruction if the clinical symptoms cannot or are only partially be explained by the visible airway obstruction[20, 35-39] (chapter10); however, PSG is a reliable method to determine and grade airway obstruction, and is a valuable tool for prospective studies to objectively compare the outcomes of different institutions. Yet, it is mandatory that important matters, such as the exact indication, frequency, and the extensiveness of the conducted tests regarding PSG, are clarified in further studies, and strict recommendations for its use in analysing RS infants can be made.

The average reported prevalence of feeding difficulties (FD) for RS is 47-100%, and an average of 55% (range: 11-100) of the infants are in need of nasogastric (NG) -tube feeding (chapter 9). This variance is due to the lack of a uniform definition of feeding problems.[40] In this thesis, feeding difficulties were defined as (parentally) reported problems regarding feeding (such as choking, regurgitation, gagging, distress, long-lasting feedings (≥30 minutes), impaired intake, and/or nasal regurgitation), which can lead to insufficient weight gain, failure to thrive, need for NG-tube feeding, and can potentiate airway or respiratory compromise. Adhering to this definition, RS patients had significantly more feeding difficulties (91%; n=63) than isolated cleft palate only (iCPO) patients

(72%; n=38) (chapter 9). Besides, NG-tube feeding was significantly more frequently necessary and for a longer period, as compared to iCPO infants. Growth in RS infants may be reduced in infancy, relative to standard growth curves and counterparts with isolated CP.[23, 41, 42] In this thesis, growth during the first two years of life was analysed; growth was significantly lower in the RS infants compared to an iCPO group, although it increased continuously in a steady line between the 0 and -1 SD of healthy Dutch infants. A possible explanation might be the presence of morphological characteristics as primary predisposing factors, supported by the finding that infants with a cleft have a tendency towards smaller cranial circumference.[43] Airway infections during 0-3 months of age are also identified as negatively affecting growth.[44] Genetic factors, especially the role of growth factors, might influence growth retardation in RS.[41] Finally, other origins, such as primary brainstem dysfunction or neuromotor disabilities (which might be more frequently present in RS infants, compared to iCPO patients), might generate feeding disorders and lead to subsequent growth retardation.[45, 46] Feeding in RS is complex, as multiple potential factors contribute to the infant's oral intake, growth, and respiratory status, and is further complicated by the presence of underlying syndromes and medical and developmental co-morbidities. Long-term effects of failure to thrive and growth impairment with regards of neurocognitive development of children have not been extensively studied;[47] however, it is known that they are prone to develop short-stature psychological problems, delayed development, and a lower IQ than children with a history of adequate growth.[47] Longitudinal follow-up to reveal possible effects of the lower weight on neurocognitive and neurobehavioral development in RS patients is needed. All in all, given the undeniable importance of early childhood in the ultimate growth and development of a child, adequate and timely management of FD is imperative for an optimal long-term outcome for the child. Prospective assessments in unbiased populations and the standard application of validated feeding assessments will be necessary to build evidence on which to base guiding standards of care for infants and children with RS.

CONSIDERATIONS REGARDING TREATMENT STRATEGY

An outline of the various treatment strategies for RS is provided in chapter 1. In accordance with the literature, the majority of the infants in our institution could be treated conservatively (chapter 10). In severe airway obstruction that improves with prone or side positioning therapy, NPA treatment should be pursued as the primary measure; however, a rather long duration of treatment, obstruction or luxation of the tube, the burden of care for the parents when the child is discharged with NPA, and persistent feeding problems during the treatment have been described (chapter 7).[48, 49] Mandibular distraction osteogenesis (MDO) has gained a lot of interest during the recent years. A literature analysis demonstrated that protocols vary and the different types of distractors all have their advantages and disadvantages. Internal MDO seems an effective option for very young infants, minimizing complications and side-effects, such as hypertrophic scarring, nerve damage,

and extensive care needs. Nevertheless, the indications for usage of an internal distractor are more limited compared to the external device, where, for instance, multivector distraction is possible and the greater strength of suprahyoidal muscles can be withstood. Proper patient selection, distractor type selection, and a multidisciplinary approach and workup to rule out associated lower airway anomalies are needed to gain optimal success rates (chapter 4).

MDO with a resorbable device in infants with RS was first described by Burstein in 2002.[50] Good short-term results are obtained, such as quick relief of the upper airway obstruction, possible quick resumption of oral feeding, and prevention of a tracheostomy or tongue lip adhesion, as previously demonstrated (chapter 5).[51-54] Yet, questions remain about the long-term results of MDO, especially with regard to tooth damage and mandibular outgrowth, compared to non-operated infants. To answer these questions, ten RS infants that underwent MDO were re-analysed, after a mean follow-up of 6.8 years (range: 5.0-7.9). In the MDO group: damage to the molars was present more often than in the control group; mandibular length was shorter but mandibular ramus height was comparable to the controls; a more vertical growth pattern was seen, compared to the control group; and 90% of cases had acceptable scar formation, lack of nerve injury, a patent airway, and good feeding capacity (chapter 6).

Complications to the molar buds are difficult to predict as these occupy a large proportion of the total infantile mandible volume, nearly approximating the inferior mandibular border. [53, 55-58][59] Prevention of damaging the molar buds is difficult, as the location of the osteotomy or the screws seems to be inevitably positioned at the location of the first permanent molar or second premolar. We think, in the long term, it will be either necessary to extract the affected first molar and reposition the second molar, or the affected molar can be restored with composite followed by orthodontic treatment. However, longer follow-up studies are mandatory and the exact consequences need to be elucidated further in the future. Mandibular length is known to be significantly shorter in both isolated RS infants and iCPO patients, with a more severe reduction in the RS group.[60-62] Greatest mandibular growth rates occur at 0.4–1 year of age, and bone growth and remodeling is a complex process characterized by a diverse set of mechanisms and contributions from primary growth centers and functional matrix of surrounding soft tissue.[59,63] Consequently, the reason for the shorter mandibular length in the MDO group can be multifactorial. It might, for instance, be explained by a preoperative shorter length of the mandibular body, compared to the RS controls. The severity of the micrognathia might be related to the severity of the airway obstruction; subsequently, these infants were more prone to receive MDO. Additionally, the smaller mandible might be the effect of a present associated disorder or syndrome.[64] Another possibility is that the smaller mandible could be a negative outcome of the distraction itself, as the intervention takes place at the moment of the highest growth velocity of the mandibular body.[63] Mandibular outgrowth might also be impeded by compromised vascularization to the condylar epiphyses, contractile forces caused by scarification of the periost due to the surgical procedure, or compression forces on the mandibular condyle by the distraction process. The more pronounced vertical growth might be partly due to the disorder

itself[65], a complication of MDO caused by an inappropriate vector, or by the pulling forces of the suprahyoidal muscles during the consolidation period. Further study is required to elucidate these matters on the long-term.

Modelling and vector planning, with the aid of 3D CT, use of surgiguides, and curvilinear internal or multidirectional external distractors, might assist in creating an optimal position of the distracted segment of the mandible. A longer consolidation period before removal of the distraction wire might reduce the forces of the suprahyoidal muscles. The application of growth factors to accelerate the consolidation period has also been investigated, but needs further study before usage in RS infants.[66, 67] In conclusion, the possibility of damage to the developing molars and the outgrowth potential and direction of the mandible, with a subsequent need for a secondary procedure, should not be underestimated, and should be weighed in the decision process for an optimal treatment strategy and management of parental expectations.

MDO is more cost-effective than tracheostomy in isolated RS infants, both with respect to direct and indirect costs. Homecare and work absenteeism made up 46% of the total costs in the tracheostomy group, compared to only 2% of the total costs in MDO. Hospital-related costs accounted for 53% of the total costs in the tracheostomy group; in MDO, these made up the majority of the total costs (89%) (chapter 8). The higher costs for tracheostomy, in both isolated and syndromic RS infants, compared to MDO were previously demonstrated.[68-70] Unfortunately, there are currently no cost-analysis studies that included the costs of tongue-lip-adhesion. Long-term data, including the cost of possible orthodontic and dental therapy for MDO, is also lacking.

The type of airway management (conservative or surgical) does not affect weight gain in infants (chapter 9). It is therefore hypothesised that adequate relief of the airway obstruction, either conservatively or surgically, is an important aspect in maintaining adequate growth.[71] This is substantiated by the findings of Daniel et al.[72], in which the degree of adequately-treated OSA (mild/moderate and severe) did not influence growth in their cohort of 39 infants with RS.[72] The type of surgery, however, does affect the prevalence of feeding difficulties and growth. After MDO, a significantly shorter postoperative duration of NG tube feeding was seen, compared to other interventions, which is in agreement with the results of Papoff et al.[54] Monasterio et al. also show that gastroesopageal reflux disappeared after MDO in 18 infants ;[73] this positive effect of MDO on feeding capacity and growth was confirmed by others.[74-79] In addition, Lidksy and co-authors[74] show that the timing of surgery (i.e., MDO within 3 months) dramatically reduces the need for feeding interventions in isolated RS patients. In contrast, Spring et al.[80] demonstrate that 7 out of 10 patients show a significant decline in weight at 6-8 weeks, 6 months, and 12 months after MDO, and stated that MDO performed at a young age may increase the risk of transient FD and growth decline post-operatively.[80] However, 70% of the infants in this study were fed orally post-operatively, which might be insufficient for these children to grow adequately.[80] The possible effect of the surgical intervention on growth remains uninvestigated. In chapter 9, we demonstrated that infants with RS receiving MDO or TLA had significantly lower weights during the first two years of life, as compared

to the tracheotomy subgroup. This might be a consequence of a disproportionate presence of comorbidities or syndromes in the various surgical subtype groups, or due to the longer NG-tube duration in infants treated with tracheotomy. Long-term studies are needed to elucidate the effects of surgical subtypes on further development and growth of infants.

CONSIDERATIONS REGARDING ASSOCIATED ANOMALIES

An additional syndrome or malformation makes the treatment regime especially challenging and a multidisciplinary approach indispensable. Significantly more infants in our series with non-isolated RS needed a surgical intervention due to severe upper airway obstruction (chapter 10). Less favourable airway outcomes are more common in nonisolated RS, potentially attributed to airway and swallowing problems independent of glossoptosis.[81-84] In addition, mandibular size and morphology vary significantly in syndromic RS (chapter 6).[64] Although we are aware that an associated syndrome could affect long-term mandibular outgrowth, this currently does not influence our initial treatment approach, as the respiratory distress still needs to be treated and will be alleviated by advancing the mandible. The need for a possible second intervention cannot be ruled out, and parents should be informed about that. No higher occurrence of feeding difficulties, need for NG-tube feeding, or longer duration of NG-tube feeding was found in the non-isolated RS infants, compared to the isolated infants. We were unable to illustrate a significant effect of the presence of an associated disorders or syndrome on growth (p=0.178), in agreement with other studies.[23, 72, 85-87] Still, infants with a syndromic diagnosis need closer follow-up to monitor growth, as concomitant disorders might negatively influence feeding capacity in the long term, which has not yet been systematically evaluated.

FUTURE PERSPECTIVES

Collaboration with the WCH/AMC/VUMC led to a consortium in order to establish a research line for RS. It is of major importance to join forces to obtain larger patient numbers to improve the quality of research. Additionally, in a rather small country like the Netherlands, it is important to breach the heterogeneity in the treatment approach and make more uniform decisions. In accordance with this, the first international consensus meeting on RS was held in Utrecht, the Netherlands in November 2014. During this two-day meeting, presentations were given by experts in specific fields of the care of RS patients. Many themes were discussed in small groups of the approximately 160 physicians and caregivers involved in the treatment of infants with RS who attended the meeting. This has led to closer international collaboration and will probably lead to more information about RS. The aim was to obtain consensus on several aspects regarding RS, which will be published in the near future. More prospective, randomized studies with large sample sizes are needed, using one single definition with objective criteria. Currently, studies investigating the reliability and value of flexible

laryngoscopy in diagnosing glossoptosis in RS and newer dynamic imaging techniques, such as cine MRI, are conducted. Also, the usefulness of 3D facial scanning to objectively determine the size of the mandible and follow its growth in and study the currently controversy of catch-up growth. Assessment of quality of life is an important facet in optimizing the care of a certain disorder. Therefore, a multicentre quality-of-life study is currently ongoing, by assessing various questionnaires to all RS infants and parents treated in the three Dutch Academic centres. Further investigation on the infant mortality rate of RS should be undertaken, as it might have implications on management and treatment and guide physicians toward effective treatment plans.[88, 89] Our knowledge on RS etiology and pathogenesis needs to increase; the possible involvement of both environmental and genetic factors need to be elucidated. Interaction between the presence of a cleft palate and micrognathia should be further investigated,[90, 91] as should the relation of relatively frequent hypodontia in RS, the micrognathia, and possible common underlying genetic causes.[65, 92, 93] This might give us further clues about the pathogenesis of RS and the role of possible yet unknown genetic influences or mechanisms.[22, 93, 94] Finally, standard application of other monitoring techniques, such as near-infrared spectroscopy oximetry as a way of monitoring cerebral oxygenation, might lead to an improvement in the treatment approach of infants with RS.[95-97] Further international collaboration will hopefully increase our knowledge in the future even more.

This thesis hopefully contributes as comprehensive guidance for caretakers involved in the care of infants with RS by revealing insights based on current knowledge. We further hope it will provide a foundation for the development and refinement of treatment approaches and an impetus for further investigations to increase our knowledge of this challenging patient group.

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12

Summary

Nederlandse samenvatting

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SUMMARY

Robin sequence (RS), a congenital malformation named after the French stomatologist Pierre Robin, consists of the triad of micrognathia, subsequently leading to glossoptosis and varying degrees of upper airway obstruction. In **chapter 1,** a description of the history, definition, etiology, symptoms, diagnostics, and different treatment options for RS is given; the most important controversies are described. Dr. Pierre Robin (1867-1950) is the one who accurately investigated and described the triad of symptoms. The currently accepted primary pathology of RS is congenital micrognathia; however, the abnormal arrest in mandibular development and forthcoming symptoms are causally heterogeneous. Moreover, the majority of infants with RS suffer an associated syndrome which can onset or aggravate the triad of symptoms. A concomitant cleft palate (CP) is often present. The expressed symptoms may vary in every child and depend on the underlying pathogenesis. Due to this complexity, a multidisciplinary approach during the diagnostic process is required. Numerous treatment options have been described to date; the primary goal is to maintain a safe airway and have adequate weight gain, growth, and development. Yet there is controversy amongst physicians regarding which treatment should be applied and when. When there is no life-threatening respiratory obstruction, a non-surgical approach is preferred, such as prone positioning or placement of a nasopharyngeal airway (NPA). Surgical intervention is currently pursued if there is a severe airway obstruction that is not alleviated by conservative measures; the most common described options include tracheotomy, tongue-lip adhesion, and mandibular distraction osteogenesis (MDO).

Data on RS epidemiology is scarce in the Netherlands. Therefore, in **chapter 2,** the frequency of RS in a CP population and the estimated birth prevalence in live births in the Netherlands, using distinct diagnostic criteria, is detailed. A retrospective population-based analysis of the National Cleft Registry was performed to obtain all CP patients registered in the Netherlands from 2000-2010, in addition to a thorough review of the medical records in three Dutch Academic Paediatric Hospitals (including data from the Wilhelmina Children's Hospital in Utrecht, the Academic Medical Center/Emma Pediatric Hospital, and the VU Medical Center in Amsterdam) for the same period. The Dutch birth prevalence of RS was estimated to be 1:5,600 live births (or 17.7 per 100,000), with a slight female predominance. RS was estimated to occur in a third of the CP population and patients with RS had a more severe cleft grade than the general CP population. An incomplete registration of the clinical characteristics of RS patients in the Registry leads to subsequent under-registration.

In **chapter 3**, the underlying pathogeneses in patients of RS are retrospectively analyzed. Over the study period of 1995-2013, 191 RS patients of the three aforementioned academic centres were re-evaluated with a team of clinical geneticists. Of the 191 patients, 72 (37.7%) had isolated RS. Of the 119 non-isolated patients, 14.3% had a chromosome anomaly, 47.1% (n=56) a Mendelian disorder, with Stickler syndrome being the most common (n=27), and in 38.7% (n=46), no detectable cause could be found. Stratification of diagnoses according to a (presumed) pathogenic mechanism showed that 43.9% had connective tissue dysplasia, 5.5% a neuromuscular disorder,

47.9% a multisystem disorder, and 2.7% an unknown mechanism. The initial diagnosis was adapted in 48 of the 191 patients (25.1%). This study demonstrated the importance of standard follow-up of all RS patients, specifically to (re-)evaluate diagnoses, during a prolonged period of time. It is emphasized that different pathogeneses for RS exist. The present limited knowledge and insight into pathogenetic mechanisms urges initiation of pathogenetic studies, as optimal patient care and the rationale behind a certain treatment strategy may depend on such studies.

In **chapter 4**, after a retrospective analysis of the literature, a general overview and information on post-operative outcomes and the complications from the different type of distractors for the treatment of upper airway obstruction in RS is provided. The primary advantage of the external distractor is the ability to use multivector movements that can be adjusted during the distraction phase. In internal MDO, there is a smaller risk of pin-associated infections, hypertrophic scarring, and damage to the marginal mandibular branch of the facial nerve. Moreover, it averts the disadvantages of a cumbersome external device during the distraction and consolidation period. The need for a second operative procedure for removal of the hardware is obviated by the use of an internal resorbable distractor. This method seems very feasible in RS infants suffering upper airway obstruction and is a good alternative for a tracheotomy.

In the Wilhelmina Children's Hospital, MDO with a resorbable device has been performed as surgical treatment for infants with RS since 2007. In **chapter 5,** the short-term results of twelve patients are described. The infants (mean age 32 days, range: 11-94) could be extubated after a mean of 7.6 days, (range: 5-11) and stayed, on average, 17 (range 11-27) days in the hospital. Short-term complications comprised a low-grade skin infection at the entry site of the distraction wire (n=1), resolved with antibiotic ointment and oral antibiotics; an incomplete osteotomy (n=1); and technical failure of one distraction drive screw after 95% of the distraction was completed (n=1). Complications did not hamper distraction. Oral feeding was resumed within four weeks after MDO in all infants. MDO reveals good short term results; however, the long-term effects, especially with regard to teeth development and mandibular outgrowth, are unknown.

Therefore, our long-term experience with MDO with a resorbable device in 10 infants is provided in **chapter 6**. Mean age at the time of surgery was 3.7 months (median: 19 months; range: 11 days to 27 months). Mean follow-up was 6.8 (5.0–7.9) years. Ten RS infants without MDO (mean follow-up, 7.4 (6.7–8.9) years) were used as controls. Panoramic and lateral cephalometric radiographs were analyzed by a dentist, maxillofacial surgeon, and plastic surgeon. Patients were also recalled for physical examination. Shape anomalies, positional changes, and root malformations of molars were seen significantly more often in MDO patients than in the control group. Mandibular length was shorter, but mandibular ramus height was comparable with the non-MDO group. A more vertical growth pattern was seen in the MDO group. These results might be partly due to the heterogeneity of RS or a possible underlying syndrome. Compared with healthy controls, all RS infants had a significantly shorter mandibular length. Acceptable scar formation, lack of nerve injury, a patent airway, and good feeding capacity were seen in 90% of cases. A comparable DMFT (Decay Missing

Filled Teeth, in mixed dentition) score was seen between the two groups. MDO with a resorbable system reveals an effective surgical option in the treatment of upper airway obstruction in infants with RS, but the possible effects on developing molars and mandibular outgrowth likely necessitate secondary procedures on the long-term. This factor should be considered when deciding on treatment options and counselling of parents.

In NPA treatment, an endotracheal tube is inserted (under endoscopic vision) into the nose, so that it ends just superior to the epiglottis and thus opens the obstructed nasopharyngeal space. This technique has, since 1982, been successfully applied in infants with RS suffering upper airway obstruction and many authors confirmed the benefits and demonstrated clinical improvement. Still, possible drawbacks include blockage of the tube, dislodgment, irritation of the larynx by inadequate positioning, prolonged treatment duration, and parental burden of care. In **chapter 7**, the results of a study, in which the first long-term results of NPA applied to 104 infants with RS are described, are discussed. In conclusion, some infants can be successfully treated with a NPA and it is a feasible, relatively minor invasive treatment option, which should be incorporated in a treatment algorithm for infants with RS as a primary measure; however, we want to stress that each case should be individually analyzed and that MDO should be considered a possible alternative in the treatment regime, due to the relatively quick process, less cumbersome home care situation, and good results regarding respiratory and feeding problems.

For a long time, tracheostomy was considered the 'gold standard' for the treatment of severe respiratory distress in infants with RS. However, it is known that tracheostomy is related to a high percentage of both early and late complications, such as (airway) infections, granulation or fistulae, feeding and swallowing difficulties, or accidental decannulation and cannula obstruction. As the medical system requires both functional outcomes and cost-effectiveness, in **chapter 8,** a cost-analysis study between distraction osteogenesis and tracheostomy is presented. Average direct costs (hospitalization, diagnostics, surgery, and homecare) were three times higher for tracheostomy. Average indirect costs (work absenteeism) were almost five times higher. There was a threefold increase in average total costs per patient (both direct and indirect) for tracheostomy and four times as many complications were encountered. Tracheostomy seems only indicated as a surgical option to treat a subglottic problem in infants with RS.

In addition to the varying degrees of respiratory problems, infants with RS frequently have feeding difficulties that can lead to growth retardation. In **chapter 9,** a retrospective, comparative cohort study is presented, consisting of 69 infants diagnosed with both RS and a cleft palate, and 64 isolated cleft palate only (iCPO) infants. Data regarding FD, growth, and airway intervention were collected during the first 2 years of life. RS patients had significant more FD than iCPO patients. In RS patients, nasogastric-tube feeding was necessary significantly more frequently and for a longer period than in iCPO infants. Growth was lower in RS than iCPO infants; however, both weight curves were in between the 0 and -1 SD line of healthy counterparts. Growth was not affected by the kind of airway management (conservative/surgical), cleft palate grade, or associated disorders. FD is

present in a large proportion of infants with RS, which indicates the need for early recognition and proper treatment to ensure optimal growth. Long-term studies are needed to evaluate the effect of the lower growth on further development of infants with RS.

RS is a heterogenic group with a wide spectrum of associated anomalies; a review of the literature illustrates that the approach and treatment is just as variable. In **chapter 10**, the results of this review and a retrospective cohort study among 75 infants diagnosed with RS and managed at our institution in the 1996-2012 period is presented. The majority of the infants (59%) were treated conservatively. A significantly larger proportion of non-isolated RS infants needed surgical intervention than isolated RS infants. A mandibular distraction was conducted in 24% (n=18) of cases, a tracheotomy in 9% (n=7), and a tongue-lip-adhesion in 8% (n=6). The decision process is challenging and a multidisciplinary, uniform approach to treatment is desirable. The results of clinical observation and additional investigations are carefully analyzed and the different treatment options are weighed, both with the involved caregivers and the parents. Although an individual plan per patient is recommended, we present our institutional approach in a pragmatic way. We provide a comprehensive and pragmatic approach to the analysis and treatment of infants with RS, which could serve as useful guidance in other clinics to allow better comparison of results, particularly prospective studies.

In **chapter 11,** the main results and conclusions of this thesis are described. The current knowledge, remaining controversies, and future perspectives are discussed. The purpose of a multidisciplinary and uniform approach is emphasized. There is an essential need for an evidence-based management strategy with objective measures to further optimize the treatment of RS patients in the future. We hope this thesis will provide a foundation for the development and refinement of treatment approaches and an impetus for further investigations to increase our knowledge of this challenging patient group.

NEDERLANDSE SAMENVATTING

Robin sequentie (RS), is een aangeboren afwijking veroorzaakt door een te kleine onderkaak ("micrognathie"), wat leidt tot een te ver naar achter gelegen tong ("glossoptosis"). Dit kan uiteindelijk weer verschillende gradaties van ademhalings- en voedingsproblemen veroorzaken. In **hoofdstuk 1** wordt een uiteenzetting gegeven van de geschiedenis, definitie, etiologie, symptomen, diagnostiek en verschillende behandelopties voor RS. Ook worden de belangrijkste controversen over deze aandoening aangehaald. RS is vernoemd naar de Franse hoogleraar Mondziekten, dr. Pierre Robin (1867-1950). Hij is de eerste die de drie belangrijkste bij de aandoening behorende symptomen, uitgebreid onderzocht en beschreef. Er bestaan verschillende theorieën over de ontstaanswijze van de micrognathie en de daaropvolgende symptomen. In de meerderheid van de gevallen is er ook sprake van een bijkomstig syndroom of chromosomale afwijking, hetgeen de directe aanleiding kan zijn van RS of de symptomen kan verergeren. Veel kinderen met RS hebben daarnaast een gehemeltespleet. Vanwege de complexiteit van RS is bij de diagnostiek een multidisciplinaire aanpak vereist. Er zijn talrijke benaderingen beschreven maar er is nog geen algemeen geaccepteerd beleid in de diagnostiek van RS. Ook zijn er veel verschillende behandelmethodes beschreven, welke allen het doel hebben om een vrije ademweg te creëren. Initieel wordt gekeken of dat bereikt kan worden met conservatieve methoden, zoals buik- of zijligging (zodat de tong naar voren valt) of een buisje door de neus ("nasopharyngeale tube"). Als dit onvoldoend effect sorteert, kan overgegaan worden tot chirurgische behandeling. Tracheotomie, tong-lip-adhesie en mandibulaire distractie osteogenese zijn de meest beschreven chirurgische methoden.

Het voorkomen van RS in Nederland is nog niet eerder onderzocht. Dit wordt in **hoofdstuk 2** opgehelderd. Door gebruik te maken van de data van de Nederlandse Vereniging voor Schisis en Craniofaciale Afwijkingen (NVSCA) en de medische dossiers van alle schisiskinderen, behandeld in het Wilhelmina Kinderziekenhuis Utrecht (WKZ), Emma Kinderziekenhuis/Academisch Medisch Centrum Amsterdam (AMC) en de Vrije Universiteit Amsterdam (VUmc) over de periode 2000-2010, werd de geboorte prevalentie berekend. Het geschatte voorkomen in Nederland ligt op 1:5.600 pasgeborenen (of 17,7 per 100.000 pasgeborenen). Eén derde van de kinderen met een gehemeltespleet blijkt ook RS te hebben. RS is onder geregistreerd in de NVSCA database, waarschijnlijk ten gevolge van onduidelijkheid over de definitie of omdat de diagnose ten tijde van de registratie nog niet gesteld was.

In **hoofdstuk 3** worden alle kinderen met RS die in de periode van 1995-2013 in het WKZ, AMC en het VUmc behandeld zijn, opnieuw geëvalueerd door klinisch genetici uit het betreffende schisisteam. Het doel van deze studie was de diagnose en pathogenese te onderzoeken. Van de 191 patiënten geanalyseerde patiënten bleken 72 (37,7%) een geïsoleerde vorm van RS te hebben. Van de 119 niet geïsoleerde patiënten had 14,3% een bewezen chromosomale afwijking die het fenotype verklaarde. Een Mendeliaanse aandoening was in 47,1% (n=56) aanwezig, waarbij Stickler syndroom het meest vaak voorkwam (n=27). In 38,7% (n=46) kon er geen oorzaak voor de symptomen gevonden

worden. In 43,9% was er sprake van een bindweefsel dysplasie, in 5,5% van een neuromusculaire oorzaak en in 47,9% een multisysteem aandoening. In 2,7% bleef de pathogenese onduidelijk of onbekend. De diagnose werd in 25,1% (n=48) van de gevallen aangepast. Deze studie bevestigt de heterogeniteit in de pathogenese en het belang van een klinisch genetische analyse en een langdurige follow up. Meer kennis van de achterliggende pathogenese zou de uiteindelijke keus voor behandeling kunnen beïnvloeden.

Eén van de chirurgische behandelmethodes die voor RS beschreven wordt, is mandibulaire distractie osteogenese (MDO). Door het doornemen van de onderkaak en deze vervolgens mechanisch te verlengen, komt de tongbasis meer naar voren te liggen met als doel de luchtweg te verruimen. Er zijn verschillende methodes van MDO beschreven welke in **hoofdstuk 4**, na een review van de huidige literatuur, worden uiteengezet. Het voordeel van een externe distractor is de mogelijkheid tot multivector distractie. Voordelen van een interne distractor zijn minder littekenweefsel, minder kans op huidinfectie en zenuwschade en een doorgaans makkelijkere verzorgbaarheid en acceptatie door de ouders (doordat er minder osteosynthese materiaal aan de buitenkant zichtbaar is). Nadeel van beide technieken is dat er altijd een tweede chirurgische ingreep noodzakelijk is om het osteosynthese materiaal te verwijderen. MDO met een oplosbaar distractie systeem lijkt met name bij zeer jonge kinderen met RS en bovenste luchtwegobstructie, welke niet conservatief te behandelen is, een goed alternatief voor een tracheotomie.

MDO met een oplosbare distractor wordt sinds 2007 in het WKZ voor de behandeling van neonaten met RS toegepast. In **hoofdstuk 5** worden de korte-termijnresultaten hiervan bij 12 patiënten beschreven. De kinderen werden gemiddeld 32 dagen (range 11-94) na de geboorte geopereerd. Ze konden gemiddeld 7,6 dagen (range 5-11) na de operatie gedetubeerd worden en bleven in totaal gemiddeld 17 dagen (range 11-27) in het ziekenhuis. Complicaties bestonden uit het spontaan luxeren van de distractieschroef tijdens de consolidatiefase (n=1), een incomplete osteotomie (n=1) en een milde wondinfectie (n=1). De complicaties genazen zonder verdere interventie en hadden geen effect op het uiteindelijke resultaat van de distractie. De helft van de patiënten verliet het ziekenhuis zonder sondevoeding en de andere helft kon binnen vier weken na de operatie overgaan op volledige fles- of borstvoeding. Vragen over de lange-termijnuitkomsten van MDO bleven echter bestaan. Met name het effect en de eventuele schade aan de tandkiemen en de invloed op de kaakontwikkeling verdienen aandacht.

In **hoofdstuk 6** worden de lange-termijnresultaten van tien kinderen met RS die MDO met een oplosbaar systeem ondergingen, beschreven. De gemiddelde follow-up was 6,8 jaar (range: 5,0-7,9). De controle groep bestond uit tien kinderen met RS die geen MDO ondergaan hadden. De gemiddelde follow up van de controle groep was 7,4 jaar (range: 6,7-8,9). Zowel het orthopantomogram als een röntgenschedel-profiel-foto werden geanalyseerd door een tandarts, orthodontist, kaakchirurg en plastisch chirurg. Ook werden de kinderen opgeroepen voor een tandheelkundig en lichamelijk onderzoek. Er werden in de MDO groep meer positionele afwijkingen, wortelschade en hypoplasiën van de (kiemen) van de molaren gezien, in vergelijk met de controle groep. De lengte van de

onderkaak was significant korter, maar de lengte van de ramus was gelijk. Er werd ook een meer verticaal groeipatroon gezien. Deze verschillen kunnen het gevolg zijn van de heterogeniteit van de aandoening of aanwezigheid van een onderliggend syndroom. De gemiddelde DMFT (Decayed Missing Filled Teeth, in wisseldentitie) score was vergelijkbaar tussen de twee groepen. Tenslotte werd er een fraaie littekengenezing gezien in de MDO groep en een goede functie van de ramus marginalis mandibulae van de n. facialis en de n. alveolaris inferior. Bij één kind was er sprake van een recidief obstructief probleem van de luchtweg, waardoor een nieuwe distractie plaatsvond met een curvilineaire distractor op vijfjarige leeftijd. MDO met een oplosbaar distractiesysteem is een effectieve chirurgische optie bij de behandeling van ademwegproblematiek bij neonaten met RS. De noodzaak voor secundaire (orthodontische) behandelingen en correcties op de lange termijn kunnen echter niet worden uitgesloten en moeten in overweging genomen worden bij het bepalen van de behandelstrategie en bij de voorlichting aan de ouders.

Nasopharyngeale airway (NPA) is een conservatieve behandelmethode voor RS, waarbij een flexibele canule via een neusgat tot vlak boven de epiglottis wordt ingebracht, om zo de nasopharyngeale ruimte open te houden. De techniek wordt sinds 1982 met succes bij kinderen met RS met een luchtwegobstructie toegepast. Toch kleven er ook enkele nadelen aan deze techniek, zoals accidentele luxatie van de canule, mogelijke irritatie van de larynx bij verkeerde positionering en een vaak langdurig behandeltraject met bijkomstige belasting van de ouders. In **hoofdstuk 7** wordt een publicatie -waarin de eerste lange-termijnuitkomsten van NPA bij 104 kinderen met RS worden beschreven- bediscussieerd. NPA is een effectieve methode die, indien mogelijk, in het eerste stadium toegepast moet worden als behandeling van bovenste luchtwegobstructie bij kinderen met RS. Echter, andere behandelopties zoals MDO, moeten in het behandeltraject niet per definitie uitgesloten worden. Het verdient aanbeveling de voor- en nadelen van de mogelijke alternatieven per individu af te wegen en met de ouders te bespreken.

Tracheotomie werd lange tijd als "gouden standaard" gezien in de chirurgische behandeling van bovenste luchtwegobstructie bij kinderen met RS. Het is echter bekend dat een tracheotomie kan leiden tot complicaties zoals stenosering, fistels, overmatig littekenweefsel, luchtweginfecties of zelf accidentele decannulatie. Aangezien naast uitkomsten van een bepaalde behandeling ook aandacht besteed moet worden aan de kosteneffectiviteit, is in **hoofdstuk 8** een kostenanalyse tussen tracheotomie en MDO verricht. In een retrospectieve analyse van negen geïsoleerde RS patiënten werd gezien dat de gemiddelde directe kosten (ziekenhuis, diagnostiek, operatieve ingreep en thuiszorg) drie keer zo hoog waren voor de tracheotomiegroep als voor de MDO groep. De gemiddelde indirecte kosten (werkverzuim) waren vijf keer zo hoog. Tenslotte werden er vier keer zoveel complicaties gezien in de tracheotomie groep. Tracheotomie lijkt als chirurgische optie bij de behandeling van RS alleen geïndiceerd bij ademwegobstructie ten gevolge van een subglottisch probleem.

Naast de ademwegobstructie, hebben kinderen met RS ook vaak problemen bij de voeding, waardoor uiteindelijke groeiretardatie kan ontstaan. In **hoofdstuk 9** wordt het gewicht van 69

kinderen met RS vergeleken met 64 kinderen met een geïsoleerde palatoschisis (iCPO), gedurende de eerste twee levensjaren. Ook werd gekeken naar de invloed van verschillende parameters op de groei. Voedingsproblematiek kwam significant vaker voor bij kinderen met RS dan kinderen met een iCPO. Ook was er significant vaker sondevoeding nodig bij de RS groep gedurende een langere periode dan in de iCPO groep. De groei was in de RS groep significant lager dan in de iCPO groep, maar beide groeicurves bevinden zich tussen de 0 en de -1 SD lijn van de gezonde populatie. Groei in de RS groep werd niet beïnvloed door de soort interventie (conservatief vs. chirurgisch), de schisis gradatie of de aanwezigheid van geassocieerde afwijkingen. Het is van belang dat de groei bij kinderen met RS nauwkeurig wordt vervolgd, en een afwijking in de groei tijdig en adequaat wordt behandeld. Lange-termijn prospectieve studies zijn nodig om het effect van de slechtere groei op de ontwikkeling van kinderen met RS te kunnen evalueren.

Patiënten met RS vormen een heterogene groep. Een literatuurstudie laat zien dat ook de benadering en behandeling minstens zo variabel is. In **hoofdstuk 10** worden de resultaten van deze literatuurstudie en van een retrospectieve analyse van 75 patiënten met RS, die tussen 1996-2012 in het WKZ behandeld zijn, beschreven. De meerderheid (59%) van de patiënten met RS kon conservatief behandeld worden. In de chirurgisch behandelde groep zaten significant meer kinderen met een aanvullend syndroom of geassocieerde afwijking. In 24% (n=18) van de chirurgisch behandelde patiënten werd MDO verricht, in 9% (n=7) een tracheotomie en in 8% (n=6) een tong-lip-adhesie. Hoewel een individueel aangepaste aanpak per patiënt vereist is, trachtten we de institutionele benadering op een pragmatische wijze weer te geven. Er wordt gestreefd naar een multidisciplinaire aanpak waarin de resultaten van klinische observatie en aanvullend onderzoek zorgvuldig geanalyseerd worden. Hierna worden de verschillende behandelopties afgewogen, zowel met de betrokken artsen als met de ouders. Met het beschreven algoritme wordt gepoogd een handvat te bieden aan centra waar kinderen met RS behandeld worden. Uitkomsten, liefst van prospectief onderzoek, kunnen in de toekomst dan ook beter met elkaar vergeleken worden.

In **hoofdstuk 11** worden de belangrijkste bevindingen van dit proefschrift beschreven. Zowel de huidige kennis waarover we beschikken als de bestaande controversen worden bediscussieerd. Het doel van een gezamenlijke, eensgezinde aanpak wordt benadrukt. Tevens worden de toekomstige ontwikkelingen en de noodzaak tot vervolg onderzoek uitgewerkt, in de hoop meer kennis op te doen over deze interessante patiënten populatie en de behandeling ook in de toekomst verder te kunnen optimaliseren.

ADDENDUM

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LIST OF ABBREVIATIONS

RS	Robin sequence
MG	micrognathia
RG	retrognathia
Gl	glossoptosis
CP	cleft palate
iCPO	isolated cleft palate only
ORD	obstructive respiratory distress
UAO	upper airway obstruction
NPA	nasopharyngeal airway
MDO	mandibular distraction osteogenesis
Tr	tracheotomy
TLA	tongue lip adhesion
PSG	polysomnography
NG-tube	nasogastric tube
FD	feeding difficulties

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ABOUT THE AUTHOR

Emma Paes was born on April 19th, 1984 in Mainz, Germany. She moved to the Netherlands at the age of eight and graduated from the Bernardinuscollege in Heerlen in 2002, after which she started to study medicine at the University of Utrecht. During her studies she participated as a member of the UNICEF Student Committee and worked as a teacher at the skills lab of the anatomy department of the University of Utrecht. She was also a tour guide at the university's anatomical museum "Bleulandinum" and at the Dom Tower of Utrecht. Whenever possible she held internships abroad, and spent several months in Brazil, Surinam, Tanzania, and Dubai. She always had a passion for surgery; perhaps due to the great stories of her parents, who worked in a missionary hospital in Kenia for three years as general surgeon and nurse. Her interest in plastic surgery primarily developed through her activities in the anatomy department. This is also where she conducted her first scientific work under the guidance of Dr. P.P.A. Schellekens, by performing cadaver dissections to investigate the anatomic features of the internal mammary artery perforator flap.

After finishing medical school in 2009, she worked for a year as a resident in the plastic surgery department of the Erasmus Medical Centre in Rotterdam, and for another four months at the pediatric plastic surgery department at the Wilhelmina Children's Hospital in Utrecht. During the latter residency, she was given the opportunity to start her training in plastic surgery in Utrecht. Thanks to Dr. C.C. Breugem she became interested in Robin sequence and all the research that could still be conducted in this field. Awaiting the start of her training, Emma chose to work another year as a junior teacher in head and neck anatomy under the auspices of professor R. Bleys in the anatomy department. She also continued her work on her PhD thesis on the Robin sequence. In 2011, she commenced her first two years of residency at the surgical department of the Diakonessenhuis in Utrecht (Dr. T. van Dalen). Currently, she is continuing her training at the University Medical Center Utrecht (Dr. A.H. Schuurman). Recently, she was given the opportunity to go on a cleft surgery mission in Morocco together with Breugem. This experience increased her enthusiasm for pediatric and reconstructive plastic surgery.

Besides her work, she loves running, triathlons, traveling, nature and cooking. Emma is married to Victor van den Berg.