Pierre Robin Sequence

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KEYWORDS

• Pierre Robin sequence • Cleft palate • Micrognathia • Glossoptosis • Distraction

KEY POINTS

- Pierre Robin sequence (PRS) consists of the clinical triad of micrognathia, glossoptosis, and airway compromise with variable inclusion of cleft palate.
- Management of airway obstruction in PRS consists of nonsurgical maneuvers, such as prone positioning and nasopharyngeal stenting; surgical management includes mandibular distraction and tongue-lip adhesion.
- Diagnostic evaluation of patients with PRS includes nasoendoscopy and bronchoscopy for the airway and a multidisciplinary approach for multisystemic anomalies in syndromic patients.

Video content accompanies this article at http://www.plasticsurgery.theclinics.com.

INTRODUCTION

Pierre Robin sequence (PRS) consists of the clinical triad of congenital micrognathia, glossoptosis, and airway obstruction with variable inclusion of a cleft palate (**Fig. 1**). When this constellation of findings occurs in the absence of other congenital anomalies, it is termed isolated PRS; however, PRS oftentimes finds itself a component of a more complex syndromic picture. This phenotypic heterogeneity arises from a permutation of mechanical, genetic, and environmental derangements. The variable complexity of the patient presentation lends itself to a multidisciplinary approach in uncovering the diagnosis, managing the airway obstruction, optimizing the feeding, and addressing the multisystemic abnormalities intrinsic to the syndromic patient. Although nearly a century has passed since the description of Robin's eponymous triad, incongruities remain regarding treatment protocols among different centers. This lack of consensus reflects the high degree of difficulty in the management of such a diverse patient population, a challenge that cannot be overstated.

HISTORICAL PERSPECTIVE

In 1835, Von Siebold described a case of micrognathia, microglossia, and glossoptosis in an infant who ultimately succumbed to asphyxia.[1] Nearly a century later, French stomatologist Pierre Robin's[2] seminal 1923 paper described the same constellation of findings, namely glossoptosis in the presence of micrognathia, highlighting the dire consequences to the airway. The historical literature is littered with various authors who separately encountered and described this set of findings, including St. Hillaire in 1822, Fäsebeck in 1842, Fairbairn in 1846, and Shukowski in 1911.[3] Ultimately, these collections of findings assumed the eponymous title of Pierre Robin sequence.

EPIDEMIOLOGY

The incidence of PRS ranges from 1 in 8000 to 1 in 14,000.[4,5] Mortality for infants with PRS ranges from 1.7% to 11.3%; the rate increases to 26% when examining only the subset of syndromic patients.[6] Although cleft palate is not a strict criterion

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Fig. 1. Lateral view of infant with PRS, which consists of the clinical triad of retromicrognathia, glossoptosis, and airway compromise with variable inclusion of a cleft palate.

for the diagnosis of PRS, 85% of these patients present with a concomitant cleft.[4] The incidence of these patients presenting with an associated syndrome is 38% to 44%. Male and female individuals are affected at an equal rate.[4,5,7]

INTRAUTERINE DEVELOPMENT

Craniofacial morphogenesis begins with delamination of neural crest cells from the dorsal neural tube into ventral pharyngeal arches.[8,9] The first pharyngeal arch forms the maxilla and mandible through intramembranous ossification. The Meckel cartilage serves as the initial scaffold onto which mandibular intramembranous ossification occurs, orienting mandibular growth in a proximo-distal configuration.

Maxillary development occurs concomitantly with mandibular outgrowth. Lateral palatal shelves extend from the maxillary arches at approximately the seventh week of gestation and begin to grow in a sagittal plane adjacent to the tongue.[8]

As mandibular outgrowth continues, the tongue is flattened and distracted anteriorly by the genioglossus, originating on the lingual surface of the mandible.[8] This facilitates reorientation of sagittal palatal shelves into a transverse plane. The medial edge epithelia fuse in coordinated fashion in an anterior-to-posterior direction on the eighth week, as illustrated in **Fig. 2**.

Classically, the inciting insult in PRS is a micrognathic mandible that obligates retropositioning of the tongue base, predisposing the infant to glottic airway compromise. Inability of the tongue base to descend from the roof of the nasopharynx causes a physical blockade to palate formation, preventing appropriate elevation, medialization, and fusion of the palatal shelves.[8]

GENETIC FINDINGS

There is no classic causal relationship between PRS and a single genetic mutation, but rather a wide swath of genetic errors that have been associated with a variety of phenotypic presentations. **Box 1** contains a list of associated syndromes.

Approximately 26% to 83% of PRS diagnoses are part of a syndrome, most commonly Stickler syndrome, 22q11.2 Deletion Syndrome, Treacher Collins syndrome, and Campomelic Dysplasia, among others.[10,11] Approximately 11% to 18% of patients with PRS are diagnosed with Stickler syndrome, a connective tissue disorder impacting collagen metabolism.[8] Ocular findings are most prominent, presenting as myopia, vitreous abnormalities, glaucoma, retinal detachment, and cataracts. Skeletal sequelae, hearing loss, and craniofacial anomalies may be present. Velocardiofacial syndrome accounts for approximately 11% of patients with PRS.[10] Now known as 22q11.2 Deletion Syndrome, findings include learning disability, micrognathia, cleft palate, long philtrum, conductive hearing loss, hypoparathyroidism, and thymic aplasia.

DIAGNOSIS AND INITIAL MANAGEMENT

Patients with PRS frequently have other systemic anomalies that warrant a multidisciplinary approach to their diagnosis and management.[12] A comprehensive evaluation may require involvement of specialties such as maternal-fetal medicine, genetics, neonatology, pulmonary and sleep medicine, developmental pediatrics, plastic surgery, oral surgery, orthodontics, dentistry, otolaryngology, ophthalmology, pediatric surgery, cardiology, speech pathology, feeding specialists, audiology, and neurology.

PRENATAL IMAGING

Diagnostic workup may start in the prenatal period with ultrasound or MRI.[12] Micrognathia may be difficult to diagnose via ultrasound, with sensitivity of 72.7%.[13] Normalization of the mandibular anteroposterior length by the biparietal skull width creates a jaw index, which improves ultrasound sensitivity to 100% and specificity to 98.1%.[14] The positive predictive value for diagnosing PRS versus isolated micrognathia correlates directly with the maxillomandibular discrepancy.[13,15] Polyhydramnios is

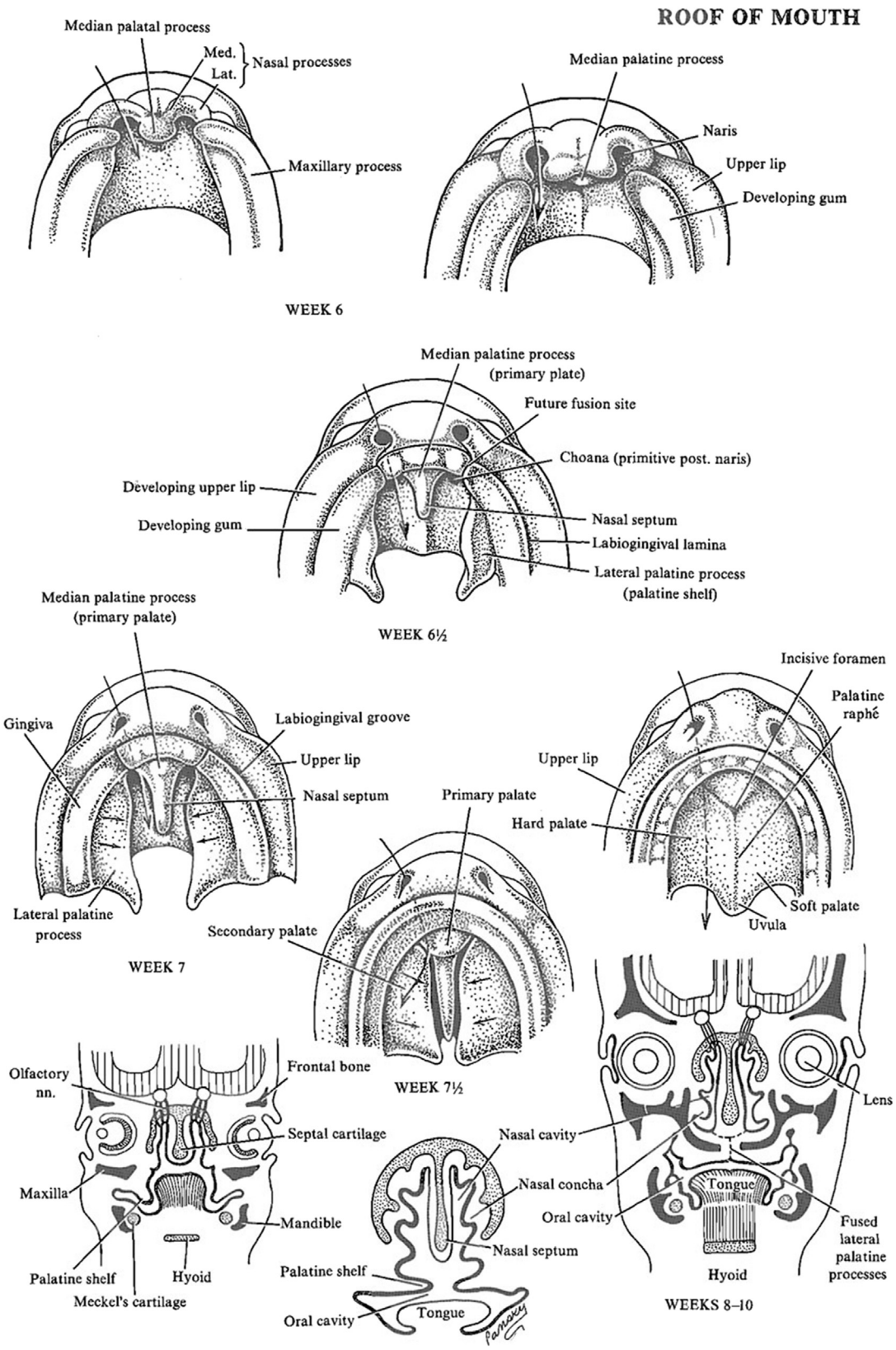

Fig. 2. Normal intrauterine development of primary and secondary palate with reorientation of the palatal shelves from a vertical to horizontal position. A retrognathic mandible leads to retropositioning of the tongue, which impedes this fusion process. (*From* https://discovery.lifemapsc.com/library/review-of-medical-embryology/chapter-55-development-of-the-palate. Accessed May 1, 2018.)

Box 1
List of syndromes most frequently associated with Pierre Robin sequence

Associated Syndromes
Stickler syndrome
22q11.2 Deletion syndrome
Treacher Collins syndrome
Campomelic dysplasia
Marshall syndrome
Nager syndrome
Miller syndrome
Kabuki syndrome
Catel-Manske syndrome
Congenital myotonic dystrophy
Carey-Fineman-Ziter syndrome
Fetal alcohol syndrome
Maternal diabetes
Spondyloepiphyseal dysplasia congenita
Hemifacial microsomia
Glass syndrome
Mandibulofacial dysostosis

associated with impaired swallowing secondary to glossoptosis.

AIRWAY EVALUATION

Airway obstruction is life-threatening for the neonate. Prolonged obstruction results in hypoxia, apnea, respiratory tract infections, aspiration, compromised feeding, and failure to thrive.[16] Chronic hypoxia leads to increased pulmonary vascular resistance, cor pulmonale, heart failure, and cerebral hypoxia.[16]

Robin[2] attributed neonatal airway compromise to posterior displacement of the tongue base. This decreases the cross-sectional area of the oropharynx, limiting mass flow rate of oxygen during respiration and predisposing the upper airway to collapse during inspiration.[17]

Physical examination provides a clinical gestalt of the patient's respiratory effort through observations of stridor, positional retraction of the chest and neck, positional desaturation, cyanosis, and feeding difficulty (Video 1).[6] Nasopharyngoscopy may reveal synchronous lesions, such as subglottic stenosis, laryngomalacia, tracheomalacia, bronchomalacia, choanal atresia, tracheal stenosis, and aspiration bronchitis.[18]

Polysomnography quantifies obstruction events and gas exchange disturbances, although utility of the apnea-hypopnea index (AHI) is limited by the lack of standardized neonatal normative values.[13] Sleep studies differentiate between obstructive and central sleep apnea, the latter prompting greater consideration before surgical intervention. Polysomnography as a diagnostic tool is not uniformly adopted. Opponents highlight the absence of an objective threshold with which to gauge the clinical severity of the airway obstruction.[13] Syndromic patients may be longitudinally assessed through serial polysomnography, nasopharyngoscopy, and physical examination as they mature.

FEEDING

Feeding may be dysfunctional secondary to the cleft palate (if present), hypoplastic mandible, and dynamic exacerbation of airway obstruction. Speech pathology monitors feeding sessions for signs of dysphagia, such as coughing, choking, or feeding refusal.[13] Videofluoroscopy, nasoendoscopy, and swallowing studies aid in evaluating dynamic function.

Supplemental feeding is required in 38% to 62% of patients with PRS.[6,13] Temporary nasogastric tube feeding may suffice; however, syndromic patients may develop chronic feeding difficulty, requiring placement of a gastrostomy tube. Tongue-lip adhesion has a nearly threefold risk of eventual gastrostomy tube placement when compared with mandibular distraction.[19] Average weight gain of 20 to 30 g/d is considered satisfactory for the neonate.[20,21] Consistent weight gain allows for transitioning of continuous nasogastric tube feeding to bolus feeds, and eventual oral intake.[19] Oral feeding and swallowing training should be implemented to limit oral aversion. The pediatric gastroenterologist may longitudinally follow the patient to ensure appropriate growth and development.

MANAGEMENT

Treatment of PRS may be divided into nonsurgical and surgical methodologies. Protocols vary across different centers and may be a function of individual surgeons' training and experience, each with their own criteria for pursuing surgical versus nonsurgical intervention.

NONSURGICAL MANAGEMENT

Airway obstruction is initially addressed via prone or lateral positioning with a success rate of 70%.[22] Should the obstruction prove recalcitrant, a nasopharyngeal stent may be placed to mitigate the retroglottic obstruction (**Fig. 3**). Custom stents tailored to the infant's weight may minimize dead

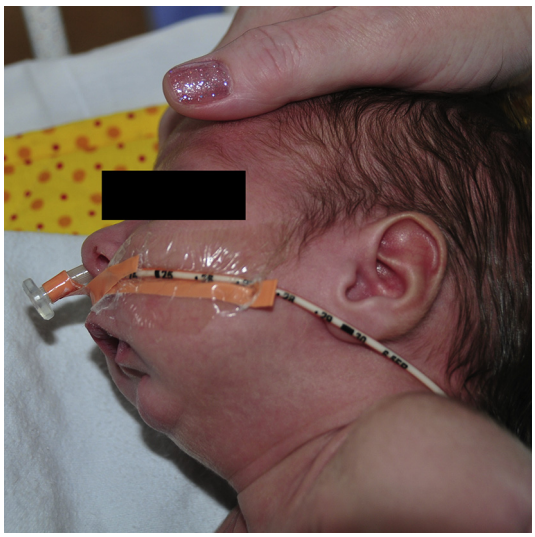

Fig. 3. A nasopharyngeal stent may be used to maintain the retroglottic airway should prone and lateral positioning prove insufficient in relieving retroglottic airway obstruction.

space and permit delivery of supplemental oxygen via nasal cannulas.[23] Positioning and nasopharyngeal stenting alone may be sufficient in infants who maintain a weight above the 25th percentile and AHI less than 19.2 events per hour.[24] Supportive stenting may last 2 to 4 months and can continue at home.

Noninvasive continuous positive airway pressure (CPAP) can obviate the need for surgical intervention in a subset of infants with moderate obstruction who can breathe spontaneously while possessing an AHI greater than 10.[25] Once initiated, CPAP is weaned to use only during sleep periods over a period of 1 to 2 weeks, and may be applied for up to 6 months.[25]

Should a noninvasive airway prove inadequate, the patient may undergo endotracheal intubation or placement of a laryngeal mask airway.

SURGICAL MANAGEMENT

Tongue-Lip Adhesion

Tongue-lip adhesion (TLA) acts to increase the cross-sectional area of the oropharyngeal airway by anteriorly tethering the posteriorly displaced tongue base to the hypoplastic mandible. Its indication is limited to when upper and lower airway evaluation has excluded additional subglottic, synchronous lesions. Some view TLA as a first-line surgical treatment for those who fail nonoperative management.

The procedure begins with placement of anterior traction sutures at the lateral aspects of the tongue.[26] The frenulum is released if found to limit outward movement. The ventral tongue is coapted to the lower lip mucosa and the contact area is identified. A rectangular inferiorly based lower lip musculo-mucosal flap and a congruent superiorly based ventral tongue flap are developed, measuring approximately 2 × 1 cm each (**Fig. 4**). Attention must be paid to avoid injury to the submandibular and sublingual ducts.[27] The leading edge of the lip flap is sutured to the inferior edge of the tongue wound, the exposed labial muscle is sutured to the lingual muscles, and the leading edge of the tongue flap is sutured to the superior edge of the lip wound, in sequential fashion. Apposition of the muscular planes is critical to minimizing risk of dehiscence. Retention sutures secure the tongue base to the lingual surface of the mandible, exiting through the submenton and tied over a button to preserve the underlying skin (**Fig. 5**).[27,28] Endoscopic evaluation of the airway confirms resolution of the retroglottic obstruction. Nasopharyngeal stenting is performed for 2 to 3 days to account for postoperative edema.[28] Nasogastric feeds should be administered for a week to prevent contamination of the wound during the acute healing phase.[28] Muscular adhesion occurs over 2 weeks, after which the retention sutures are released. Division of the TLA occurs between 12 and 18 months postoperatively either concomitantly or in sequence with palate repair.[26] TLA has a success rate of 71% to 89% in relieving the airway obstruction.[26,29]

Complications from TLA include dehiscence, abnormal eruption of deciduous incisors, infection, lip scarring, and tongue edema.[26] The former has largely been mitigated through modifications by Rutledge in the 1960s, with dehiscence rates at 4.2% to 17.2%. Mucosa-only adhesions have reported dehiscence rates of 41.6%.[30] Persistent airway obstruction following TLA on up to 20% of cases likely stems from a failure of elucidating the complete etiology of airway obstruction beyond the tongue base.

AHI can be improved from 30.8 to 15.4 events per hour following TLA.[31] TLA has been shown to improve mean lowest oxygen saturation from 75.8% to 84.4% and mean oxygen saturation from 90.8% to 95%. Feeding outcomes remain disparate with 0% to 54% of infants requiring eventual gastrostomy tube placement depending on the study.[18,26,32]

Floor of Mouth Release

Subperiosteal floor of mouth release (FMR) is based on the assertion that airway obstruction occurs due to a posterior rotation of the tongue secondary to abnormally tight attachments of lingual

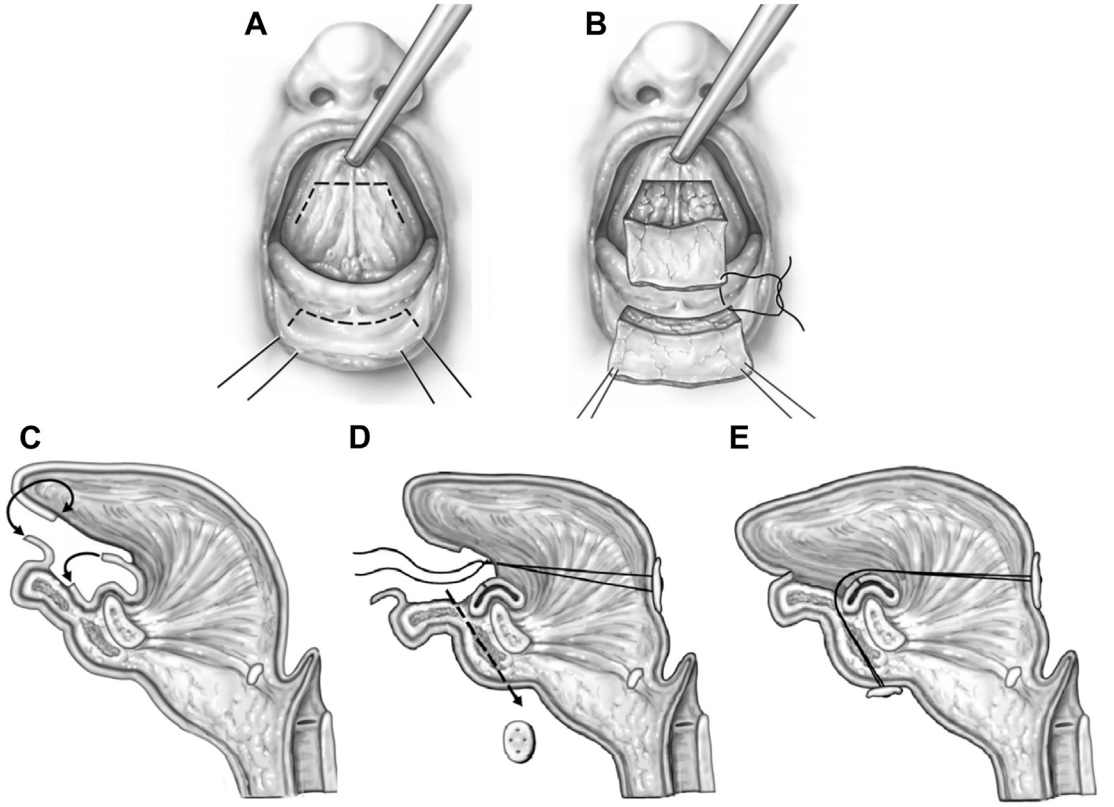

Fig. 4. TLA acts to increase the cross-sectional area of the oropharyngeal airway by anteriorly tethering the posteriorly displaced tongue base to the hypoplastic mandible. A rectangular inferiorly based lower lip musculomucosal flap (*A*, *B*) and a congruent superiorly based ventral tongue flap (*C, D*) are developed and approximated to each other (*E*). (*From* Qaqish C, Caccamese J. The tongue-lip adhesion. Operat Tech Otolaryngol Head Neck Surg 2009;20(4):274–7; with permission.)

musculature onto the lingual mandible.[33] Release of anterior belly of the digastric, myohyoid, geniohyoid, and genioglossus insertions facilitates derotation of the tongue.

Caouette-Laberge and colleagues[34] reported an 84% success rate in infants developing independence from nasopharyngeal stenting following FMR and a decrease in the AHI from 46.5 to

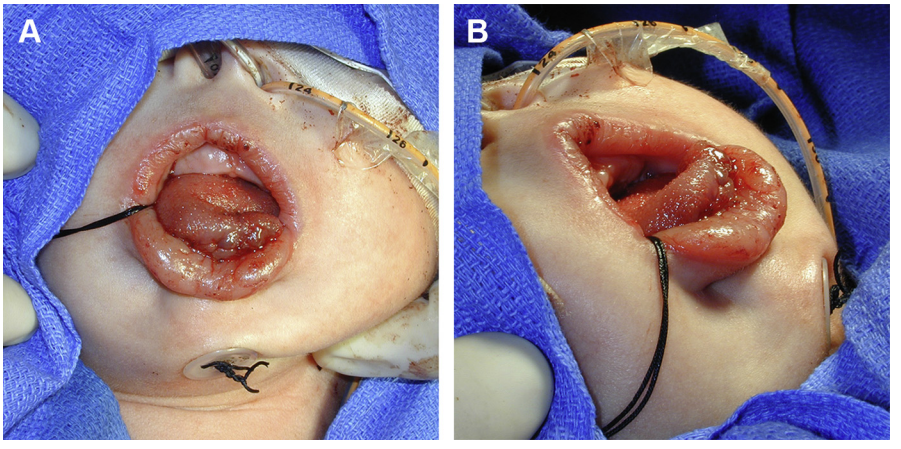

Fig. 5. (*A*) Anteroposterior and (*B*) lateral view of a transcutaneous retention suture that may aid in apposing the tongue base to the lingual surface of the mandible. The button dissipates the chronic stress of the suture and minimizes injury to the skin.

17.4. Gastrostomy feeding was able to be avoided in 73% of cases, with half of patients being orally fed within 11 days postoperatively.

Mandibular Distraction Osteogenesis

McCarthy and colleagues[35] published their experience with mandibular distraction osteogenesis (MDO) on a series of patients with congenital mandibular hypoplasia in 1992, introducing the technique to the field of craniofacial surgery. In the decades since, MDO has experienced wider acceptance among the craniofacial community for treatment of mandibular hypoplasia.[35]

Distraction devices are available in external or semi-buried internal forms. External devices allow for multiple vectors of distraction that can be adjusted following the initial osteotomy and greater distraction length (**Fig. 6**).[36] Disadvantages include buccal scarring, risk of pin dislodgement, decreased precision, greater relapse, patient discomfort, and pin site infections.[36]

Alternatively, distraction can be performed by placement of internal devices. By their nature, internal distractors are less conspicuous with lower scar burden; however, they provide only univector distraction and require precise preoperative planning. Nonresorbable devices require a second surgery for removal. Advantages include patient comfort, prolonged retention period for optimal ossification, and decreased risk of pin site infection.[36]

A brief description of the distractor placement is given. Illustrative photos are shown in **Fig. 7**. A submandibular Risdon incision is made. Dissection continues through the platysma, avoiding injury to the facial vessels and marginal mandibular branch of the facial nerve. The periosteum is incised and a subperiosteal plane is developed, exposing the coronoid and antegonial notch as reference. Distraction vector may be sagittal, vertical oblique, or obtuse depending on the degree of vertical deficiency and occlusal relationship.

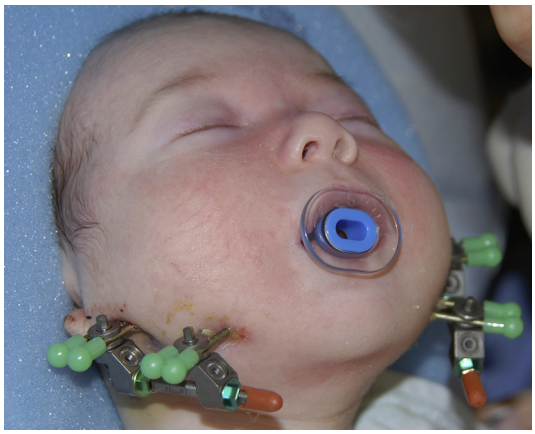

Fig. 6. External distraction allows for multivector changes to the mandible, although having multiple pieces of exposed hardware poses a chronic infectious burden.

A 270° osteotomy is completed of the anterior, posterior, and buccal cortices with a conventional or piezoelectric saw, taking care to spare the inferior alveolar nerve. The internal distraction device is secured with monocortical screws, and the lingual osteotomy is completed. Initial activation of the distractor confirms bony separation and the bony edges are then returned to their original positions. The soft tissue is closed.

Osteotomy design may be aided by virtual surgical planning to minimize injury to developing tooth buds and the inferior alveolar nerve.[37] Configurations include linear oblique, inverted-L, and multiangular. The inverted-L osteotomy is frequently advocated because it proceeds distal to the tooth buds, better preserving these structures.[37] While damage to deciduous teeth can be minimized with imaging and planning, injury to permanent dentition is difficult to predict.

In neonatal MDO, our institution begins the process of distraction the day after surgery at a rate of 2 mm/d. Older patients are allowed a latency period of 2 to 5 days followed by distraction rate of 1 mm/d. The former accelerates the process of distraction, allowing extubation within approximately 1 week postoperatively. The patient is closely monitored during the distraction phase with a goal of moderate prognathism. In the neonate, it is the common practice of Dr Woo AS to attempt 25 to 30 mm of distraction. Once distraction is completed, the externalized portion of the distractor is removed. A bony consolidation phase of 6 to 8 weeks ensues, followed by removal of the internal device. The patient is longitudinally followed to track mandibular growth (**Fig. 8**).

Success rate of MDO for relieving airway obstruction is 94%.[38] A systematic review conducted by Master and colleagues[39] compiled complication rates from MDO, including relapse 64.8%, tooth injury 22.5%, hypertrophic scarring 15.6%, nerve injury 11.4%, infection 9.5%, inappropriate distraction vector 8.8%, device failure 7.9%, fusion error 2.4%, and temporomandibular joint injury 0.7%. Predictors of failure include preoperative intubation, gastroesophageal reflux, low birth weight, syndromic diagnosis, neurologic anomalies, intact palate, airway anomalies other than laryngomalacia, and late surgery.[38] Transition to oral feeding occurs in 82% of distracted patients within 12 months postoperatively; however,

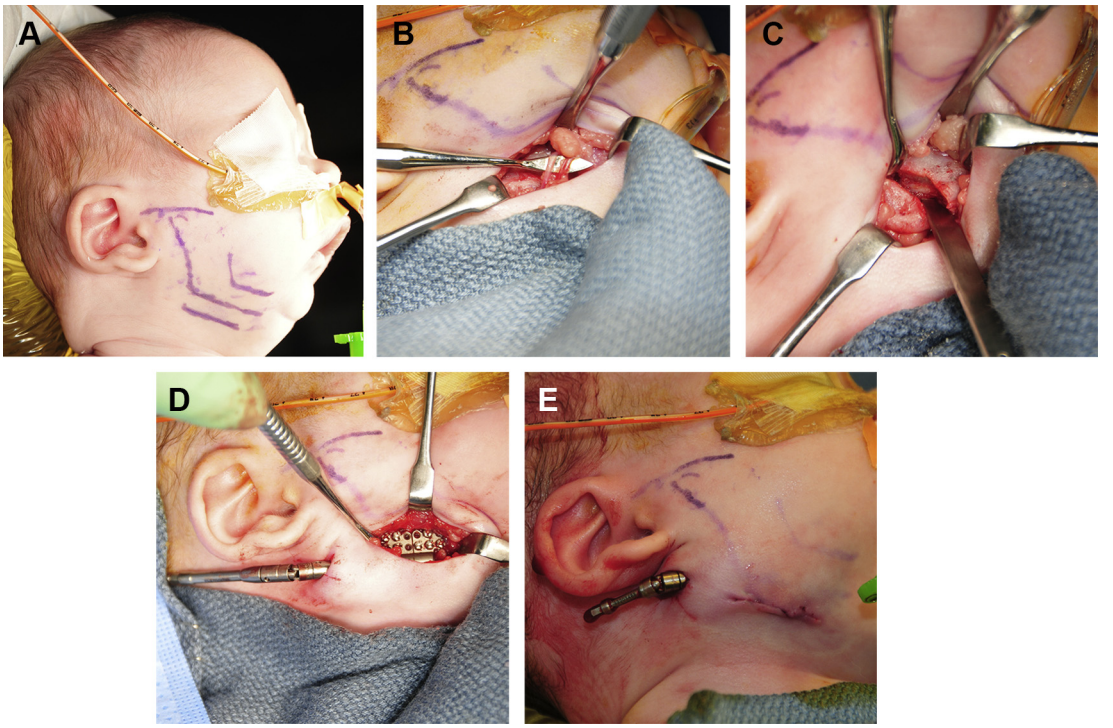

Fig. 7. (*A*) Operative markings of the mandible including the zygomatic arch, mandibular condyle, angle, and proposed submandibular incision, which should be placed at least 1 cm caudal to the inferior mandibular border to avoid injury to the marginal mandibular facial nerve branch. (*B*) Facial artery and vein may be encountered during the soft tissue dissection and exposure of the mandible. (*C*) Completion of the bicortical mandibular osteotomies with mobilization of the distal and mesial segments. (*D*) Application of a uni-vector, semi-buried mandibular distractor to the osteotomized mandible. (*E*) Soft tissue closure of the submandibular incision and application of a universal joint to the extruded distractor arm.

syndromic patients are 5 times more likely to require adjunctive feeding.[40]

TREATMENT PROTOCOL

Universal agreement with respect to diagnosis and management of PRS has yet to be achieved. Lack of randomized controlled trials, limited patient population, training disparities, suboptimal standardization of published studies, and individual biases impede standardization of care.

Evaluation of the patient with PRS begins with history and physical examination by otolaryngology, pulmonology, neonatology, genetics, and plastic surgery. Patients are monitored in a neonatal intensive care unit with continuous pulse oximetry and recording desaturation episodes, followed by a formal sleep study to stratify the degree of obstruction. Consideration is placed toward feeding status, weight gain, and desaturation episodes with feeding. Feeding difficulty in the absence of desaturation is addressed by nasogastric feeds and swallow studies.

Desaturation on clinical examination and abnormal polysomnography prompt a comprehensive airway examination with nasoendoscopy and bronchoscopy to evaluate for synchronous lesions. Those with subglottic obstruction may have a suboptimal response to TLA or MDO and undergo tracheostomy.

Tongue-base obstruction is managed with increasing invasiveness. Nonsurgical maneuvers, such as prone and lateral positioning, nasopharyngeal stenting, and noninvasive CPAP, are trialed. Should this fail, the senior author performs MDO in accordance with certain centers[41,42]; however, others may elect to pursue TLA initially, reserving MDO only for those who have failed TLA.[43]

In a recent survey of surgeon members of the American Cleft Palate-Craniofacial Association, nearly half preferred MDO as first-line treatment for airway obstruction.[44] Some advocate for a predictive management algorithm as a function of the maxillo-mandibular discrepancy, severity of glossoptosis, persistent desaturations with prone positioning, feeding difficulties, nasogastric tube dependence, concomitant airway anomalies, and failure of nonsurgical management.[44]

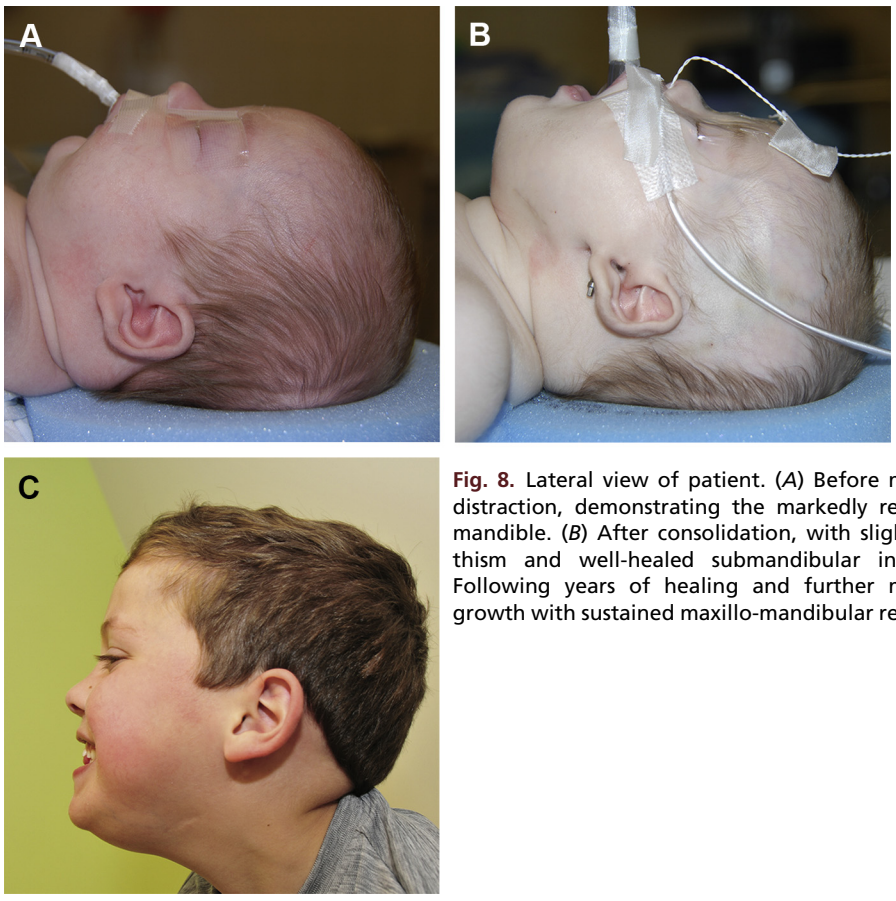

Fig. 8. Lateral view of patient. (*A*) Before mandibular distraction, demonstrating the markedly retrognathic mandible. (*B*) After consolidation, with slight prognathism and well-healed submandibular incision. (*C*) Following years of healing and further mandibular growth with sustained maxillo-mandibular relationship.

Although some centers argue for stratification of severity of obstruction as a node in the decision tree between pursuing TLA versus MDO, others consistently perform TLA as a first-line treatment, reserving MDO for failure of TLA.[43,44] As referenced earlier, a growing majority of craniofacial surgeons view MDO as definitive treatment of airway obstruction, excluding TLA from their management algorithm.[41,42] In light of the variability in diagnostic criteria and disagreement concerning the role of MDO and TLA in the surgical management of PRS, further multicenter work should be undertaken toward achieving a standardized treatment protocol.

SUMMARY

PRS is the clinical triad of micrognathia, glossoptosis, and airway obstruction found within a diverse spectrum of nonsyndromic and syndromic patients. A comprehensive evaluation by a multidisciplinary team helps to establish a diagnosis and guide treatment. Nonsurgical positional and nasopharyngeal stenting maneuvers should be trialed before surgical intervention. Airway interventions must be undertaken only after nasoendoscopy and bronchoscopy to delineate sites of airway compromise beyond the tongue base, as patients with subglottic anomalies may be poor candidates for distraction and should undergo tracheostomy. Surgical options include TLA, subperiosteal FMR, and MDO. Disagreement remains invariant among institutions regarding a uniform treatment algorithm for this diverse group of patients.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.cps.2018.11.010.

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