Acta Paediatrica

WILEY

ACTA PÆDIATRICA
NURTURING THE CHILD

REVIEW ARTICLE OPEN ACCESS

Robin Sequence: From Dilemmas to Developing an Adaptable Standardized Stepwise Approach

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Received: 16 September 2024 | **Revised:** 26 December 2024 | **Accepted:** 4 February 2025

Funding: This work was supported by perth children's hospital foundation.

Keywords: adaptable pathway | Robin sequence | standardised pathway | treatment | upper airway obstruction

ABSTRACT

Aim: To review the literature to identify key issues causing variation in clinical practice, assess the knowledge gap, and develop a standardised pathway for managing upper airway obstruction (UAO) in infants with Robin sequence (RS).

Methods: The tripartite framework of evidence-based practice, which included a systematic review of the literature, extensive consultation with a multidisciplinary team of experts, and feedback from the patients was used.

Results: Of the 2672 articles from the initial search, 66 were studied in detail. We identified five pivotal issues prevalent while managing UAO in RS. These issues were addressed systematically to develop an adaptable stepwise standardised pathway. The main pillars of the pathway are (a) early objective assessment of the severity of UAO using polysomnography, (b) graded treatment approach based on centre-specific preferences, (c) early and regular multidisciplinary team discussions and (d) clearly defined criteria for treatment escalation or cessation, discharge and follow-up.

Conclusion: This unique pathway is based on available evidence, consensus of experts and parents' feedback. It provides a stepwise guide to the clinician for the management of UAO in infants with RS, adaptability for centre-specific treatment preferences and framework for future comparisons of different treatments.

1 | Introduction: Review of Literature

Pierre Robin sequence, more recently known as the Robin sequence (RS), is characterised by the clinical triad of micrognathia, glossoptosis and upper airway obstruction (UAO) [1]. Glossoptosis is defined as a backward and downward fall of the tongue base [2]. Glossoptosis is also defined as a posterior movement of the tongue during sleep, reinforcing its dynamic nature and its main manifestations predominantly during sleep [3]. A systematic review of 34 studies ($n = 2722$) reported a pooled prevalence rate for RS of 9.5 per 100,000 live births (95% CI 7.1–12.1) [4]. A slightly higher birth prevalence of 12.0 per 100,000 births (95% CI 9.9, 14.5) was observed in a recent European study [5].

RS has a wide phenotypic spectrum and nearly 50%–70% are associated with genetic or other congenital anomalies [6, 7]. The subgroups of RS are (a). isolated RS (no other associated abnormalities), (b). syndromic RS (associated with genetic

Abbreviations: aFFL, awake flexible fibre-optic laryngoscopy; AHI, apnea hypopnea index; ASSA, adaptable standardized stepwise approach; CPAP, continuous positive airway pressure; FEES, functional endoscopic evaluation of swallowing; HFNC, high flow nasal cannula; LTB, laryngo-tracheo-bronchoscopy; MDO, mandibular distraction osteogenesis; MDT, multidisciplinary team; MOAI, mixed obstructive apnea index; NPA, nasopharyngeal airway; OAHI, obstructive apnea hypopnea index; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; PSG, polysomnography; RS, Robin sequence; SGP, supraglottoplasty; TBAO, tongue based airway obstruction; TLA, tongue lip adhesion; TPP, tubingen palatal plate; UAO, upper airway obstruction.

Summary

- The lack of a standardised approach to treat upper airway obstruction (UAO) in infants with Robin sequence (RS) leads to prolonged hospital stays and increases the burden on families and the healthcare service.
- Early objective assessment of UAO using daytime polysomnography and a graded approach to treatment supports improved outcomes.
- We developed an evidence-based and patient-centric, standardised stepwise approach for managing UAO in infants with RS.

syndromes) and (c). RS plus (associated with non-syndromic congenital abnormalities) [8]. About 70%–90% of infants with RS have a cleft palate [5–7]. The clinical features in the neonatal period are respiratory distress, obstructive sleep apnea (OSA), feeding difficulties and failure to thrive due to UAO (Figure 1).

The pathophysiology of UAO in RS is predominantly due to micrognathia causing tongue-based airway obstruction (TBAO). Tongue-based airway obstruction worsens during sleep due to the relaxation of muscles and the gravitational backward fall of the tongue. It is also thought to worsen in the first few weeks of life and improve partially or completely by 18–24 months of age due to mandibular growth [1, 2]. Additional levels of airway (non-tongue base) narrowing may occur in infants with RS due to synchronous airway lesions such as laryngomalacia, subglottic stenosis, vocal fold paralysis, tracheomalacia and bronchomalacia [7, 9].

The goals of management for RS in infancy are to relieve the UAO effectively and support feeding and growth. Delay or incomplete resolution of UAO leads to poor sleep, hypoxia or hypercarbia, poor feeding, suboptimal growth, and neurodevelopmental impairment.

1.1 | Assessment of the Severity of UAO

Methods used to assess the severity of UAO and thresholds for treatment vary widely based on centre-specific practices and available resources [10]. The assessment methods are broadly categorized as (1) measures of the severity of micrognathia; (2) measures of the severity of glossoptosis; (3) measures of the clinical impact of UAO such as clinical symptoms, effect on gas exchange (hypoxia or hypercarbia) or severity of OSA; (4) a combination of these methods. Table 1 describes these methods, practical considerations and evidence to support or refute their clinical use.

Measuring the severity of micrognathia based on facial anthropometric measurements may have some role in early prediction of severity of UAO, need for invasive ventilation or

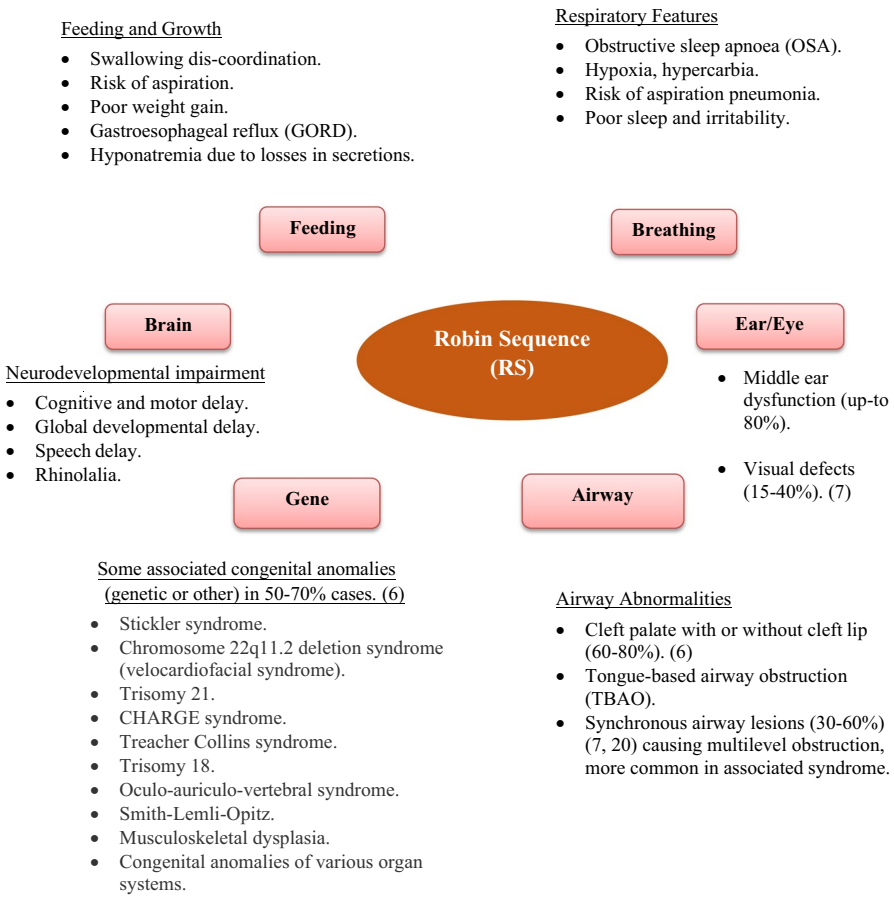

FIGURE 1 | Common clinical features and medical complications in Robin sequence (RS).

TABLE 1 | Methods to assess the severity of upper airway obstruction (UAO)/obstructive sleep apnea (OSA) in Robin sequence (RS) infants.

Method	What is it measuring	Consideration of method	Evidence supporting clinical use	Evidence refuting clinical use	Authors comment
Severity of micrognathia					
2D Facial photo	Visual inspection of micrognathia	Non-invasive tool conducted at the bedside. Impacted by significant inter and intra-observer variability.	NA	Assesses micrognathia in a two-dimensional plane hence unreliable in assessing the retro-position of the jaw [47]. Morice et al. in a retrospective study of 50 RS infants found that the grade of micrognathia on visual inspection was not predictive of the severity of respiratory and feeding disorders [48].	Unlikely to be reliable tool to assess severity of UAO
3D facial photo	Facial anthropometric measures such as: Mandibular length Facial angles Jaw index defined as alveolar overjet × maxillary arch/ mandibular arch [13].	Non-invasive tool Conducted at the bedside. No exposure to ionising radiation	Wiechers et al. showed catch-up jaw growth in infants with RS using 3D facial photography (jaw index) [13]. Stereophotogrammetry 3D method validated for quantitative longitudinal assessment of facial dimensions in children until 6 years of age [49]	Scarce evidence to validate its use for diagnosis or assessing severity of UAO or its relationship with clinical outcomes in RS children.	Facial anthropometric measurements may have a role in assessing the severity of UAO. 3D imaging requires further validation for clinical use
CT scan of face	Mandible body length Mandible ramus length Facial angles	Exposure to ionising radiation in early weeks of life. Requires mobilisation of the infant with an unstable airway to the radiology department.	Duarte et al. reported that every 1 mm increase in mandible length on a CT face was associated with a 27% reduction in the need for respiratory support [11]. Lee et al. found a composite score of five upper airway measurements on CT face (mandibular total length, gonial angle, tongue length, tongue relative position to palate, inferior pogonial angle) had 86% sensitivity and 74% specificity to predict the need for tracheostomy [12].	Anatomical abnormalities on CT face may not directly assess the dynamic functional impact on airway during sleep.	Facial anthropometric measurements may have a role in assessing the severity of UAO. Given risks of radiation, CT scan is not recommended routinely for initial work-up. Its current clinical role should be limited to infants undergoing MDO as part of the preoperative work up

(Continues)

TABLE 1 (Continued)

Method	What is it measuring	Consideration of method	Evidence supporting clinical use	Evidence refuting clinical use	Authors comment
Severity of glossoptosis/tongue-based airway obstruction (TBAO)					
Awake flexible fibre-optic laryngoscopy (aFFL)	Grade severity of glossoptosis Some widely used classifications are by Sher [50], de Sousa [51] and Yellon [36].	Performed at the bedside by an ENT specialist in the awake state.	Duarte et al. reported an association between grade 3 glossoptosis (on Yellon classification) and poor respiratory outcomes [11]. Manica et al. showed that. severity of glossoptosis (Yellon and de Souza classification) has low sensitivity but moderate to high specificity in detecting patients with severe clinical manifestations [14].	In RS infants' respiratory distress typically occurs when infants are relaxed, sleeping or lying on back. Therefore, awake FFL is confounded by the muscular tension and upright position. Studies have shown that aFFL fails to identify TBAO in up to 50% of infants with RS [14, 52]. The low sensitivity of aFFL could be due to patient factors, subjectivity in grading the degree of glossoptosis, and some due to coexisting synchronous airway lesions [53].	Grading severity of glossoptosis may have an adjunct role in assessing severity of UAO
Complete airway evaluation under general anaesthesia (laryngo-tracheo- bronchoscopy: LTB)	Complete evaluation of airway Identifies synchronous airway lesion.	Require general anaesthesia.	The presence of multilevel airway obstruction is a predictor of the need for tracheostomy, especially in syndromic RS [24]. A systematic review suggested that undiagnosed laryngomalacia, tracheal stenosis, or subglottic stenosis were present in 15/22 (68%) cases of MDO failure [54].	Not a diagnostic test for TBAO.	Minimal role as first line method to assess severity of UAO. Second line investigation for complete airway evaluation prior to surgical treatment
Dynamic CT (4D-CT) or MRI	Evaluate the upper airway throughout the respiratory cycle [55, 56].	Require general anaesthesia. CT scan involves exposure to ionising radiation. Requires mobilisation of the infant with an unstable airway to the radiology department.	A recent study compared the 4D-CT with aFFL and found fair interrater agreement [57].	Like aFFL, 4D-CT underestimates UAO severity [57]. There is no evidence of its validation or use in the assessment of the severity of UAO in infants.	Research tool at present

(Continues)

TABLE 1 (Continued)

Method	What is it measuring	Consideration of method	Evidence supporting clinical use	Evidence refuting clinical use	Authors comment
Impact of upper airway obstruction (UAO)					
Cole classification	Grade 1: no respiratory distress when nursed supine. Grade 2: intermittent mild respiratory obstruction when nursed supine or while feeding. Grade 3: moderate to severe respiratory distress when nursed supine, unable to feed orally. [58] nursed supine or while feeding.	Subjective variation Clinical symptoms evolve over weeks, delaying decision making.	There is some correlation between Cole grade 3 and severity of glossoptosis on aFFL [59].	18%–25% of Cole Grade 3 were noted to have mild glossoptosis on aFFL [59]. Runyan et al. found no significant differences in clinical features, such as respiratory distress and poor feeding, between the surgical and non-surgical group [23]. Scarce evidence assessing the ability of Cole's classification to predict short-term or long-term outcome.	Clinical symptoms may underestimate degree of UAO, and symptoms may change over days. Subjective but important clinical adjunct to assess severity of UAO.
Sleep oximetry	Oxygen desaturation duration sleep	Continuous non-invasive monitoring	Ehsan et al. ($n = 38$) showed cut off of oxygen desaturation index (ODI4%) of 3 events/h on oximetry has 100% sensitivity and 35% specificity to diagnose OSA in infants of mean age 5.7 months when obstructive apnea and hypopnea index (OAHI) was > 5 on PSG [60] Gyapay et al. ($n = 78$) showed cut- off of oxygen desaturation index (ODI3%) of 6 events/h on oximetry has sensitivity of 95.7% and specificity of 51.9% to diagnose OSA in infants of mean age 2 months when OAHI was > 10 on PSG [61]	Infants with OSA may not have oxygen desaturation [62]. Standardised McGill score for reporting sleep oximetry is not validated for use in < 1 year of age [63]. Variable cut-off on sleep oximetry used to assess respiratory compromise for infants with RS [64]. Doesn't differentiate central and obstructive sleep apnea.	Require validated criteria to screen or grade UAO in infants < 6 months of age. Sleep oximetry may have a role to screen for severe OSA. But can underestimate or overestimate severity as doesn't differentiate central and obstructive events.

(Continues)

TABLE 1 (Continued)

Method	What is it measuring	Consideration of method	Evidence supporting clinical use	Evidence refuting clinical use	Authors comment
Oxycapnography	Simultaneous monitoring of oxygen and carbon dioxide levels.	Continuous non-invasive monitoring	Some evidence of its use as screening tool to assess adequacy of breathing in children with complex multisystem disorder or neuromuscular conditions [65]	Gyapay et al. ($n = 78$, 44 RS infants) comparing transcutaneous CO_2 levels with obstructive index (OAHI) on PSG found transcutaneous capnography to be insufficient to predict OSA in infants <4 months old [61].	Not validated to diagnose or grade severity of UAO.
Capillary gas	Single heel prick blood test	Bedside test Easily available in most hospital setting	Kwan et al. ($n = 111$ RS infants) reported CO_2 levels on capillary blood gas of 55 mmHg and compensatory rise in bicarbonate (HCO_3^-) level to 30 mmHg to have a sensitivity of 55.71% and specificity of 91.3% to predict the need for airway intervention [66] Fahradyan et al. ($n = 73$ RS infants) found higher CO_2 levels of 56 mmHg and HCO_3^- levels of 30 mmHg in the surgical intervention group compared to 43 and 27 mmHg, respectively in the non-surgical group ($p < 0.001$) [67]	Normal CO_2 levels in the first 10 days of life are falsely reassuring as a sufficient period has not elapsed to detect mild to moderate CO_2 retention [66] The carbon dioxide levels are likely to be modified by the type of airway support provided.	Not validated to diagnose or grade severity of UAO. Rise in carbon dioxide (CO_2) levels is more consistently seen in setting of hypoventilation which is a late finding in infants with UAO
Respiratory polygraphy	>3 MOAI (mixed obstructive apnea index)	In hospital overnight limited channel sleep study [68] Its use in the neonatal population is limited due to the challenges of reliably scoring PSG without complete set-up.	A study used respiratory polygraphy to score mixed apneas using a cut-off of >3 MOAI for commencing treatment for RS infants [68]	Scarce evidence of its validity. In a paediatric study, Apnea-hypopnea index (AHI) was underestimated on respiratory polygraphy when compared with gold standard AHI on PSG, significantly affecting management decisions especially in mild and moderate OSA [69]	Alternative to PSG in resource limited setting Require validated criteria to screen or grade UAO. May underestimate severity of OSA due to incomplete information on sleep architecture and arousal.

(Continues)

TABLE 1 (Continued)

Method	What is it measuring	Consideration of method	Evidence supporting clinical use	Evidence refuting clinical use	Authors comment
Polysomnography (PSG)	OSA is graded based on PSG indices Apnea-Hypopnea Indices (AHI) or Obstructive Apnea- Hypopnea Indices (OAHI) as: mild: (≥1 to <5 events/h), moderate: (≥5 to <10 events/h), severe: (≥10 events/h) based on [70]	In hospital monitoring lack of accessibility in resource limited setting	Runyan et al. found pre-intervention PSG to be the most reliable predictor of the need for surgical intervention (OAHI of 42.4 in the surgical group versus 12.9 for the conservative group; $p < 0.001$) [71] PSG parameters are associated with the severity of clinical features in RS [72] McGrath et al. ($n = 122$ RS infants) defined PSG factors (EARN): ETCO2 (max) > 49 mmHg, AHI > 16.9 events/h, OAHI REM > 25.9 events/h, OAHI non-REM > 23.6 events/h as most predictive of failure of conservative treatment [73]	NA	Gold standard test for diagnosing and assessing the severity of OSA in all ages especially infants [15].
Combined methods					
Vancouver classification	4-grade system based on severity of glossoptosis, maxillary- mandibular discrepancy, oxygen desaturation, feeding difficulty and coexisting airway morbidity.	Combination of three or more of above- described assessments.	Developed based on retrospective review of 63 infants with RS. The classification prescribes different surgical intervention based on the grade (0–3) [41].	Scarce evidence of correlation with improved outcomes.	Needs validation. Given study design, no pre-defined criteria for treatment choice. Therefore, the results can't be translated to different clinical settings.
MicroNAPS	4-point classification (0–3) based on five elements: micrognathia, nutrition, airway, palate, syndrome/comorbidities.	Combination of three or more of above-described assessments.	Developed based on retrospective review of 100 infants with RS. This classification provides a framework for consistent decision-making and don't prescribe treatment [74].	Scarce evidence of correlation with improved outcomes.	Classification for benchmarking rather than guiding treatment

Note: Reference numbers [47–93] support the contents in Tables 1–3 and are enlisted in the Supporting Information.

tracheostomy [11, 12]. Whist these measurements can be obtained on CT scan of the face, it carries the risk of radiation exposure in the early weeks of life and hence is not recommended routinely for initial work-up (Table 1). An alternative method is 3D facial photography (measures jaw index) which although easily conducted at the bedside currently lacks validation and evidence to guide its use as a diagnostic tool (Table 1) [13]. Awake flexible fibre-optic laryngoscopy (aFFL) is an important adjunct to diagnose and grade the severity of glossoptosis but can underdiagnose tongue-based obstruction in about 50% of cases [14].

Complete airway assessment under general anaesthesia, also called laryngo-tracheo-bronchoscopy (LTB) is not required as a first-line investigation. However, it is important to consider LTB when conservative therapy is unsuccessful, especially before considering surgical intervention to assess the presence of synchronous airway lesions. Attended PSG is the most reliable and validated tool to diagnose and grade the severity of OSA which is the clinical marker for UAO (tongue-based obstruction or other levels) [15]. Other tools such as sleep oximetry, oxy-capnography or blood gas are not validated to grade the severity of OSA in infancy and can underdiagnose UAO but may be considered in resource-limited settings (Table 1).

In a systematic review ($n = 91$ studies), Logjes et al. reported on the frequently used objective tools for assessment of UAO: PSG was the most frequent (76%) followed by oximetry (20%) and blood gas (11%) [10]. The most commonly used PSG indices were the apnea-hypopnea index (AHI), obstructive apnea-hypopnea index (OAHI), oxygen saturation, carbon dioxide levels and oxygen desaturation index (ODI) [10].

Diagnostic criteria on PSG for neonatal OSA are based on paediatric criteria, AHI of ≥ 1 to < 5 is considered mild OSA, AHI of ≥ 5 to < 10 moderate OSA, and an AHI of ≥ 10 is severe OSA [16]. The AHI counts both central, mixed and obstructive events whereas the OAHI counts specifically obstructive and mixed events [17]. Since infants have a higher number of central apneas, the AHI values can overestimate the severity of infant OSA [18, 19]. Therefore, OAHI is the preferred index to assess UAO in infants < 6 months of age.

However, the OAHI counts both apneas and hypopneas. Classifying hypopneas as central or obstructive is challenging in infants and hence can result in scoring variations in infants [20]. Brockmann et al. reported OAHI of 0–10 in healthy infants at < 1 month of age, of which about half were attributed to hypopneas [21]. Given the above two findings, there is a suggestion to count only apneas (obstructive or mixed obstructive apnea index) for assessing the severity of OSA in infants [22]. It is also important to consider age-appropriate PSG cut- offs to grade the severity of OSA in infants [18].

1.2 | Treatment of UAO in RS

There is wide variation in the management of UAO in infants with RS. Treatment can be broadly divided into conservative and surgical approaches. The *conservative approach* includes prone positioning, nasopharyngeal airway (NPA) insertion, Tubingen palatal plate (TPP), continuous positive airway pressure (CPAP), and high-flow nasal cannula (HFNC). The *surgical approach* includes supraglottoplasty (SGP), mandibular distraction osteogenesis (MDO), tongue-lip adhesion (TLA), and tracheostomy. Table 2 outlines the advantages, disadvantages, indications and current evidence of efficacy for these treatment options.

The existing literature suggests that all treatment options have their strengths and limitations regarding efficacy, side effects, specific skill requirements, practical considerations and carer burden (Table 2). However, the majority of studies are retrospective and suffer from inherent bias due to different approaches in grading the severity of UAO and centre-specific preferences for managing RS (Table 2).

Based on current literature, there appears to be a consensus that mild UAO could be managed conservatively. However, the evidence highlights polarised views regarding the management of moderate to severe UAO. Table 3 supports this view and provides evidence of successful management of UAO with or without surgical intervention. The variability in practice could be a consequence of pre-determined clinician bias towards an approach to treatment wherein some prefer earlier surgical intervention in severe cases [23] and others consider surgical approach only when conservative management is unsuccessful [24, 25].

Whilst early relief of UAO with mandibular distraction osteogenesis may improve feeding, growth and development [26], surgical interventions requiring general anaesthesia are associated with a higher risk of neurodevelopmental delay [27]. The study cohorts with a higher rate of surgical intervention ($> 50\%$) reported neurodevelopmental delay of up to 36%–57% [7, 8, 28] as compared to 0%–30% in study cohorts with a predominantly conservative approach [29–33]. Since no randomised controlled trials have evaluated different treatments, it is difficult to tease out the cause-effect relation of the surgical intervention from the effects of confounders such as the severity of OSA, timing of the intervention and the presence or absence of associated anomalies on neurodevelopmental outcome.

There may be a role for surgical intervention in severe UAO especially in cases of treatment failure. However, the evidence raises caution against the too-early use of an invasive surgical approach even in infants with moderate to severe UAO. The aim of management should be to promptly grade the severity of UAO and choose an available treatment associated with the least patient morbidities but still effective for the given UAO severity.

2 | Summary

The above review of the literature highlights the existing variability in the objective assessment of UAO, strengths and limitations of available objective tools, treatment thresholds and difficulties in choosing between treatment approaches. These factors lead to variation in practice within and between centres which impacts patient outcomes and cause staff and patient dissatisfaction. Additionally, given the equipoise in the literature for the most suitable first-line treatment, there is an urgent need to individualise treatment based on the objective assessment of UAO and centre preferences. We developed a standardised

TABLE 2 | Summary of available treatment approaches to treat upper airway obstruction (UAO)/obstructive sleep apnea (OSA) in Robin sequence (RS) infants.

Treatment	Advantages	Disadvantages	Current evidence of efficacy	Authors comments
Conservative approaches				
Prone positioning	Non-invasive. No additional burden of care on families.	In healthy infants higher odds of dying from sudden infant death syndrome (SIDS) in first 6 months of life [75, 76] Need for home monitoring (pulse oximeter). Parental education.	Prone position is still used successfully in clinical practice in many centers [1, 2, 25, 31, 33] and also a recognised treatment in literature [1] Effective in mild obstruction with incomplete correction of OSA in majority. [77, 78] Improves sleep efficiency and decreases apneic events [77, 78] Amaddeo et al. reported successful management of 31 (70%) of 44 infants with prone positioning [79]	Effective in mild OSA. Used as adjunct to other conservative treatments in many centres.
Nasopharyngeal airway (NPA)	Effective in moderate to severe OSA. Support feeding and growth.	Requires centre-specific specialised programme. Follow-up home support. Parental education. Suction at home.	Rate of successful management of UAO using NPA alone is reported to be 67% of 45 (25), and 81.8% of 77 (2) infants with RS. Abel et al. reported NPA reduced severe/moderate OSA to moderate/mild immediately after inserting NP on PSG [2] The average duration of NPA use is 5–8 months [2, 25].	Effective in moderate to severe OSA Interim measure to support natural growth of the mandible.
Tubingen palatal plate (TPP)	Effective in moderate to severe OSA. Support feeding and growth. Associated with mandibular catch-up growth.	Need specialist skill to make TPP. Requires centre-specific specialised programme. Follow-up home support. Parental education.	Successful management of UAO in all RS infants ($n = 122$) with TPP. Reduction of median (IQR) MOAI on PSG from 8.8 (2.1–19.7) to 1.8 (0.6–5.4); $p < 0.001$ and need for nasogastric tube feeding from 66% to 8% at discharge [68] Further improvement in jaw size measured by median (IQR) jaw index at admission and 3-month follow-up from 8.8 (6.3–11.3) to 2.1 (2.0–4.0), respectively; $p < 0.0001$ [80]	Effective in mild, moderate, or severe OSA Facilitates mandibular catch-up growth.
Continuous positive airway pressure (CPAP).	Effective in moderate to severe OSA.	Requires centre-specific specialised programme. Follow-up home support. Parental education. Require specialised CPAP equipment at home.	Low success rate of about 20%–30% for treatment of UAO in RS infants [79, 81] Improved breathing patterns and respiratory outcomes in severe OSA [82] Low CPAP adherence rates of 40% at 6–12 months of age [79] Long-term CPAP use is associated with midface hypoplasia [83], a significant consideration in RS with hypoplastic mandibles.	Physiologically effective in moderate to severe OSA but challenges for treatment adherence. Useful as interim measure for stabilisation until more effective treatment is possible. Long-term use unfavourable for mandibular growth

(Continues)

TABLE 2 (Continued)

Treatment	Advantages	Disadvantages	Current evidence of efficacy	Authors comments
High-flow nasal cannula (HFNC)	As compared to CPAP proposed to be better tolerated by infants and not Associated with midface hypoplasia.	Scare evidence for its efficacy and long-term compliance. Requires specialised HFNC equipment at home.	A study of eight patients with a mean age of 8.9 years (six Down syndrome, one RS, one Pfeiffer syndrome), OSA corrected in the five (62%) compliant children [84].	Alternative to CPAP for non-compliant infants. Interim measure for stabilisation until more effective treatment is possible.
Surgical approaches				
Supraglottoplasty (SGP)	Widely available Technically simpler surgical procedure	Scarce evidence for efficacy May adversely affect feeding and increase risk of aspiration. Not effective for relieving tongue-based airway obstruction	Bakeman et al. found no significant improvement in OSA with SGP alone as measured by PSG indices [85]. Flores et al. describe their experience of using supraglottoplasty in 11 RS patients with laryngomalacia and discuss its role in avoiding tracheostomy [86].	May be used as an adjunct surgery before considering MDO. Ineffective to treat tongue-based airway obstruction.
Mandibular distraction osteogenesis (MDO)	Effectively relieves tongue-based obstruction. Advances the jaw. No additional home support needed. Improves growth and feeding. Avoids tracheostomy	Highly operator dependent with improved outcomes in centres where it is regularly performed. Invasive procedure with associated short and long-term complications.	Systematic review of 49 studies ($n = 1209$), mean follow-up of 43.78 months showed MDO to be reliable and effective with low mortality (0.99%) and high tracheostomy avoidance rate (94%) [87]. MDO is also safe and effective when performed in infants < 3 kg at < 1 month of age (25 ± 20 days) [88]. Postoperative complication rate of 28.9% of which most common being surgical site infection (10.5%), while dental and nerve injuries are seen in 7.9% and 3.2%, respectively [87].	Severe OSA due to tongue- based obstruction which is refractory to conservative approach. Timing and indication for MDO varies globally.
Tongue-lip adhesion (TLA)	Technically simpler surgical procedure as compared to MDO.	Special skills for surgery May require multiple secondary procedure. Higher complication rate May not improve feeding and growth.	A systematic review of 13 studies ($n = 268$) showed successful resolution of OSA in 81.3% ($n = 218$) at mean age of 30.5 days [89]. No significant improvement in growth and feeding when compared to MDO [90] Highest reported complication rates with TLA (odds ratio of 2.80 as compared to MDO and 5.39 as compared to tracheostomy) [26]	Temporising procedure or an alternative in infants in which MDO is not possible.

(Continues)

TABLE 2 (Continued)

Treatment	Advantages	Disadvantages	Current evidence of efficacy	Authors comments
Tracheostomy	Provide safe airway in complex medical condition. Effective in multi-level airway obstruction.	Requires home support. Prolong hospital stay. Burden of care on families. Impact on quality of life of infant and families. Healthcare cost and resource burden.	Percentage RS children requiring tracheostomy varies in literature from 4% to 30% [7, 25, 81]. Threefold increase in overall total cost per patient and 4 times more complications with tracheostomies as compared to MDO in RS infants [91]	Last resort if other treatments fail. Often required in multi-level airway obstruction, associated multiple comorbidities (syndromic RS or RS plus).

Note: Reference numbers [47–93] support the contents in Tables 1–3 and are enlisted in the Supporting Information.

TABLE 3 | Variations within and between countries of conservative versus surgical approach for management of upper airway obstruction in Robin sequence infants.

Author, year	Study design	Country	*N*	Predominant treatment approach	% Successfully treated
Abel et al. [2] 2012	Retrospective	UK	104	Conservative	86.5%
Alencar et al. 2017 [33]	Retrospective	Brazil	62	Conservative	100%
Buchenau et al. [92] 2017	Retrospective	Germany	122	Conservative	100%
Caouette-Laberge et al. [93] 1994	Retrospective	Canada	125	Conservative	82.4%
Theile et al. [25] 2024	Retrospective	Australia	45	Conservative	96.0%
Fleurance et al. [31] 2023	Retrospective	France	143	Conservative	95.1%
Chocron et al. [24] 2024	Retrospective	Canada	59	Surgical	52.5%
Malarbi et al. [8] 2022	Retrospective	Australia	45	Surgical	66.7%
Runyan et al. [71] 2018	Retrospective	USA	171	Surgical	71.4%
Weaver et al. [7] 2022	Retrospective	USA	175	Surgical	70.9%

Note: Reference numbers [47–93] support the content in Tables 1–3 and are enlisted in the Supporting Information.

pathway to achieve early and effective treatment of UAO that will promote timely discharge from the hospital, and likely improve sleep, feeding, growth and development.

3 | Methods

We used the tripartite framework of evidence-based practice (EBP) to develop a standardised pathway for managing UAO in infants with RS [34]. This framework included a review of the best available literature, extensive consultation with a multidisciplinary team of local and national experts, and consideration of patient factors and feedback from families (Figure 2). A literature review was conducted in PubMed, Embase, and Cochrane databases, from the time of inception to 1 July 2024 using broad search terminology 'Pierre Robin sequence' OR 'Robin Sequence'. All clinical studies discussing diagnostic tests or therapeutic approaches, and directly or indirectly comparing diagnostic or treatment modalities were selected and read in detail. Consultations were held with our hospital's multidisciplinary team named Complex Airway Team, the Australia New Zealand Network of Neonatology (by presenting at the national neonatal conference), the Australia New Zealand Paediatric Sleep Specialists (by presenting at the national sleep conference) [35], the Australasian Cleft Lip and Palate Association (by presenting at the national conference), hospital ear-nose-throat (ENT) surgeons, plastic and craniomaxillofacial surgeons, clinical nurse specialists, speech pathologists, geneticists, and audiologists. Most importantly, input was obtained from the families with RS children by collaborating with the consumer group 'PRS Australia' (Pierre Robin Australia). Some of the parent feedback and themes cited with permission are as follows: 'Families are frustrated by inconsistencies in treatments offered across Australia, between states and even within hospitals'; 'They should not have sent my child home without a formal sleep study first. The sleep study saved my child's life, I can't help but think that if a complete sleep study had been available early on, even in NICU'; 'Early access to testing that can help determine the level of obstruction is crucial'; 'More information about RS and parenting challenges, link in with Australian PRS page for support and information, consistent approach between specialist doctors and nurses, link in with respiratory team, not just ear-nose throat surgeon'.

Considering all the above input, evidence and local experience, consensus was reached over 12 months period through regular meetings of the group consisting of the hospital's neonatologists, respiratory and sleep specialists, ENT specialists, plastic and craniomaxillofacial surgeons, dentists, geneticists and speech pathologists.

4 | Result: Adaptable Stepwise Standardised Approach/Pathway (ASSA)

Of the 2672 articles from the initial search, 66 articles were read in detail. We identified a paradigm of 5 pivotal issues affecting the assessment and treatment of UAO in RS. These are: (1) how to gain consensus; (2) how to assess the severity of UAO/OSA; (3) which treatment to choose; (4) how to assess treatment effectiveness; and (5) when to follow-up or stop treatment (Figure 3).

We addressed these five pivotal issues to construct an adaptable stepwise standardised approach (ASSA) for the assessment and management of UAO in infants with RS (Figure 4). ASSA has two phases: phase 1 is the conservative arm and phase two is the escalation arm to more invasive treatment.

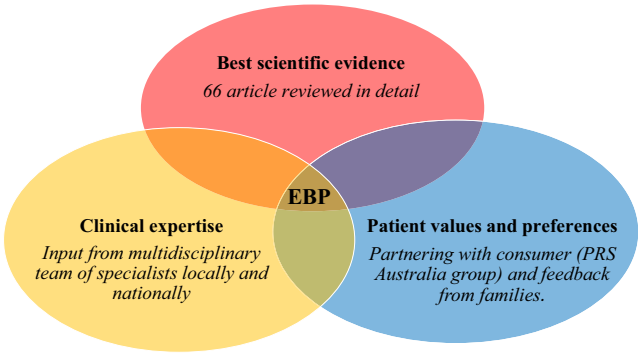

FIGURE 2 | Evidence-based practice framework (EBP).

Firstly, the pathway involved seeking consensus through early multidisciplinary input by involving neonatology, ear-nose-throat, respiratory and sleep medicine, speech pathology, plastic surgery and genetic specialists. The pathway advocates for microarray to be sent in all infants with RS, with an inpatient genetic review if clinically suspected to have syndromic RS (Figure 4). Also, an awake flexible fibre-optic laryngoscopy should be performed at 0–7 days of life with findings reported using standardised evidence-based grading of glossoptosis [36], laryngomalacia [37] as well as the presence or absence of additional airway abnormalities [38].

Secondly, the pathway suggests the performance of an attended PSG at 7–14 days of life as PSG is the gold standard for diagnosing and assessing the severity of OSA/UAO. PSG objectively assesses all levels of obstruction (tongue-based airway obstruction and others). To address the feasibility and availability of a timely PSG, we suggest that this PSG be performed at the bedside (neonatal intensive care unit or ward) using a mobile unit (Compumedics, Grael 4k PSH: EEG). The PSG can be performed during the day because of the daytime sleep patterns and very short REM latency of infants < 3 months of age [18, 19, 39].

Third, the pathway suggests a graded approach to treatment, starting with conservative treatment as first-line and escalating to a more invasive approach in cases of treatment failure. In phase one of the pathway, there is provision for no treatment if there is no OSA on PSG, prone positioning for mild OSA and conservative treatment for moderate to severe OSA (nasopharyngeal airway, continuous positive airway pressure or palatal plate) as per centre-specific preferences enabling coexistence of adaptable and standardisation. The main goal of treatment is to relieve UAO early and effectively irrespective of the choice of treatment.

Fourth, to ensure the safety and efficacy of the treatment, a repeat PSG is to be performed within 3–10 days of commencing treatment. If treatment is found to be ineffective, then there can be escalation to the second line of conservative treatment in mild cases and to phase two of the pathway in moderate to severe OSA.

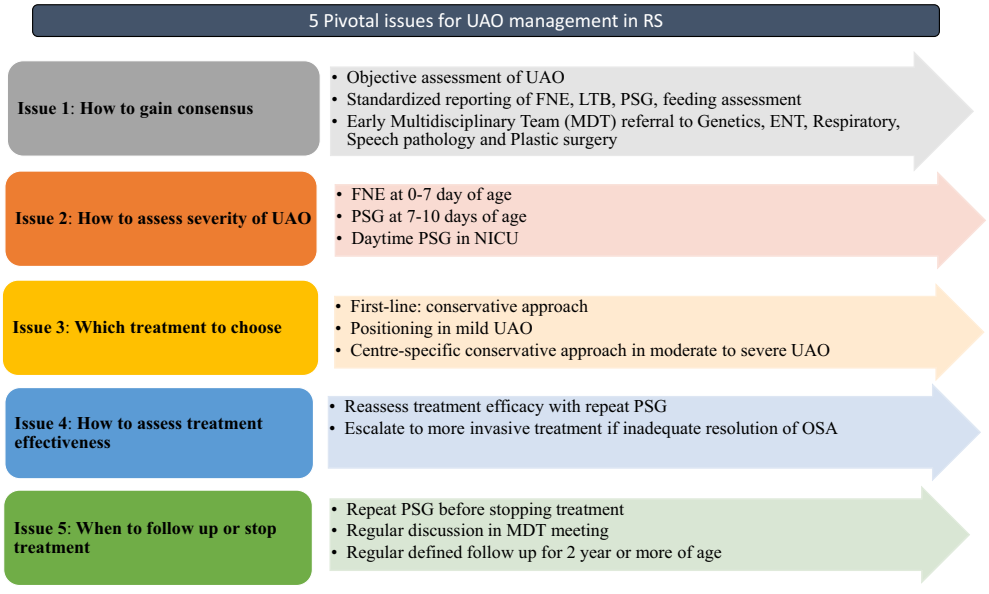

FIGURE 3 | Five pivotal issues identified impacting the management of upper airway obstruction (UAO) in Robin sequence (RS).

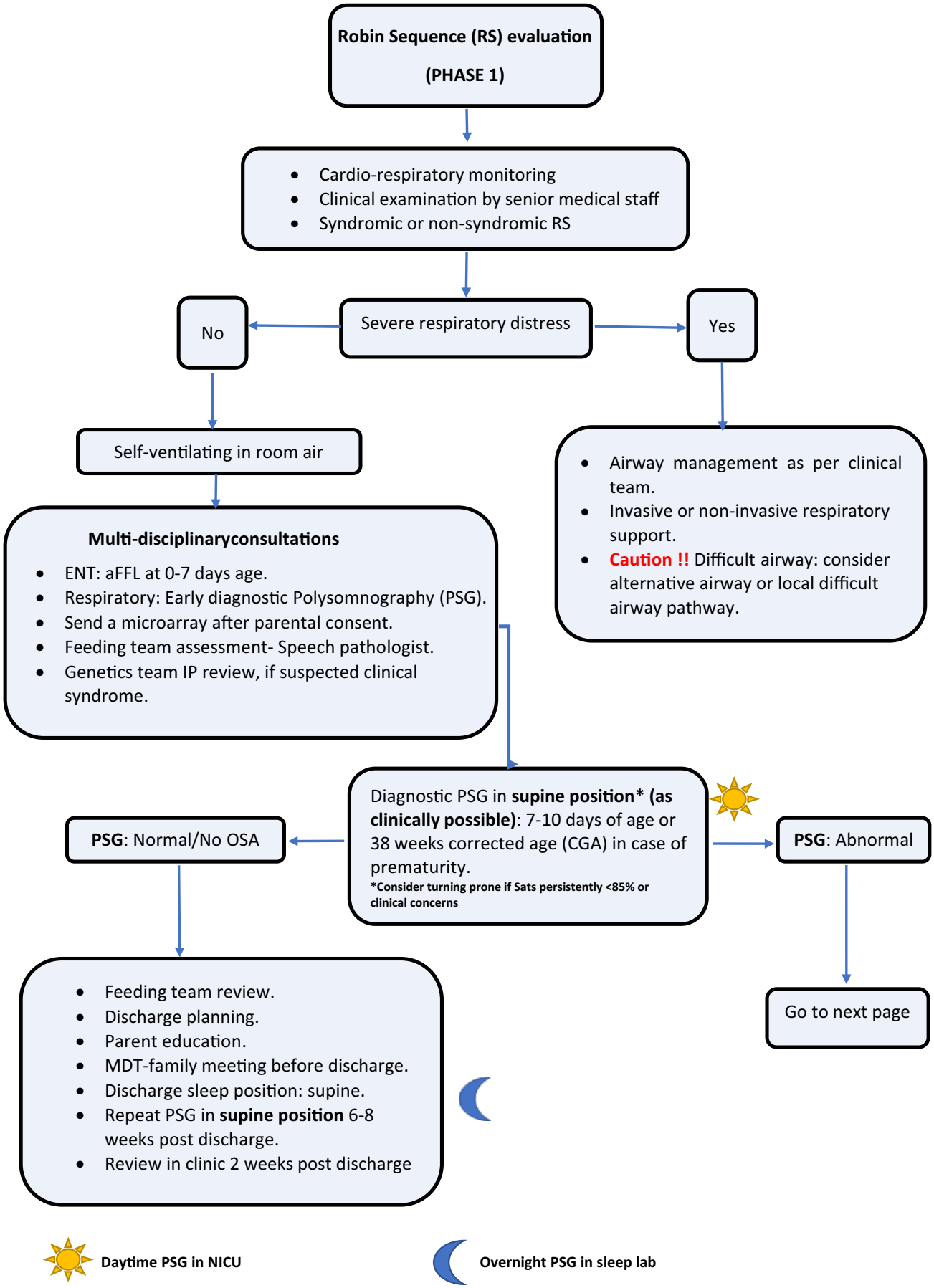

FIGURE 4 | Adaptable stepwise standardised approach (ASSA) for management of upper airway obstruction (UAO) in Robin sequence (RS).

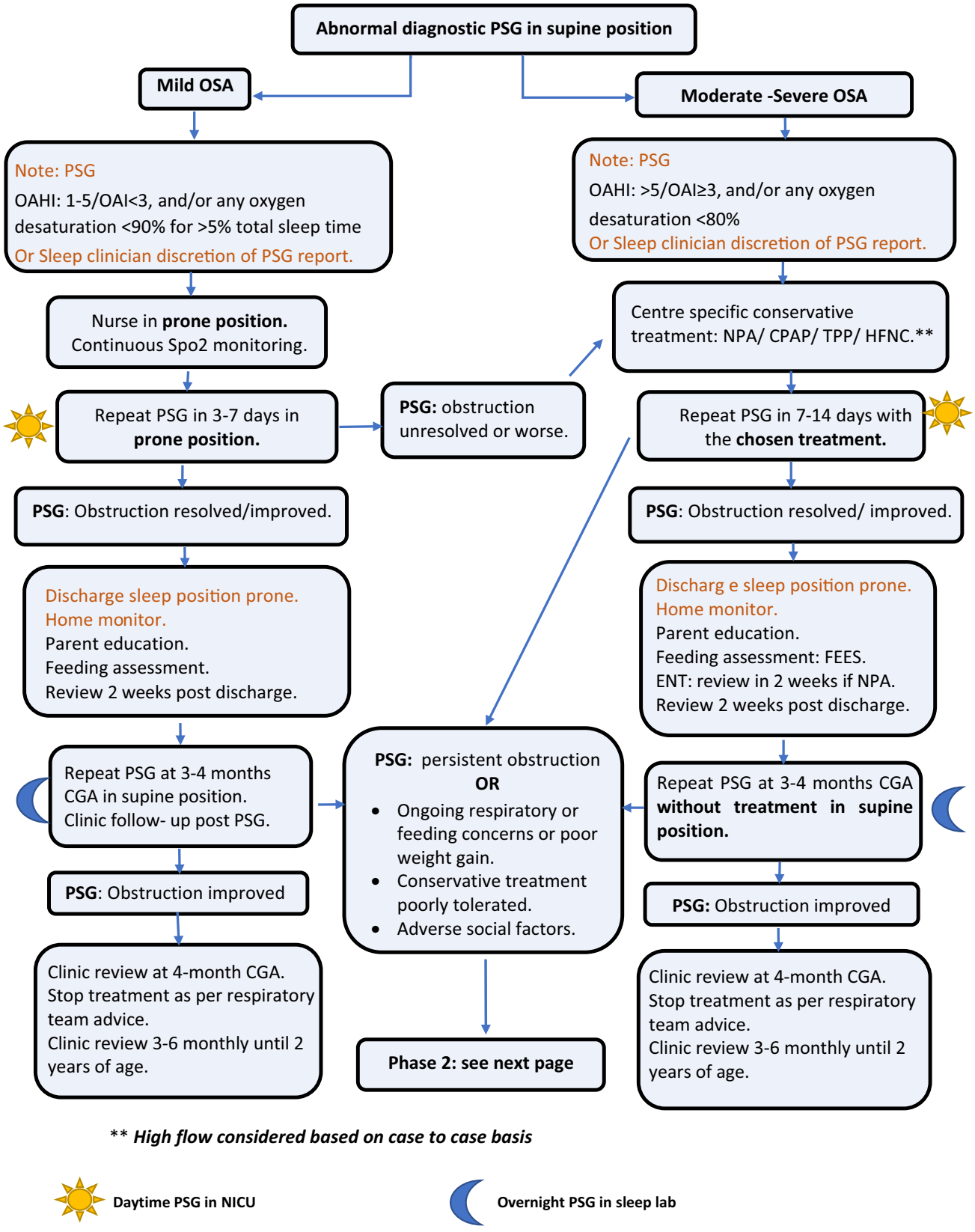

FIGURE 4 | (Continued)

Phase two of the pathway starts by gathering more information on associated anomalies, and additional airway lesions by performing a complete airway evaluation under general anaesthesia (LTB). Supraglottoplasty may be considered at the time of LTB if significant laryngomalacia is observed. The effectiveness of each treatment is assessed by performing a post-intervention PSG. Mandibular distraction osteogenesis is the preferred surgical option if conservative treatments fail to correct the OSA/UAO.

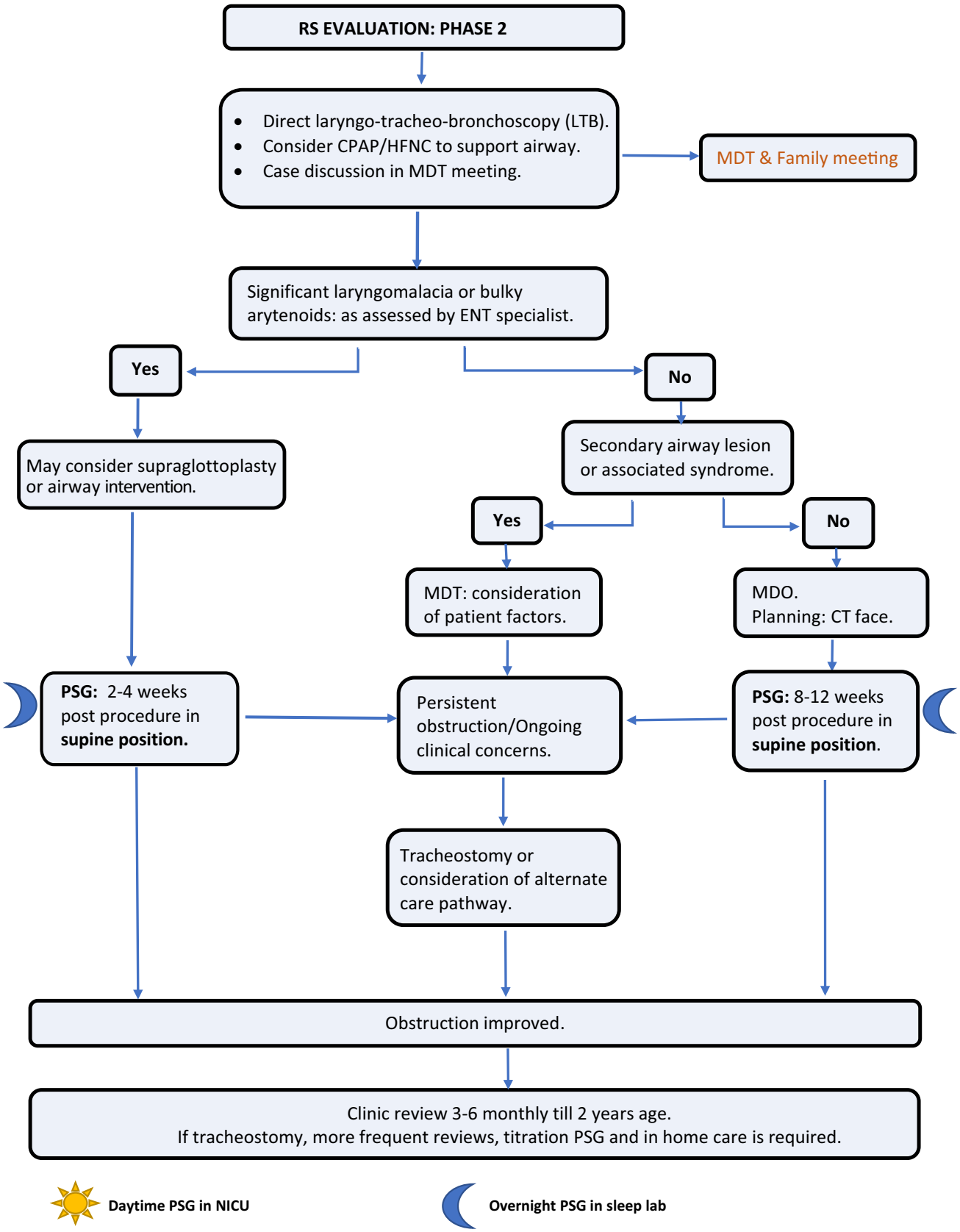

FIGURE 4 | (Continued)

Tracheostomy should be carefully considered in infants with an associated syndrome, synchronous airway lesions or if mandibular distraction osteogenesis does not correct the OSA/UAO (Figure 4).

Fifth, if no OSA is found on the initial PSG, repeat assessment, and follow-up is planned. In the presence of OSA which resolves with treatment, clearly defined discharge, follow-up and time

point of stopping treatment are outlined. Additional patient factors, such as distance from the hospital to residence or adverse socioeconomic conditions are to be considered when planning discharge on conservative treatment and when considering the need for surgical intervention (Figure 4).

5 | Discussion

Given the need for standardisation of assessment and treatment of UAO in infants with RS, we developed the ASSA based on evidence, consensus, and most importantly patient feedback. We believe this unique approach will guide clinicians while managing infants with RS globally.

Implementation of a standardised pathway decreases the length of hospital stay and increase the value of care for multiple paediatric conditions [40]. We expect standardisation of UAO management for RS infants will not only decrease the length of stay but also result in early and effective relief of UAO. Hence, we expect the standardised pathway will improve breathing, feeding, growth and neurodevelopmental outcomes.

An earlier attempt by Evans et al. [1] to standardise care for RS infants was limited to providing a framework for multidisciplinary involvement and identifying the need for objective assessment of UAO, but it didn't provide a practical stepwise pathway to do so.

Subsequently, attempts to standardise the management of UAO in RS infants were directed towards the identification of predictors for early surgical intervention such as PSG parameters [23], serial oximetry, weight gain and response to positioning [24], and Vancouver classification (degree of glossoptosis, maxillary-mandibular discrepancy, oxygen desaturation, feeding difficulty and coexisting airway morbidity) [41]. All these recommendations were based on a retrospective review of site-specific practice and again didn't provide a practical stepwise pathway.

Subsequently, two international surveys of experts were conducted to obtain consensus to standardise the assessment and management of UAO in RS infants. Based on the survey response of the International Paediatric ORL Group, Fayoux et al. [42] proposed clinical examination, flexible laryngoscopy or oximetry as first-line investigations and PSG as a second-line investigation to assess UAO. They didn't define the timing or criteria for grading the severity of OSA. Additionally, they proposed both conservative and surgical intervention as first-line treatment. However, we advocate for early and objective assessment of UAO with attended daytime PSG and a graded approach to treatment (conservative as first line followed by surgical intervention).

After an international survey, Resnick et al. proposed grading the severity of OSA based on PSG, similar to our approach [43]. However, they didn't define the timing of the initial PSG or the value of PSG indices or cut-offs for grading the severity of OSA. Also, they recommended surgical intervention as the first-line approach for moderate to severe OSA, which differs from our graded approach that allows a centre-specific conservative approach. Similar to ours, Resnick et al., recommended repeating the PSG to assess treatment efficacy, but the timing was significantly longer (4–6 weeks post-treatment) as compared to our proposed timing (3–14 days). It is important to note the recommendations by Resnick et al. [43] and Fayoux et al. [42] were based on survey responses of clinicians that are reflective of variation existing in practice, equipoise in literature and affected by reporting bias.

Gomez et al. proposed a pathway based on a systematic review of 23 articles [44]. They used oximetry as the first line tool to grade the severity of OSA, and PSG or awake flexible fibre- optic laryngoscopy as second line investigations. Their proposed pathway uses variable UAO assessment tools and hence may be difficult for practical use. Due to the lack of a defined time frame for individual steps, this pathway risks causing delay in decision making, prolongation of the hospital stay and variation in practice.

The pathway developed by Hicks et al. was based on a retrospective review of 31 children with RS [45]. Their approach differed from others and aligned with ours regarding the systematic use of pre-intervention and post-intervention PSG. They used AHI for grading the severity of OSA whereas we suggest OAHI given the higher number of central events seen in infants. Hicks et al. provided guidelines for initial management but didn't define the timing for individual steps, follow-up or treatment cessation which was one of the pivotal issues identified in our literature search. Their pathway advocated for the use of NPA as conservative management, while we provide adaptability for centre-specific treatment preference in our pathway.

Most of the available recommendations are difficult to translate into clinical practice as they don't clearly define objective timelines or criteria for treatment, individualise treatment, or provide reassessment or escalation plans or follow-up timelines. Our suggested pathway ensures early diagnosis and assessment of the severity of UAO and aims to treat UAO effectively, starting with the least invasive option but ensuring a clearly defined escalation pathway towards surgical intervention. This pathway has been implemented in our centre, adapted for our centre-specific preferences [Reference Pierre RS (health.wa.gov.au)] [46].

5.1 | Limitations

Our suggested pathway relies on performing PSG regularly, which could create resource issues, even in tertiary care centres. However, the availability of portable PSG equipment provides a solution by enabling the conduct of a PSG at the bedside rather than in a sleep laboratory.

5.1.1 | Strengths

The strength of the pathway lies in its evidence-based approach and the fact that it is driven by patient feedback, and multidisciplinary consultation. The pathway also provides well-defined timelines and provides options for interventions that can be chosen based on local preferences and resources.

6 | Conclusion

We have developed a standardised pathway for the management of UAO/OSA based on the best available evidence, patient feedback, and extensive multidisciplinary consultation. The pathway is the first of its kind, allowing clinicians to choose treatment based on local resources and preferences, while still ensuring standardisation of management. Using standardised pathway is likely to improve short and long-term outcomes in RS infants. It also provides a framework for future comparisons of different treatment strategies enabling further research in this important condition. The success of the pathway in achieving its objectives needs to be evaluated with respect to acceptability to patient families and improvement in clinical outcomes.

Author Contributions

Dimple Goel: conceptualization, methodology, data curation, writing – original draft, writing – review and editing, investigation, validation, resources, funding acquisition, project administration. **Andrew Wilson:** validation, writing – review and editing, supervision, resources, project administration, methodology, funding acquisition. **Shripada Rao:** writing – review and editing, supervision, resources, project administration. **David Gillett:** supervision, resources, project administration, writing – review and editing, validation. **H. Hayley Herbert:** writing – review and editing, project administration, resources, supervision, validation. **Anne O'Donnell:** supervision, resources, project administration, methodology, writing – review and editing, validation.

Acknowledgements

We thank all the medical, nursing, and allied health staff of the Neonatal Intensive Care Unit, Neonatal, Respiratory and Sleep department, and Complex Airway Team (CAT) of Perth Children's Hospital for collaborative support. A special thanks to the clinical nurse manager Catherine Dunstan, clinical nurse specialist Kellie Francis, Senior sleep scientist Tracey Verstandig, sleep scientist Chloe Lappin and Rhiannon Plavsic, senior speech pathologist Basia Hamden, and geneticist Nick Patcher for support in the development and implementation of standardised approach (ASSA) at Perth Children's Hospital. We also thank Professor Gareth Baynam, Professor Karen Waters and Professor Jane Pillow for their supervision and support. Open access publishing facilitated by The University of Western Australia, as part of the Wiley - The University of Western Australia agreement via the Council of Australian University Librarians.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Individual study or patient data is not available to be shared as this is a review paper.

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