

Dysphonia in very preterm children: Prevalence, presentation, influencing factors and response to treatment.

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STATEMENT OF CANDIDATE CONTRIBUTION

In submitting this thesis for the degree of Doctor of Philosophy of the University of Western Australia, the candidate, Mary Victoria Reynolds, declares having received the assistance of the individuals acknowledged herein, as well as from the authors of scholarly works cited herein.

Study design

The candidate and her supervisors were responsible for the major aspects of the study design. The candidate reviewed the literature relevant to the clinical utility and diagnostic accuracy of outcome measures in paediatric dysphonia and selected the clinical and instrumental assessment measures utilised in each Phase of this study. The candidate was responsible for designing the intervention trialled in Phase III, based on a further literature review of therapy efficacy in paediatric dysphonia.

Data collection

The candidate conducted all clinical voice assessments in Phase I of this study and all intervention sessions and post-intervention clinical assessments in Phase III of this study. The candidate jointly conducted the laryngeal examinations in Phase II of this study, with Clinical Associate Professor Shyan Vijayasekaran operating the laryngoscope and determining medical diagnoses during the exam, and the candidate undertaking all preparatory work for the exam, providing patient instruction for assessment tasks during the exam and all procedural work following the exam. The candidate was jointly responsible, with the assistance of a research assistant, for abstracting data from medical charts for Phase I of this study.

Data analysis

The candidate conducted all statistical analysis, with advice from Dr Suzanne Meldrum and Dr Brad Zhang. The candidate calculated AVQI scores for all clinical assessments in Phases I and III of this study.

Write-up

The candidate wrote each chapter of this thesis, with review and critical feedback from her supervisors as required. The candidate conducted the literature reviews which formed the basis of Chapters 1, 2 and 5. In those chapters representing published works arising from this thesis, the candidate was responsible for the primary drafting of each manuscript, and design and execution of tables and figures. The co-authors were responsible for editing for critical feedback and approval of the final manuscript for publication.

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THESIS SUMMARY

Introduction

Dysphonia is a potential long-term outcome of extreme prematurity and has been linked with female gender, multiple intubations, extremely low birth weight, birth at <27 weeks gestation, complicated intubation procedure and surgical ligation of patent ductus arteriosus (**Chapter 2**). Dysphonia in extremely preterm children may be persistent (**Chapter 3**). The aforementioned risk factors may also be experienced following very preterm birth, yet systematic investigations of voice outcomes in very preterm children are lacking.

Aims

This thesis presents the prevalence of dysphonia in very preterm children aged between 6 and 12 years old in Western Australia, with reference to a term-born comparison group recruited from the same community (**Chapters 6 and 7**). Demographic and medical data were abstracted from medical charts to identify factors correlated with adverse voice outcomes at school age. Perceptual and acoustic data from the clinical voice assessments were used to determine the external validity of an index score of dysphonia severity, the Acoustic Voice Quality Index, in childhood voice disorders. Laryngeal examinations were conducted on consenting children with voice problems of at least moderate severity to document the nature and extent of any laryngeal injury underlying disturbance to the vocal signal. Finally, a trial of behavioural voice therapy was conducted, to determine whether non-invasive vocal exercises would have any effect on voice quality in very preterm children.

Results

The prevalence of dysphonia in this very preterm cohort was 61.2%, a higher prevalence than in the term-born reference group, at 30.5%. Perceptual judgements of voice quality were supported by the use of an acoustic evaluation of disturbance to the vocal signal (**Chapter 11**). Laryngeal examinations demonstrated that very preterm children present with laryngeal damage affecting the structure and function of the larynx during phonation, of varying degrees of severity (**Chapter 8**). The most common pathologies were incomplete glottic closure resulting from posterior chink and vocal fold atrophy and immobility. Each child presented with tightening of the supraglottic musculature during phonation, resulting in a strained vocal quality. Some preterm children experienced acceptable improvements in voice quality following behavioural intervention; however, most did not (**Chapters 9 and 10**).

Conclusions

Mild voice disorders, resulting from inefficient use of the vocal mechanism, are common in childhood, as demonstrated by the prevalence identified in this term-born cohort. However, the incidence of voice problems in very preterm children is higher than would be expected from voice overuse alone. The element of strain present in the voices of very preterm children, is hypothesised to be a maladaptive attempting to compensate for glottic incompetence. It is further hypothesised that those children who experienced improvements in voice quality had succeeded in reducing the supraglottic hyperfunctional component to their phonation. However, resolution of voice to a perceptually normal quality was not achieved, in part because of the likely persistence of structural laryngeal pathology. Implications of these findings in the context of the wider literature are discussed. Clinical recommendations arising from these findings are also presented (**Chapter 12**).

DECLARATION FOR THESIS CONTAINING PUBLISHED WORK AND/OR WORK
PREPARED FOR PUBLICATION

This thesis contains published work and/or work prepared for publication, **some of which has been co-authored**. The bibliographical details of the work and where it appears in the thesis are outlined below. Written consent has been obtained from each co-author to include published work and/or work prepared for publication within this thesis, as per the list below. The full statement of candidate contribution is provided on page i.

PUBLICATIONS ARISING FROM THIS THESIS

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GLOSSARY OF TERMS AND ABBREVIATIONS

- Aesthenicity: perception of weakness, lack of power or underlying respiratory support¹
- AUC: area under receiver operator curve
- AVQI: Acoustic Voice Quality Index²
- BPD: bronchopulmonary dysplasia
- Breathiness: perception of excess air escape through the glottis during phonation³
- BW: birth weight
- CA: chronological age
- CAJ: cricoarytenoid joint
- CAPE-V: Consensus Auditory Perceptual Evaluation of Voice scale⁴
- CP: cerebral palsy
- CPAP: continuous positive airway pressure ventilation
- CSID: Cepstral Spectral Index of Dysphonia⁵
- EMG: electromyography
- ETT: endotracheal tube
- GA: gestational age
- GCQ: Growing and Changing Questionnaire⁶
- GRBAS: Grade, Roughness, Breathiness, Aesthenia, Strain scale³
- Hypernasality: excess air escape through the nasal cavity during speech⁷
- Hyponasality: insufficient air escape through the nasal cavity during speech⁷
- ICC: intraclass correlation coefficient
- Jitter: cycle-to-cycle variability of vocal fold vibration resulting in pitch fluctuations⁸
- LVCP: left unilateral vocal cord paralysis
- nCPAP: nasal continuous positive airway pressure
- NICU: neonatal intensive care unit
- PDA: patent ductus arteriosus
- pVHI: Pediatric Voice Handicap Index⁹
- ROC: receiver operator curve

GLOSSARY OF TERMS AND ABBREVIATIONS (CONT.)

Roughness: perception of variations in pitch and amplitude of vocal signal³

SD: standard deviation

SERF: Stroboscopy Evaluation Rating Form¹⁰

SGA: small for gestational age

SGS: subglottic stenosis

Shimmer: cycle-to-cycle variability of vocal fold vibration resulting in amplitude fluctuations⁸

SNR: signal to noise ratio

Strain: excess muscle tension used to initiate or sustain phonation³

VC: vocal cord

VP: very preterm

Chapter 1

Introduction and background

1.1 Executive summary

Dysphonia is defined as deviance in the sound quality of the voice produced during speech. An individual's voice is considered dysphonic when it differs perceptually from norms associated with gender, age, stature and culture, or when it impedes the activities of daily living.¹¹ Dysphonia is recognised in the World Health Organisation's International Classification of Diseases: it may arise as a primary condition, or secondary to disease, illness or structural abnormality, such as laryngeal carcinoma or vocal fold paralysis.¹²

Children born very preterm are at high risk of long-term voice problems, as many are treated with endotracheal intubation in the neonatal period. Endotracheal intubation has been associated with laryngeal injury in neonates.¹³ It is hypothesised that there will be a high prevalence of dysphonia among preterm children, with incidence decreasing with increasing gestational age.

The presence and severity of dysphonia should be assessed in this population using a thorough protocol consisting of acoustic, perceptual and quality of life measures validated for use in paediatric voice disorders. Instrumental assessment is also required to accurately diagnose laryngeal pathology and inform treatment. Data pertaining to the variables relevant to medical care in the neonatal period should be investigated to explore any relationships between medical care and adverse voice outcomes. Finally, there is a need to investigate treatment efficacy to mitigate the effects of prematurity and associated treatment on voice quality in the long term.

1.2 Introduction to paediatric voice disorders

Voice production requires efficient and timely coordination of several body systems. Voice is produced when exhaled air passes through the larynx, yet respiratory patterns for speech differ from those of non-speech tasks. Respiratory rate decreases, proportion of total lung volume is greater than for respiration at rest, and duration of exhalation is longer, suggesting that voice production is dependent on the nature of an individual's respiration behaviour and on efficient coordination between laryngeal functioning and respiration.⁷

Production of aesthetically pleasing voice is dependent on the source (larynx), power (lungs and lung capacity) and filter (the vocal tract, including the oral and nasal

cavities).¹⁴ As air is exhaled from the lungs, the membranous portion of the vocal folds adducts and creates turbulence in the airflow.¹⁵ The elastic recoil of the vocal fold mucosa reacts to the alternating pressures in the glottis to produce sound, the quality of which will alter depending on factors such as the mass and tension of the vocal folds.^{15,16} The sound is filtered as it passes through the vocal tract and oral or nasal cavity; the positions of the lips, tongue and jaw determine the pitch, amplitude, resonance and physical characteristics of the sound signal.¹⁷ Voice quality will be optimal when these structures are intact.

Aspects of vocal quality such as pitch, volume, and regularity in the sound signal are produced via a complex combination of respiratory coordination and control of the laryngeal structures.⁷ The cricoarytenoid muscle controls the superior and inferior movement of the thyroid cartilage, altering the longitudinal tension of the vocal folds, contributing to the perception of pitch.⁷ Expiratory volume contributes to vocal loudness.⁷ A disruption to, or lack of coordination between, any of these processes can result in decreased voice quality. Aetiology of dysphonia may be attributable to one or a combination of causes: i). organic, resulting from structural anomalies in the respiratory and phonatory systems attributable to a known disease, disorder or injury; ii). functional, resulting from the way in which the structures are used and cared for by the voice user, including vocal abuse and poor laryngeal hygiene; and iii). psychogenic, meaning the absence of any identifiable physiological cause for the voice disorder, with individuals having a normally-appearing larynx.^{18,19} However, early changes in the structures of the larynx can occur with dysfunctional voice production and hyperfunctional strategies to initiate and sustain phonation occur when individuals attempt to produce a more perceptually acceptable voice to compensate for structural abnormalities.¹⁹ Thus, aetiology of dysphonia can be complex.

1.3 Rationale for investigating paediatric dysphonia

1.3.1 Incidence of dysphonia across the life span

Calculating the incidence of paediatric voice disorders is problematic as estimates vary widely. Earlier research proposed that the incidence is in the order of 6 – 9%²⁰; whereas more recent research has shown that up to 40% of children may be affected by dysphonia at some stage of childhood.^{18,21-23} Differing incidence figures may be partly accounted for by definitions of dysphonia adopted by various studies: one study found

“hoarseness” in 3.9% of preschool children,²⁴ while a 40% incidence figure was established including children with very mild perceptual disturbances in breathiness, roughness and resonance that may not be apparent to an untrained listener.^{21,24} One study found an incidence of observable laryngeal lesion using the more objective method of endoscopic evaluation of 30.3%.^{21,23} The true incidence of dysphonia in childhood continues to be debated. One reason for this increase may be the increased identification of hyperfunctional voice disorder, which is the maladaptive use of the structures used to initiate and sustain voicing, commonly seen in behaviours associated with the use of a loud voice, such as shouting and yelling.²⁵ Such behaviours are increasingly recognised as normal in childhood, and while the majority of children do not develop dysphonia, it can be seen that the higher figures reported in recent studies are consistent with increased recognition of the factors surrounding childhood voice use.²⁶

The most common paediatric voice disorder is nodules, produced by hyperadduction of the vocal folds and resultant microtrauma.²² Nodules are hypothesised to occur in 15 – 78% of children with chronic hoarseness.^{22,27} Other common causes of dysphonia in childhood also result from mucosal lesions and include epidermal cysts, with a reported incidence of 15.47% of children with chronic hoarseness.²⁸ Less common causes of dysphonia include juvenile onset recurrent respiratory papillomatosis, glottic web and vocal fold paralysis; each is indicated in less than 2% of children with dysphonia.²⁸ Iatrogenic causes of dysphonia are also reported. Incidence figures prove difficult to calculate due to the varying nature of the underlying medical conditions and the treatments instituted.²⁹ Adverse voice outcomes following surgical intervention such as laryngotracheal reconstruction, as well as for resection of juvenile onset recurrent respiratory papillomatosis, have been reported in small-scale studies, suggesting that incidence figures are low.^{30,31}

In adulthood, the lifetime prevalence of voice disorders is estimated to be 30%, however just 7% report a current voice disorder.³² This comparatively low incidence, together with clinical observation, has led to the hypothesis that nodules resolve with maturation.^{18,33} However, recent studies have found that up to 24% of post-mutation adolescents with a history of vocal nodules experience persistent dysphonia, with girls less likely to experience resolution than boys.^{22,34} Further, whilst some adults develop

dysphonia de novo in adulthood, some paediatric dysphonias persist over time unless treatment is instituted.^{22,34,35}

1.3.2 Adult and paediatric dysphonia as separate entities

Differences in the mechanisms of voice production in adults and children mean that each should be treated as separate clinical entities. Voice production is initiated when the anterior edges of the vocal folds interact with expiratory airflow from the lungs in both adults and children.¹⁵ The mucosa of the vocal folds is elastic and vibrates in response to pressure in the glottis, causing inferior-to-superior vibratory movement that sustains phonation.¹⁵ However, differences in anatomy and physiology in the mechanisms of voice production exist and are summarised below.

Table 1 contains a summary of the physical differences between the adult and paediatric phonatory systems. The differences between the size, shape and position of the paediatric larynx compared to that of an adult is to allow simultaneous swallowing and respiration in infancy, to facilitate coordination of the suck-swallow-breathe cycle.¹⁵ Several developmental processes are outlined, disruption of which may impair voice production.

Histological differences between child and adult larynges are known to exist but are not yet well understood.³⁶ Research into the developmental processes of the mucosa of the vocal folds continues, but there is consensus that the cellular structure of the laryngeal mucosa begins to transform in infancy and continues into adolescence. The histology of the mucosa in infancy is thought to protect infants from phonotrauma; such protection exists to a lesser degree in adults, particularly females, amongst whom phonotrauma is more prevalent.³⁶ Hyaluronic acid is a glycosaminoglycan interstitial “filler” matrix molecule, thought to provide a cushioning effect in tissue subject to microtrauma by supporting collagen and elastin fibres: it offers protection from the high frequency vocal fold vibration of infant cries.³⁷

In terms of respiratory capacity and function, differences have been found in the performance of children compared to adults.³⁸ These data suggest that differences in respiratory capacity and function between children and adults result in differences in voice production.

Table 1.1 Characteristics of adult and paediatric phonatory systems.

		Paediatric	Adult
Gross anatomical	Position of larynx	<i>Infancy</i> C3-4 ¹⁵ <i>Two years</i> C5 ³⁹	Between C6-7. ³⁹
	Composition of vocal folds	<i>Infancy</i> Membranous portion equal in length to cartilaginous portion. Growth of membrane during childhood ⁴⁰	Membranous portion is twice the length of the cartilaginous. ⁷
	Cartilage	Soft; yields easily to introduced structures. ⁴¹	More ossified than that in infants and children. ⁷
	Pharyngeal space	Short; lengthens as larynx descends. ⁴²	Elongated.
Fine anatomical	Composition of vocal fold mucosa	<i>Infancy</i> Single layer of diffuse cells immediately deep to the epithelial layer of the vocal folds. ^{37,43} Differentiation occurs throughout childhood. ³⁶	<i>Thirteen years</i> Layers of elastin and collagen fibre differentiated. ⁴³ <i>Post-maturation</i> Well-differentiated, tri-layered lamina propria deep to the epithelium established. ⁴⁴
	Hyaluronic acid concentration	High in membranous portion of vocal fold. ³⁷	Present in intermediate and deep layers of lamina propria, in lower concentration than in infants. ^{45,46}
	Maintenance of vocal intensity	<i>Four years</i> Required pulmonary pressure is double that of an adult. ³⁸ Greater rib cage incursion. ³⁸	Similar pulmonary pressure observed in ten year-olds and adults. ¹⁵
Respiratory subsystem	Proportion of respiratory vital capacity used during speech	High; may relate to decreased ability to regulate airflow through glottis during voice production. ³⁸	Lower than children. ³⁸

Perceptual differences exist between adult and child voices. Decreases to the fundamental frequency of voice are associated with physical changes to the larynx which occur between infancy, childhood and adolescence.⁴¹ Further, acoustic analysis of adult and child voices has shown that children have higher jitter⁸ and shimmer⁸ values, meaning there is greater irregularity in vocal fold vibration in normophonic children's voices than in adults.⁴⁷ Analysis of nonlinear parameters of the acoustic voice signal supports the theory that children's voices are less stable than those of adults.⁴⁸ Children also produce a lower harmonics-to-noise ratio, indicating more turbulent air leakage through the vocal folds during phonation, leading to the perception of breathiness.⁴⁴ The pitch range of children's voices is narrower than that of adults; the differences in histological structure of child and adult vocal folds are hypothesised to influence pitch control.⁴³

These data suggest that the acoustic properties of adult and child voices differ significantly and supports the hypothesis that they are two separate, yet related, clinical entities. The area of paediatric voice is now regarded as a clinical sub-speciality as clear differences exist between voice production in children and adults.

1.4 Nature of disturbances in voice quality

Voice quality can be disrupted in a number of ways: disturbance in voice timbre, resonance variations, pitch changes and loudness difficulties.^{15,18,19} Voice timbre, or quality, refers to the aesthetics of the sound of the voice.²⁵ Primary disruptions are: roughness, breathiness, aethenicity and strain.³ Resonance variations refer to inappropriate partitioning of the oral and nasal cavities during speech, by the function of the soft palate or structural abnormalities.¹⁸ Pitch variations occur as a symptom of disturbance in voice timbre, where a decrease in the fundamental frequency during speech results from decreased oscillation frequency of the vocal folds due to a lesion such as vocal fold nodules, polyps or scar tissue.^{18,19} However, pitch variations occur as a stand-alone dysphonia, related to mutation, where high pitch is maintained throughout and beyond puberty in males.¹⁸ Loudness problems may be behavioural in origin and refer to an individual's routine use of inappropriately loud or soft volume during speaking.²⁵

For accurate diagnosis and treatment, an understanding of the cause and extent of dysphonia is essential. Thus, the nature and aetiology must be considered, considering

the high incidence of dysphonia in childhood, the possibility for untreated paediatric dysphonia to persist into adulthood, and the adverse effects on the quality of life of affected individuals.

1.5 Consequences of dysphonia on quality of life

Dysphonia adversely impacts the quality of life of those affected, including their participation in social, academic and employment activities.^{49,50} Both adults and children with dysphonia report negative emotional experiences, such as anger, sadness and frustration at their voices, as well as physical symptoms such as pain and running out of air while speaking.^{35,50} There is a significant cost to the community associated with diagnosis and treatment.⁵¹ Based on patient report, voice disorders have been found to impose more limitations on social, physical and emotional functioning than angina pectoris, sciatica and chronic sinusitis.⁵²

Early investigations of societal attitudes towards adults with dysphonia demonstrated that listeners made adverse judgements about appearance and personality based on voices with disordered timbre and resonance.^{53,54} More recent research has focussed on children, and demonstrated that children with dysphonia demonstrate insight into their voice disorder from a young age.³⁵ Younger children focus primarily on physical symptoms, while adolescents describe limitations in activities requiring vocal participation.^{35,55} Both children and parents report emotional difficulties associated with dysphonia, including frustration, anger and sadness, with child reports of emotional difficulties increasing in adolescence.³⁵ Additionally, lay adults were also found to make adverse judgements about personality characteristics of children with disordered voices, suggesting that negative societal attitudes to people with dysphonia are also relevant to affected children.⁵⁴ A recent study into attitudes of teachers towards adolescent females with voice disorders confirmed these findings, suggesting significant potential for dysphonia to impact on academic success for affected children.⁵⁶ A further study of the attitudes of teachers and university students towards Cantonese-speaking children with voice difficulties showed that negative evaluations based on deviant voice quality also occur in non-Anglophonic cultures.⁵⁷ Speech-language pathology students have also compared personality traits of children with dysphonia more negatively than those with normal voices, suggesting that prejudices against children with voice disorders are pervasive, even amongst health professionals.⁵⁷ Therefore, due to the

potential adverse effects of dysphonia on quality of life during childhood, paediatric dysphonia is worthy of clinical and research attention.

1.6 Consequences of dysphonia on employment capacity

Approximately one-third of occupations in the developed world require professional use of the voice: that is, a clear and reliable voice quality is required to effectively discharge employment duties.⁵⁸ Some, unskilled occupations, such as telephony and sales, may be suitable for individuals with longstanding voice difficulties as their contact with listeners is short-term and transient. From a listener perspective, an individual with dysphonia in such an occupation may present similarly to an individual with voice disturbance resulting from an active upper respiratory tract infection. However, occupations requiring more learned and prolonged interaction with listeners should be considered differently. The cognitive demands of analysing and interpreting the speech of an individual with dysphonia are such as to detract from a listener's linguistic processing capacities.⁵⁹ Therefore, occupations in the fields of health, medicine and education may not be suitable for individuals with dysphonia due to the potential for adverse impact on a listener's health and education.

Due to the potential for untreated childhood voice difficulties to persist into adulthood, children with dysphonia may experience limitations on their employability. This may increase the burden of disease to the community, in terms of income and social support. Therefore, childhood voice disorders should also be considered in the context of future negative economic impact at an individual, workforce and societal level.

1.7 Risk factors associated with the development of voice disorders in children

In population studies, specific groups of children have been found to be more at risk of voice disorders, including those with: one older sibling, conductive hearing loss and/or frequent upper respiratory tract infections.²⁰ Production of excessive secretions, leading to frequent throat-clearing and coughing, and use of inhaled cortico-steroids are also hypothesised to increase an individual's risk, although there is no data supporting these hypotheses in children to date.²⁰

Intelligible speech production requires appropriate lung capacity for adequate breath support. Respiratory support is essential for pitch and volume control.⁷ Decreased respiratory capacity and control have been associated with loss of pitch, intonation and

volume, or decreased variability in any of these factors.⁷ Therefore, children with lung disease may be at risk of developing dysphonia, from this, as well as other causes. However, there are no relevant publications in the literature.

Traumatic injury to the larynx in childhood is rare, reported in 0.5% to 1% of paediatric trauma hospital admissions.⁶⁰⁻⁶² Blunt force or penetrating injuries from external sources can affect airway and voice outcomes, and reported to be increasing in incidence.⁶⁰⁻⁶² In these cases, dysphonia can result from the primary injury, surgical airway management or both.^{61,63} Laryngeal trauma can also result from iatrogenic causes, most commonly through ventilation practices and particularly from the use of endotracheal intubation.^{29,63}

1.7.1 The nature and extent of intubation injuries to the larynx in infancy

Several factors predispose the infant and child larynx to intubation injury relative to adults, which include the anatomy and physiology of the developing larynx, the nature of the intubation and the properties of the tracheal tubes used. Cartilage in the infant larynx is softer and more susceptible to damage from introduced structures.⁶⁴ There are differences in the shape of the laryngeal space, where infants have a funnel-shaped opening which predisposes injury to the cricothyroid membrane during intubation.²⁹ The narrowest lumen in children younger than eight years begins at the level of the vocal cords and extends to the sub-vocal cord level (c.f. the vocal cord opening in adults), which predisposes mucosal changes to the cricoid space if the tracheal tube touches the lumen and exerts pressure on the mucosa.^{29,65} The reported success rate of 44% of attempts at intubation of neonates suggests that there is a degree of difficulty associated with the procedure.⁶⁶ Further, mucosal injury sustained in infancy may disrupt the differentiation of the layers of the lamina propria, which commences after the first month of life. This may permanently alter the composition of the vocal folds, as the tissue differentiation occurs in the context of wound healing.

The incidence of children requiring long-term endotracheal intubation and tracheostomy has increased since the practice became widespread in the 1960s.^{18,67} The introduction of a tracheal tube inevitably results in trauma to the vocal folds, including lesions to the mucosal epithelium and granulation.¹⁸ Less severe lesions, including oedema and minor ulceration may be reversible on extubation, but severe, long-term damage has been documented.^{29,64,68} In addition, airway suction is associated with laryngeal injury.⁶⁹

Children with a history of intubation should be considered at high risk of dysphonia, as severe injuries to the airway have been reported in up to 47% of survivors on extubation.⁷⁰⁻⁷²

Mechanical ventilation is initiated to relieve immediate or impending respiratory distress at any time across the lifespan.^{73,74} Ventilation may be invasive or non-invasive; non-invasive ventilation does not require placement of an endotracheal tube.⁷⁴ Invasive procedures have been associated with greater and more permanent laryngeal sequelae.⁷³ The nature of ventilation required is determined by factors such as patient premorbid health, requirement for emergency intubation, the nature of respiratory distress (e.g., airway obstruction or pulmonary dysfunction) and institutional practices.^{75,76}

Intubation injuries to the larynx have been documented across demographics, and a particularly high rate of injury has been reported in infants compared to adults.^{64,75,77-80} In general, mild changes to the larynx, in particular oedema and early mucosal change, have been found to resolve within three days to three weeks following extubation in adults.^{75,81} However, long-term changes have also been documented.⁸¹ Deep ulceration is a precursor to permanent, laryngeal injury.⁶⁴ Traumatic injury to the infant larynx, such as tracheal rupture, avulsion of the vocal folds and cricoarytenoid fixation and subluxation, has also been documented.^{69,82,83}

Cuffed tracheal tubes have been routinely used in adults, however, controversy persists regarding their suitability for use in children and as such they are never used for routine neonatal management.^{84,85} Generally, there is consensus that they should be used for short periods only (e.g., in surgical procedures of a short duration) or when an airway seal is necessary to measure metabolic function perioperatively (e.g., in some cardiac surgery).⁸⁵⁻⁸⁷ Whilst the use of appropriately-sized cuffs is the primary predictive factor in avoiding post-extubation laryngeal sequelae with the use of cuffed tubes,⁸⁸ calculations of cuff size prior to the administration of anaesthetic may result in overestimation, particularly in infants where the margin of error is smaller than in adults.^{29,88}

Use of inappropriately-sized endotracheal tubes is associated with increased likelihood of intubation injury.^{29,64,89} The smallest lumen possible for effective ventilation represents a high body weight: tube size ratio in very low birth weight infants. This is inevitable for preservation of life. Regardless of tube size or placement, the pressure of

the tube will inevitably exceed the pressure of capillary flow in the mucosa at some point along its insertion and lead to mucosal changes, only some of which will be reversible.⁶⁴ Movement of the tracheal tube in situ may also lead to damage.⁸¹ Preterm infants have been shown to exhibit movement-based stress cues in response to pain stimuli.⁹⁰ Infant restlessness and agitation has been associated with unplanned extubation events.⁹¹ Additionally, oral placement is preferable to nasal placement due to the risk of nasal deformities.⁹² Yet the orotracheal tube is less secure and is more mobile in situ,⁹³ thus it can be seen that decisions regarding appropriate ventilation in children born very preterm are complex.

Severity and permanence of intubation injury has been associated with duration of intubation, traumatic intubation and frequency of reintubation.^{64,69,75,77,82} Reintubation is preferred over surgical intervention in cases of extubation failure as it results in less severe laryngeal injury.⁷¹ However, intervention in cases of extubation failure will inevitably result in further laryngeal injury, and severity of laryngeal injury prior to extubation increases the likelihood of extubation failure.⁷¹ Where intubation is initiated to relieve acute respiratory distress in infancy and childhood, these factors may never be completely obviated, and it can be seen that there is a complex, multifactorial relationship between intubation and laryngeal injury.

It may be possible to limit laryngeal injury in older infants through the use of non-invasive ventilation, however, injury to the lungs can occur.⁷³ Dysphonia can result from decreased respiratory capacity or control in the absence of laryngeal injury. Injury to the lungs may be structural, such as overdistention following high tidal volume ventilation or atelectasis following low tidal volume ventilation.⁹⁴ Histological changes such as damage to the epithelial cells of the alveoli also occur following volutrauma.⁹⁴ Therefore, children who require non-invasive ventilator support may also be at risk of long-term dysphonia, and a link between bronchopulmonary dysplasia and limitations on voice-related quality of life has been reported, although there is no extant research investigating functional voice outcomes in such children.⁹⁵

1.8 Particular circumstances of very preterm children

The gestational age range of 23⁰ to 25⁶ is considered to be the “grey zone” of survival, with the greatest uncertainty about the likelihood of mortality or significant morbidity.⁹⁶ However, the likelihood of surviving extremely preterm birth is increasing^{97,98} and will

result in greater numbers of survivors actively participating in society.⁹⁷ This number can be expected to grow in proportion to population growth and commensurate with advances in medical technology, therefore, the susceptibility of children born extremely preterm to voice disorders should be investigated.

1.8.1 Congenital and medical issues

There are a number of congenital and medical factors that predispose respiratory and laryngeal damage in extremely preterm infants and increase the risk of dysphonia.

1.8.1.1 Ventilation

Mechanical ventilation is necessary to preserve life in the perinatal period for many children born very preterm, as they are at high risk of developing respiratory distress syndrome.^{73,74} It is estimated that 60% of children born at 28 weeks gestation are affected, decreasing to less than 5% of children born at 34 weeks.⁸⁶

Use of non-invasive ventilation reduces iatrogenic damage to the airway and lungs. Short-term continuous positive airway pressure ventilation (CPAP) is used in infants who are more medically stable and thus the demonstrated association with decreased risk of respiratory failure and death is due to a combination of ventilation practices and medical stability of the infants.⁷³ Trials of CPAP in the perinatal period, prior to the introduction of endotracheal intubation, have shown decreased incidence of bronchopulmonary dysplasia (BPD);⁷⁴ therefore, where neonates have good respiratory drive, CPAP is generally preferred, but this is not the case for earliest or sickest neonates who may require intubation for several weeks.^{86,98} Long-term use of CPAP has been linked with increased risk of pneumothorax and damage to the external nares.^{73,74} Additionally, early extubation to nCPAP is less successful in extremely preterm infants, leading to multiple intubations in the first month of life.⁹⁹ Some very low birth weight infants continue to experience respiratory distress or failure with CPAP. Therefore, invasive ventilation techniques such as endotracheal intubation are often necessary in the perinatal period following extreme preterm birth to preserve life, and this is often performed under emergency conditions.^{86,100} Thus, the use of certain ventilation practices is unavoidable.

1.8.1.2 Gastrooesophageal reflux

Children born extremely preterm receive parenteral or enteral nutrition as the ability to suck, swallow and coordinate these actions does not develop until later gestational ages, preventing oral feeding.^{101,102} The presence of a nasogastric tube to deliver enteral nutrition alters the pressure in the oesophagus and predisposes the reflux of gastric contents via a relaxed lower oesophageal sphincter.¹⁰³ In addition, preterm infants have higher incidence of gastrooesophageal reflux than their term-born counterparts generally, due to increased frequency of episodic relaxation of the lower oesophageal sphincter, resulting from gastric immaturity.¹⁰³⁻¹⁰⁵ Gastrooesophageal reflux is associated with exacerbations to intubation injury due to aspiration of refluxate, with affected individuals more likely to experience longer-term damage.⁶⁴

1.8.1.3 Persistence of patent ductus arteriosus

Persistence of patent ductus arteriosus (PDA) is a common feature following extremely preterm birth.¹⁰⁶ Incidence of PDA increases with decreasing gestation and birth weight.¹⁰⁷ The ductus arteriosus is patent in utero and forms a mechanism via which blood gases are exchanged in the absence of external respiration. At or shortly after birth, the ductus arteriosus closes due to the commencement of pulmonary respiration.¹⁰⁸ Haemodynamic flow through the duct after birth is associated with pulmonary complications, and closure is desirable.¹⁰⁶ Both surgical and medical closure of clinically significant PDA can be considered, however, due to higher fatality rates associated with surgical ligation, pharmacological therapy is preferred as a first resort.¹⁰⁹ Surgical ligation of patent ductus arteriosus has been associated with injury to the left recurrent laryngeal nerve, which innervates the vocal folds (see below).¹¹⁰ Adults with left unilateral vocal cord paralysis (LVCP) following PDA ligation surgery report voice symptoms, specifically hoarseness, as a primary concern.¹¹¹ However, research into long-term outcomes is limited to one study that did not assess the voice quality of adults with pharmacologically-treated PDA. Thus, it is possible that the presence of the PDA or the shunting of blood through the duct may also exert pressure on the left recurrent laryngeal nerve.¹¹¹

1.8.2 Laryngeal pathology following very preterm birth

1.8.2.1 Mucosal injury

There is a demonstrated association between duration of intubation and depth of mucosal injury in very low birthweight infants, where injuries were confined to the posterior glottis and the portion of the subglottis inferior to the arytenoid cartilage.¹¹² Of the 44 laryngeal specimens examined, all demonstrated a degree of mucosal injury and 27 were from infants born very preterm. However, the authors did not comment on any association between gestational age and severity of injury.¹¹² Superficial mucosal injury was observed after as little as ten minutes of intubation in this population.¹¹² Mucosal bridge (a.k.a, laryngeal web) has also been reported as part of a case series.¹¹³

1.8.2.2 Subglottic cysts

Subglottic cysts are thought to result from scarring and blockage of subglottic mucous glands associated with neonatal intubation.¹¹⁴ Subglottic cysts were considered rare, but have been increasingly reported in children born extremely preterm.¹¹⁴ The occurrence is reported to be 7.2% of extremely preterm infants requiring prolonged intubation.^{115,116} Early case study reports described hoarse infant cries as a symptom of subglottic cysts, some of which were recurrent.¹¹⁶ Subglottic cysts have been found in infants born at 28 weeks gestation who were intubated for as little as 24 hours.¹¹⁶ Subglottic cysts may also cause stridor or obstruct the airway.¹¹⁵

1.8.2.3 Acquired subglottic stenosis

Acquired subglottic stenosis (SGS) develops when fibrous tissue proliferates in the wound-healing process following removal of a tracheal tube, and can arise weeks or months following extubation.¹¹⁷ Acquired SGS has been reported to arise in up to 10% of preterm infants who undergo prolonged intubation.¹¹⁷ Factors related to intubation that increase the risk of SGS include length of intubation, frequency of reintubation, tube movement, tube size and respiratory tract infection during intubation.^{93,118-120}

Case study reports have also associated persistent dysphonia beyond infancy in children born extremely preterm with grade III and IV SGS requiring laryngotracheal reconstruction.¹³ It is unclear whether the dysphonia was related to the stenosis or the reconstruction or both, as it is not possible reliably determine the presence of dysphonia

from pre-surgery voice samples from young infants who require reconstruction. However, the source of the dysphonia may not be relevant for diagnosis or intervention; the presence of acquired SGS is indicative of risk of later voice difficulties.

1.8.2.4 Cricoarytenoid joint injury

Cricoarytenoid joint (CAJ) fixation and subluxation has been attributed to childhood dysphonia in a case study report.¹³ This hypothesis is supported by a post-mortem study demonstrating changes in the CAJ space in the larynges of children born extremely preterm who underwent endotracheal intubation, where seven of the 15 samples were found to have changes in the CAJ.⁸² One post-mortem case study of preterm twins found that the CAJ space was infiltrated initially by granulation tissue, and by fibrous matter as healing occurred.¹²¹ Whilst post-mortem studies provide important information about laryngeal pathology, the sample may be biased toward children who could not survive and may overestimate the incidence and severity of pathology in surviving children. Nonetheless, there is a clear relationship between neonatal intubation, CAJ pathology and childhood dysphonia.

1.8.2.5 Vocal cord injury and denervation

Surgical intervention in the neonatal period is an acquired cause of vocal fold paralysis.¹²² Surgical ligation of PDA has been associated with LVCP resulting from damage to the left recurrent laryngeal nerve, which extends to below the aortic arch and recurs to the level of the vocal folds.¹¹⁰ Whilst the procedure is generally considered a last resort treatment option for those infants who fail to respond to pharmacological therapy, such failure is associated with lower birth weight and gestational age.¹²³ Infants with lower birth weights and born at earlier gestations are also more likely to present with LVCP following the procedure.^{110,124} Surgical technique has not been found to correlate with the incidence of LVCP.¹²⁵

Pressure necrosis has been reported to result in injuries to the vocal folds such as posterior glottic furrow, which is associated with severely disrupted voice quality.^{113,126}

1.9 Dysphonia in children born very preterm: current evidence

As described above, injury to the larynx and lungs have been documented following prolonged intubation and preterm birth. Yet there has been little research to date

investigating voice outcomes.^{64,127} Case reports have associated dysphonia to neonatal intubation in children born very or extremely preterm. Three studies have reported on voice outcomes, in infancy, at school age and in a specific sub-population in adulthood. The lack of currently available empirical research leads to difficulties predicting, identifying and remediating dysphonia in these children in clinical settings. Further, it appears that dysphonia in preterm children is persistent. A case series is presented in manuscript form in **Chapter 3**.

Only four published studies have investigated voice outcomes beyond the neonatal period in those born preterm: three of those focussed on extreme prematurity and a detailed discussion can be found in **Chapter 4**.

The fourth study, by Walz and colleagues, was published after the manuscript which forms **Chapter 4**, and focussed on adverse effects of voice on quality of life in preterm children.¹²⁸ Duration of intubation greater than four weeks was associated with poorer voice-related quality of life. However, the use of parent-proxy quality of life measures, in preference to child-report measures and in the absence of any clinical assessment of voice quality, results in questionable generalisability of results. Whilst, in term-born populations parent report has been found to correlate highly with disturbance in voice quality identified on clinical assessment, this has not been the case in preterm children.¹²⁹ It is hypothesised that parents may consider dysphonia to be of relatively little concern, in comparison to the medical adversity encountered by their children at the time of their preterm birth, which may lead to inadvertent, underreporting of the effects of voice on quality of life. Therefore, clinical voice assessment is essential in the study of prematurity and dysphonia.

Dysphonia is a newly-recognised, potential long-term outcome of extremely preterm birth. Yet, the number of relevant, large-scale studies to establish this is small.

Dysphonia is known to occur in infancy and school-age, to persist into adulthood and have adverse effects on quality of life. Adverse voice outcomes have been associated with surgical ligation of PDA, and factors associated with endotracheal intubation, although to date there is no replication of any of these findings. The link between respiratory health and voice outcomes has yet to be investigated. There is a need to investigate the long-term voice outcomes in children born extremely preterm, and the association between voice outcomes and any variables surrounding treatment in the

neonatal period, as such data may inform treatment practices and contribute to the development of models of care.

1.10 Concluding remarks

The adverse effects of persistent dysphonia on social, employment, educational and quality of life outcomes are well documented. The negative impact of chronic disease is also well-documented and it is essential that every effort is made to change the long-term health outcomes of preterm children. A large body of research has focussed on long-term medical, behavioural, neurological and developmental outcomes for preterm children: it can be concluded that optimising quality of life and health outcomes is an essential aspect of research and medical care. As there has been little attention to dysphonia as a potential consequence of prematurity to date, it is essential that the incidence, prevalence, nature of the disorder and influencing factors be documented.

Additionally, a trial of voice therapy in preterm children who present with dysphonia at school age is required to determine responsiveness to behavioural treatment. The limited evidence available suggests that dysphonia in preterm children does not spontaneously resolve. It is imperative that treatment options are evaluated for efficacy and incorporated into follow-up programmes. Children born very preterm are routinely referred to ophthalmology and respiratory medicine specialists, as the effects of prematurity and associated medical intervention on pulmonary and eye health are well established. As dysphonia is hypothesised to be a frequent occurrence for children born preterm, referral to otorhinolaryngologists and speech pathologists for management of voice may also be routinely required.

This thesis is submitted as a series of chapters, five of which have been published in peer-reviewed journals, being Chapters 2, 3, 6, 8 and 9. Chapter 2 arises from the literature review required under this candidature. Chapter 3 reports the longitudinal voice outcomes of a small subset of extremely preterm participants and lends further weight to the rationale for investigating voice outcomes of preterm children as their persistence was demonstrated in this cohort. Chapter 6 describes the study protocol, incorporating each of the three Phases of this study. Chapter 8 reports on the outcomes of the second, laryngeal examination phase of this study. Chapter 9 describes the outcomes of two of the participants in the Phase three intervention trial. Another, reporting on the prevalence of dysphonia identified in Phase one of this study, has been

submitted for publication and is currently under review (Chapter 7) and a further two manuscripts under preparation (Chapters 10 and 11). Chapter 10 reports on the outcomes of the randomised, controlled trial in Phase three of this study. Chapter 11 reports on the use of perceptual and acoustic clinical assessment results from Phase one of this study to determine the external validity of the voice assessment measure, the AVQI, in childhood voice disorders. The introduction (this Chapter), study rationale, aims and hypotheses (Chapter 4), literature review of methods of assessment and intervention in paediatric dysphonia (Chapter 5) and general discussion (Chapter 12) have been prepared and presented as linking chapters.

Chapter 2

Dysphonia in preterm children: A review of the evidence

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2.1 Abstract

Introduction

Intubation is a known risk factor for dysphonia yet is essential in the perinatal care of many preterm infants. Children born preterm, who are frequently resuscitated with endotracheal intubation, may be at risk of dysphonia at school age and beyond.

Objective

To identify and describe the evidence pertaining to long-term voice outcomes and risk factors for developing dysphonia in preterm children.

Results

In addition to case studies and series, three larger-scale studies have reported on dysphonia and voice outcomes in preterm children. Studies reporting treatment outcomes were not available. Factors associated with poor voice outcomes included female gender, birth weight <1000g, birth at <27 weeks gestation, surgical closure of patent ductus arteriosus, emergency versus elective intubations and multiple intubations. Adverse voice outcomes were associated with laryngeal pathology and compensatory supraglottic compression.

Conclusions

Dysphonia is a newly-reported, long-term complication of preterm birth, yet the number of relevant studies remains limited. Further research is required to confirm the risk factors for developing dysphonia, which will inform future voice treatment studies.

2.2 Introduction

A voice is considered dysphonic when it differs perceptually from norms associated with gender, age, stature and culture, or when it impedes the activities of daily living.⁷ Dysphonia may arise as a primary condition, or secondary to disease, illness or structural laryngeal abnormality.⁷ Aetiology of dysphonia may be: i). organic, resulting from structural anomalies in the respiratory and phonatory systems attributable to a known disease, disorder or injury; ii). functional, resulting from the way in which the structures are used and cared for by the voice user; or iii). psychogenic, meaning the absence of any identifiable physiological cause for the voice disorder, with individuals having a normally-appearing larynx.¹⁹ However, such causes are not exclusive and likely to be comorbid and complex. For example, early changes in the structures of the larynx can occur with dysfunctional voice production, while hyperfunctional strategies to initiate and sustain phonation occur when individuals attempt to produce a more perceptually acceptable voice to compensate for structural abnormalities.¹⁹ Iatrogenic causes of dysphonia, such as from endotracheal intubation, are also reported but incidence figures prove difficult to calculate due to the varying nature of the underlying medical conditions and the treatments instituted.²⁹

The true incidence of dysphonia in school-aged children continues to be debated. An incidence of observable laryngeal abnormality of 30.3%, using objective endoscopic evaluation, has been reported in children aged 7 to 16 years, with a greater number of male children affected.²³ Using more subjective perceptual evaluation methods, incidence of up to 38% has been found in children aged 6 to 10 years, with slightly more girls affected than boys.²¹

Children with dysphonia demonstrate insight into their voice disorder from a young age.³⁵ Affected children report anger, sadness and frustration with their voices, in addition to physical symptoms such as pain and running out of air while speaking.^{35,50} Reports of emotional difficulties increase in adolescence, as do complaints of limitations in activities requiring vocal participation.³⁵ Listeners, including children, adolescents, teachers and speech-language pathology students, make adverse judgements about children with dysphonia.^{56,57} These judgements extend to non-voice related personality traits, suggesting that societal prejudices against children with dysphonia are pervasive.

Thus childhood dysphonia may significantly impact on social, academic and, consequently, employment outcomes.

Invasive ventilation procedures have been associated with serious and permanent laryngeal sequelae in preterm children.⁶⁴ Six studies have identified dysphonia as a symptom of laryngeal pathology following intubation in preterm children.^{13,69,71,115,126,130} Avulsion, scarring, oedema and lesions of the vocal folds have been described.^{69,71,126} Injury to the cricoarytenoid joint, such as subluxation or fixation, resulted in decreased vocal cord movement.¹²⁶ Dysphonia has also been identified as a symptom of acquired airway pathology, including subglottic stenosis and subglottic cysts.^{13,69,115,130} Surgical management of such pathology may also result in dysphonia.¹³ Surgical ligation of patent ductus arteriosus (PDA) in infancy has been associated with left vocal cord paralysis (LVCP) resulting from accidental resection of the left recurrent laryngeal nerve, which may cause dysphonia.¹¹⁰

One study reported a case of an adolescent female using supraglottic phonation as a compensatory voicing strategy secondary to ablation and scarring of the left aryepiglottic fold and vocal cord.⁶⁹ Thus, the possibility that adverse voice outcomes may be associated with maladaptive, hyperfunctional voicing behaviours must also be considered. Other causal factors may exist, but the majority of laryngeal injury reported in the literature to date is the result of intubation.

While there was inconsistency of assessment methodologies between studies, the reports lend further support to the hypothesised link between laryngeal pathology and adverse voice outcomes. Preterm children with a history of intubation should therefore be considered at high risk of dysphonia, as injuries to the airway have been reported in up to 61% of survivors on extubation.⁷¹

Whilst there is evidence regarding laryngeal injury following intubation in preterm children, the translation of this to functional voice outcomes is less clear. This review summarises the literature pertaining to dysphonia in preterm children: incidence and risk factors are discussed, and questions for future research proposed.

2.3 Results

Three large-scale observational studies reporting on the incidence of dysphonia in preterm children were identified.^{111,129,131} There were no studies reporting treatment or

therapy outcomes. The three studies report on cohorts of extremely preterm children. The literature does not yet extend to voice outcomes in very (28 - <32 weeks gestation) or moderate-to-late (32 - <37 weeks gestation) preterm children. A summary of findings can be seen in Table 2.1.

Table 2.1. Summary of voice outcomes in extremely preterm children.

Study details	Sample size	Inclusion criteria	Exclusion criteria	Dysphonia Incidence	Assessment methodology	Risk factors
Garten et al. (2011) ¹³¹	645	Birth weights <1,500g (GA not reported), NICU admission dates January 1998 – May 2006	Nil	6.6%	Retrospective review of electronic and hardcopy charts. Children identified were assessed by a speech pathologist using an in-house categorisation: all were diagnosed with dysphonia. No specific comment as to inter-rater reliability	Birth weight < 1000g History of endotracheal intubation Gestational age <28weeks Complicated intubations
Røksund et al. (2010) ¹¹¹	13	≤28 weeks GA OR ≤1000g birth weight 1982 – 1985 birthdates	Co-morbidities	54%	Self-report of voice difficulties, informal assessment of vocal weakness or hoarseness. No reliability assessment.	Surgical ligation of PDA Lower birth weight Longer periods of ventilation and oxygen treatment
French et al. (2013) ¹²⁹	67	<25 weeks GA 1996 – 2004 birthdates	Known disability likely to preclude participation in assessment tasks	58% (moderate to severe)	Prospective clinical assessment: perceptual evaluation (GRBAS) and quality of life questionnaire (pVHI). Intra- and inter-rater reliability was moderate.	Female gender >5 episodes of re-intubation

2.4 Discussion

2.4.1 Risk factors

Dysphonia was found to be associated with extreme prematurity, extremely low birth weight and emergency intubation procedures. There was a strong association with gender and frequency of re-intubation.

While the Røksund et al. study¹¹¹ was limited to a sub-section of the extremely preterm population, the Garten et al.¹³¹ and French et al.¹²⁹ studies had access to the entire cohort of neonatal intensive care unit (NICU) discharges in the respective study centres, so selection bias is unlikely. Common factors associated with dysphonia across those studies were birth at <27 weeks gestation, birth weight <1,000g and intubation. The risk factor of number of re-intubations identified by French and colleagues was not similarly found by Garten et al., yet the median number of intubations was higher in the infants with dysphonia than in the case controls in the latter paper. The variable found in the Garten et al. study, complicated procedure, was not replicated in the French et al. study due to incomplete documentation, suggesting that the quality of clinical documentation may be a potential limiting factor in risk identification. It is clear that intubation is a major contributing factor to voice outcomes in preterm children, but further investigation of intubation variables in this population is required.

One unique finding was the association between female gender and increased risk of dysphonia at school age by French et al. This is the first such finding reported in the literature and the study authors were not able to offer an explanation for this. Childhood voice disorders are more common in males than females in term-born populations, with most cases attributable to voice overuse.²³ However, the underlying cause of dysphonia in the extremely preterm cohort appears to differ from that in term-borns. One possible explanation is hormonal differences affecting laryngeal anatomy. In addition, females may more readily adopt compensatory, supraglottic tightening when producing voice, resulting in a strained vocal quality. This finding of susceptibility of females requires further investigation.

Dysphonia was identified in greater than half of extremely preterm individuals undergoing surgical ligation of PDA in the study by Røksund. Dysphonia was also reported in that study in individuals with a clinically significant PDA who did not

undergo ligation, suggesting an as-yet unexplained potential link between the presence of PDA and voice problems.

2.4.2 Mechanisms of aetiology of dysphonia in preterm infants

Mechanisms of aetiology of dysphonia in preterm infants are difficult to discern from the research conducted to date (Table 2.2). The strong association with intubation factors may be due to movement of the tracheal tube in situ or unplanned extubation due to infant restlessness and agitation leading to structural damage.^{81,91}

Røksund et al. highlight the role of surgical ligation of PDA in the development of dysphonia. Surgical ligation of PDA is often performed when attempts at pharmacological closure are unsuccessful, yet other factors associated with persistence of PDA, such as the development of pulmonary disease, may also influence voice outcomes. A quarter of participants in that study who did not undergo surgical ligation complained of voice symptoms, and the French study found a high incidence of dysphonia, but a low rate of surgical treatment of persistent PDA (4 out of 154 cases). Thus it appears that the procedure itself is not the only factor relevant to voice abnormalities, and voice outcomes of infants with a clinically significant PDA should be investigated.

None of the studies investigated hyperfunctional voicing behaviour as a possible cause or contributor to the development of dysphonia. Hyperfunctional strategies may be present in such a population to compensate for structural abnormalities, exacerbating the original condition.

Hyperfunctional voicing behaviour consisting of supraglottic constriction can only be reliably detected on fiberoptic endoscopic evaluation of the larynx. This procedure was performed in one study to assess the status of the left vocal cord, and as such no assessment of vocal hyperfunction was reported.¹¹¹ This review suggests that further research which includes visualisation of the larynx to better elucidate the mechanisms underlying dysphonia in preterm children is warranted.

2.4.3 Challenges of voice assessment

The incidence of dysphonia identified by clinical assessment of voice is higher than that identified by retrospective chart review. The studies utilising clinical voice assessment

yielded similar incidence figures, suggesting that this is a more reliable method of diagnosing voice disorders and may be preferable in future studies.

There is no consensus regarding an appropriate clinical assessment approach in childhood dysphonia. Expert consensus guidelines recommend assessment in three key areas of voice: perceptual evaluation of voice quality, acoustic analysis of the properties of the voice signal and a quality-of-life assessment.¹³² Acoustic analysis is essential in the evaluation of voice quality, as acoustic assessments are unbiased and more sensitive to change than perceptual instruments, but is rarely reported in the paediatric literature.

Each of the three studies used differing methodologies for perceptual assessment of voice quality, ranging from a subjective comment to a standard assessment tool. No study reported any objective acoustic measures. Two studies reported on quality-of-life outcomes, with dysphonia severity being associated with greater impact on affected individuals' quality of life. Controversy regarding a standardised assessment battery for dysphonia may persist, but future studies should include all three types of assessment to completely describe the nature and extent of dysphonia and its effects on preterm children. Further, in children with dysphonia, laryngoscopic assessment of voice production is desirable, to identify the precise mechanisms underlying the vocal dysfunction.

2.4.4 Future research directions

The following factors have been found to be associated with dysphonia in preterm children: low birth weight, extreme preterm birth, gender, frequency of re-intubation, complicated episodes of intubation and surgical ligation of PDA. The main foci of the three studies were demographic and iatrogenic variables. None of the studies investigated co-morbid medical conditions associated with prematurity, such as cerebral palsy which is known to affect speech and voice. One study reported the correlation between respiratory variables and left vocal cord paralysis, with positive findings, suggesting a potential link between respiratory health and dysphonia which should be further explored.

All the participants in the reviewed studies were born extremely premature; yet the risk factors identified are not limited to extremely preterm infants. The possibility that other preterm, or term, children with a similar history, may develop dysphonia cannot be

excluded. Further, all participants were intubated. The incidence of dysphonia in preterm children without a history of intubation should be explored.

Whilst some extremely preterm infants present with dysphonia following extubation, the protective effect of hyaluronic acid in infant vocal folds, and its role in tissue regeneration following phonotrauma, may mask laryngeal damage that may not fully declare until the layers of the vocal fold lamina propria begin to differentiate.³⁷

Dysphonia in infancy is not necessarily predictive of dysphonia at school age as individuals can develop dysphonia with increased language load at the time of emergence of speech or to compensate for underlying laryngeal injury – neither of which will be apparent in infancy. If follow-up is delayed to adulthood, additional costs incurred contacting patients may be incurred and the opportunity for early intervention lost. Children at risk of dysphonia related to birth and/or medical intervention in infancy may benefit from assessment at school age.

No systematic studies reporting on treatment of dysphonia in the preterm population were identified. Investigation of how to ameliorate the effects of dysphonia on the quality of life of affected children is necessary.

2.5 Conclusion

Dysphonia is a newly-reported, potential long-term outcome of preterm birth associated with female gender, extreme prematurity, extremely low birth weight, emergency intubation, frequency of re-intubation and surgical ligation of PDA. Further research into voice outcomes of preterm children is warranted, due to the small number of published studies. Long-term voice follow-up could be offered to those children at risk if efficacious management of dysphonia in this population becomes available.

2.6 Acknowledgements

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Chapter 3

Dysphonia in extremely preterm children: A longitudinal observation

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3.1 Abstract

Introduction

Dysphonia is a potential long-term complication of preterm birth. Childhood voice disorders caused by vocal hyperfunction resolve with pubertal changes to the vocal mechanism in many cases. In extremely preterm children, whose voice quality is affected by supraglottic hyperfunction adapted secondary to underlying structural laryngeal pathology sustained during neonatal intubation, the prognosis is unknown.

Methods

A pilot study was conducted to assess the incidence and severity of dysphonia in children born at <25 weeks gestation. Ten individuals, aged between 9.67 and 17.08 years, presented for repeat assessment in a replication and extension of the original study. The primary outcome measure was the severity score on the Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V), with the Acoustic Voice Quality Index score as the secondary outcome measure. Scores on the Pediatric Voice Handicap Index were also compared. The mean period between assessments was 2.85 SD 0.38 years.

Results

Perceptual dysphonia severity scores were significantly lower on repeat assessment, but no differences were observed in objective or quality of life scores. Individual variation was observed: the difference in CAPE-V scores ranged from -36 to +1. No participant presented with normal voice quality on repeat assessment.

Discussion

Analysis of group data masked individual variability in this cohort. Mechanisms underlying such individual variation are currently unknown. These data suggest that dysphonia is persistent in extremely preterm children.

Conclusion

Further investigation is warranted to elucidate the progression of voice disorders in extremely preterm children, to inform prognostic predictors and treatment decisions.

3.2 Introduction

Dysphonia is a potential complication of preterm birth (**Chapter 2**).¹³³ Dysphonia in preterm children has been associated with female gender, greater than five occasions of intubation, extreme prematurity, extremely low birth weight, emergency or complicated intubation procedure and surgical ligation of patent ductus arteriosus.^{111,129,131} Significant, long-term voice abnormalities have been reported in up to 58% of extremely preterm children.¹²⁹

Childhood voice disorders warrant clinical and research attention. The most common cause of dysphonia in children, vocal nodules, arises from hyperfunctional use of the laryngeal musculature, is amenable to behavioural voice therapy and resolves with completion of puberty in many cases.^{22,134} However, childhood dysphonia may persist into the adult years.

Listeners, both lay and professional, make adverse judgements about children with dysphonia on seemingly unrelated traits, such as intelligence and personality characteristics.^{54,56} Dysphonia may present a barrier to academic success and impede the ability to form relationships with peers.^{135,136} Dysphonia in adulthood limits participation in employment activities and adversely impacts on general health status.^{58,137} Thus it can be seen that the negative effects of voice disturbance persisting from childhood may be experienced across the lifespan.

Dysphonia following preterm birth has been reported from infancy to adulthood.^{111,129,131} Disturbances to voice quality result from a combination of structural laryngeal pathology and compensatory hyperfunctional use of the vocal mechanism and may be persistent (**Chapter 8**).^{69,126,129,138} Major structural laryngeal pathology sustained during neonatal intubation is unlikely to self-resolve.¹²⁶ However, hyperfunctional voicing behaviour may fluctuate over time, due to factors such as speaking task, maturation of neuromuscular control of the respiratory system and onset of puberty.^{22,38} It is unclear whether dysphonia severity in extremely preterm children changes over time, given the interplay between persistent laryngeal pathology and hyperfunctional voice use. Longitudinal studies are required to better inform individual prognoses yet are currently lacking in the literature.

This short communication reports the voice quality in a cohort of extremely preterm children who underwent repeat clinical assessment a minimum of two years after participating in a pilot study into the incidence of voice problems in children born at <25 weeks gestation.

3.3 Methods

The methodology of this study has been published elsewhere (**Chapter 6**).¹³⁹ A description of the method specific to these data is presented below.

Participants recruited for the pilot study who presented with moderate to severe dysphonia secondary to neonatal intubation were invited to participate in further assessment of voice quality.¹²⁹ The aims of a second study were to: identify the incidence of dysphonia in children born at ≤ 32 weeks gestation (Phase I); document the laryngeal pathology of very preterm children with significant voice abnormalities observed during videostroboscopic examination (Phase II) and trial a behavioural voice intervention (Phase III). Forty-one participants from the pilot study met the criteria for inclusion in this study. Four male and six female participants consented to laryngeal examination and repeat voice assessment. Participants were aged between 9.67 and 17.08 years at repeat assessment. The mean duration between assessments was 2.85 SD 0.38 years. No participant received voice intervention in the intervening period. Thus, we took the opportunity to examine any longitudinal changes which occurred in the intervening period. We report the outcomes of those individuals who participated in the pilot study, and who underwent further clinical voice assessment concurrently with the videostroboscopy assessments in Phase II of the larger trial. The results of Phases II and III will be published separately (**Chapters 8 and 10**).¹³⁸

Clinical assessment of voice quality consisted of:

- the Consensus Auditory Perceptual Evaluation of Voice (CAPE-V), a perceptual voice assessment where a normal voice is scored as 0 (no voice disturbance), mild dysphonia as 10, moderate dysphonia as 50 and a severe disruption in voice quality as 90.⁴;
- the Acoustic Voice Quality Index (AVQI), an objective assessment of dysphonia severity that has been validated for use in children, with an index score of >3.46 representing a dysphonic voice^{2,140}; and

- the Pediatric Voice Handicap Index (pVHI), where normative data demonstrates that children without dysphonia report a mean score of 2, and a higher score represents a higher adverse impact of dysphonia on daily activities.⁹

All assessments were conducted in a clinic room with an ambient noise level of <50dB. Perceptual assessments were conducted online by two speech pathologists with postgraduate experience in the assessment and treatment of paediatric voice disorders. To evaluate reliability of the data, the voice samples were de-identified and re-rated by the initial raters. Inter- and intra-rater reliability was calculated using intra-class correlation co-efficients (ICC) (SPSS Inc., Chicago, IL) and weighted kappa (VassarStats, Poughkeepsie, NY). The average ICC between raters for the CAPE-V severity score was .648 (95% CI .360-.806), with a weighed kappa of .36, indicating a fair level of agreement between raters. The de-identified samples were also re-rated by the first author. The average ICC within raters was .752 (95%CI .590-.856), with a weighted kappa of .56, indicating a moderate to good level of intrarater agreement. These results indicate that the CAPE-V score was a reliable measure of dysphonia severity in this cohort.

3.4 Results

To determine whether self-selection biased the data, voice, demographic and medical characteristics of participating and non-participating children were compared. Data is presented in Table 3.1. Duration of intubation was significantly lower in non-participating than participating children, yet no differences were observed in initial dysphonia severity.

Table 3.1. Characteristics of participating versus non-participating extremely preterm children

Characteristic	Participating	Non-participating	<i>p</i> value
	M (<i>SD</i>)	M (<i>SD</i>)	
	(<i>n</i> =10)	(<i>n</i> =31)	
GA (weeks)	23.70 (.48)	23.55 (.62)	
BW (grams)	602.00 (75.62)	631.77 (77.62)	.295
Number of intubations	6.70 (2.31)	5.68 (2.12)	.202
Duration of intubation (days)	56.70 (19.21)	43.48 (16.73)	.043
Maximum tube size	2.95 (.28)	2.81 (.33)	.229
Maximum tube size to body weight ratio	4.64 (.97)	4.29 (.55)	.160
CAPE-V severity score	60.00 (17.10)	58.06 (16.17)	.747
AVQI	5.44 (1.03)	5.61 (1.17)	.687
pVHI total score	35.50 (16.63)	32.48 (22.24)	.696

GA = gestational age, BW = birth weight, CAPE-V = Consensus Auditory-Perceptual Evaluation of Voice, AVQI = Acoustic Voice Quality Index, pVHI = Pediatric Voice Handicap Index.

Because of the ordinal nature of the data, we investigated non-parametric comparisons. However, normality of data distribution was investigated for each independent variable via the Shapiro-Wilks statistic and inspection of histograms, box plots and Q-Q plots and the data were found to be approximately normally distributed, with skewness and kurtosis statistics confirming that normality assumptions were not violated in this data set. Therefore, parametric tests were used to compare scores on the CAPE-V, AVQI and pVHI at initial and repeat assessment, to facilitate assessment of the clinical significance of the data.

Perceptual dysphonia severity on repeat assessment (60.00 SD 17.10) was significantly lower than initial assessment (72.20 SD 14.75) when measured on the CAPE-V, $t(9) = 3.539$, $p = .006$. However, there was no significant difference in acoustic assessment scores on the AVQI between initial (5.45 SD 1.03) and repeat (5.57 SD 1.54) assessment, $t(9) = -.358$, $p = .729$. Effects of voice on quality of life were also equivalent at initial (35.50 SD 16.64) and repeat assessment (38.80 SD 16.94), $t(9) = -.935$, $p = .374$.

Data is presented in Table 3.2 to demonstrate the individual variation observed in this cohort.

Table 3.2. Dysphonia severity in extremely preterm children at initial and repeat assessment

Case	Sex	Age at Assessment		CAPE-V Severity Score		pVHI Score		AVQI Score	
1	F	7.0	9.67	90	74	62	65	5.49	6.16
2	M	7.0	9.67	50	30	31	19	4.32	4.32
3	F	10.82	13.25	70	50	57	57	4.69	6.85
4	M	10.67	13.82	50	50	30	37	5.06	5.21
5	F	12.58	15.75	69	70	44	28	7.09	7.36
6	F	12.58	15.33	90	90	48	52	6.61	7.70
7	M	13.42	16.33	71	50	29	45	5.45	3.75
8	F	14.92	17.08	72	50	11	12	4.04	3.34
9	F	8.50	11.75	90	66	24	44	6.64	6.42
10	M	11.75	15.17	70	70	19	29	5.09	4.56

CAPE-V = Consensus Auditory-Perceptual Evaluation of Voice, AVQI = Acoustic Voice Quality Index, pVHI = Pediatric Voice Handicap Index.

3.5 Discussion

Significant voice abnormalities were present at initial and repeat assessment in this cohort of extremely preterm children. Comparison of the characteristics of the non-participating group demonstrated equivalence of voice quality on initial assessment. These results may therefore be considered representative of the extremely preterm population.

The reduction in dysphonia severity as measured by perceptual judgement was statistically significant. However, the clinical significance of the reduction is less clear. Inspection of the group means reveals a decrease in CAPE-V severity score from 72 to 60, and both scores represent a moderate to severe disturbance in voice quality. An untrained listener would consider such a voice to be noticeably impaired. Further, the CAPE-V is a subjective assessment of voice quality, and listener bias cannot be excluded. However, the AVQI, an objective assessment of disturbance to the voice signal, did not change significantly in the interval between assessments. Whilst there was some variation in individual results, no participant presented with a normal voice at repeat assessment. This suggests that, despite a minor reduction in severity of the mean

CAPE-V score across the group, dysphonia in extremely preterm children is persistent and unlikely to resolve without intervention.

The mechanism underlying individual decreases in dysphonia severity are unclear. Maturation may be a contributing factor in cases 5, 6, 7, 8 and 10, whose ages indicate that some pubertal changes may have occurred in the interval between assessments. In children with hyperfunctional voice disorders, with or without accompanying vocal nodules, completion of adolescence is associated with a reduction in dysphonia severity.³⁴ However, this is more common in males than females and it is currently unclear how voice quality is influenced by puberty in extremely preterm children.²² Cases 7 and 8 experienced a decrease in dysphonia severity, and may have experienced associated structural and hormonal changes to the larynx. However, voice quality was constant in the remaining three cases. As no participant experienced complete resolution of dysphonia, unlike term-born, non-intubated children,²² a link between puberty and normal voice cannot be drawn in extremely preterm children. However, pubertal changes may be a relevant influencing factor for some extremely preterm adolescents. The relationship between puberty and voice quality requires further investigation, with a particular focus on individual characteristics underlying improvements in voice quality.

In some cases, decreases in dysphonia severity occurred in children who were unlikely to have completed puberty (e.g., cases 1, 2, 3 and 9). Maturation of communication behaviour from the early childhood years, where phonotraumatic behaviour is common, may underlie some of this change. These data demonstrate that, regardless of the mechanism, changes in dysphonia severity across time in extremely preterm children are inconsistent, not yet predictable and do not effect resolution of voice disturbance to approximate normal phonation. Further investigation of these factors is essential, as, if any likely improvement with age and puberty can be quantified; the timing of intervention may be informed.

Given the persistence of dysphonia in extremely preterm children and the potential impediments to social relationships, employment participation and general well-being, it is essential to identify effective interventions. Surgical management has been effective in cases of posterior glottic incompetence where voice is severely disrupted, yet surgery tends to be deferred until post-adolescence to ensure complete maturation of the vocal system prior to inducing structural changes.^{126,141} Behavioural intervention is non-

invasive and its efficacy has been reported in children with primary hyperfunctional voice disorders.¹³⁴ It can be hypothesised that behavioural strategies may decrease tension in the supraglottic and laryngeal musculature and lead to improvements in voice quality in preterm children also. Full resolution of symptoms would not be expected, however, as underlying laryngeal pathology may be unaltered. Early reports support this hypothesis, but large scale studies are needed for greater ecological validity.¹⁴²

3.6 Conclusion

Dysphonia is persistent in extremely preterm children and does not follow the course of the majority of childhood voice problems. Due to potential adverse consequences on quality of life, social, academic and employment success, strategies to optimise voice quality should be investigated. This may include both surgical and behavioural treatment.

3.7 Declaration of interest

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The authors report no other declarations of interest.

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Chapter 4

Study Rationale, Aims and Hypotheses

4.1 Rationale for the study

Preterm children are at risk of persistent dysphonia as, in the care of such children in the neonatal period, many risk factors known to be associated with adverse voice quality are inevitable. Endotracheal intubation is frequently required to relieve respiratory distress, yet is known to cause structural laryngeal damage. Persistent difficulties with phonation through the school years have been reported in empirical research into voice outcomes in extremely preterm children and in case studies in very preterm children.^{64,129}

This study sought to build on the existing literature reporting on dysphonia following preterm birth, by presenting a comprehensive investigation into incidence, presentation, influencing factors and response to therapy, of voice difficulties in very preterm children.

4.2 Aims of the study

The aims of this study were to:

1. determine the targeted prevalence of dysphonia in targeted gestational age and intubation experience groups, as well as the presentation, nature and severity of voice disorders, in children born less or equal to 32 weeks gestation at school age, via prospective, clinical voice assessment in a sample of Western Australian preterm children aged between five and twelve years.
 - a. utilising the clinical assessment data from this phase, assess the external validity of the Acoustic Voice Quality Index (AVQI) in a paediatric population with a more even distribution of normal and dysphonic voices than that observed in our laboratory's pilot study, and to determine whether the AVQI retains its diagnostic utility under clinical recording conditions in the paediatric voice clinic.
2. explore the nature and extent of laryngeal pathology of preterm children with moderate to severe dysphonia, using a direct, videostroboscopy laryngeal examination with a flexible or rigid endoscope.
3. investigate the effectiveness of behavioural voice intervention, using a standardised protocol developed to address the hypothesised deficits in the areas of voice care, respiration patterns for speech, supraglottic hyperfunction

and inefficient voicing patterns, in preterm children with moderate to severe dysphonia.

4.3 Hypotheses of the study

It is hypothesised that children born at or equal to 32 weeks gestation will have a higher incidence of dysphonia than term-born children, because of the increased likelihood of exposure to a number of known risk factors for dysphonia, primarily endotracheal intubation (ETT).

It is further hypothesised that the incidence of dysphonia will decrease with increasing gestational age. It is believed that decreasing ETT exposure and increasing medical stability of the child will facilitate the recovery from any short-term laryngeal injury sustained in the neonatal period.

It is predicted that the nature and severity of laryngeal pathology in those children with moderate to severe dysphonia will be heterogeneous, due to the varying medical status of the children and nature of intervention provided in the neonatal intensive care unit (NICU).

It is predicted that behavioural voice therapy, delivered by a speech pathologist, will decrease the symptoms of dysphonia on instrumental and perceptual assessment, and decrease the impact of dysphonia on voice-related quality of life. Where significant structural laryngeal abnormalities exist, it is hypothesised that speech pathology treatment will be less effective.

It is hypothesised that the AVQI will demonstrate sensitivity to therapeutic change in this paediatric population, as this has been established in adult speakers. It is further hypothesised that the diagnostic utility of the AVQI found in our laboratory's pilot study will be consistent with the threshold for pathology in this larger paediatric population, and that the AVQI will retain its diagnostic utility in a larger sample of children with a more even distribution of vocal pathologies.

Chapter 5

Methods: Review of assessment and intervention methodologies in paediatric voice disorders

5.1 Assessment of the presence and severity of dysphonia

There is no consensus regarding an ideal assessment battery for dysphonia. Many published assessment measures lack reliability and validity data and clinical guidelines also lack evidence for some of the measures they recommend.¹⁴³ For clinical purposes, a three-pronged approach consisting of objective, perceptual and quality of life measures is considered best practice.¹⁴⁴ When used in combination, objective and perceptual measures have been found to identify, differentially diagnose and assess severity of dysphonia with greater accuracy than with either measure alone.¹⁴⁵

Additionally, instrumental assessments such as videolaryngostroboscopy visualise the larynx and examine the movement of the vocal folds during voicing.³⁶ However, there is disagreement about the diagnostic accuracy of many individual assessment instruments, although several have been trialled for use in paediatric populations.

5.1.1 Instrumental evaluation

Objective, instrumental visualisation of the structure and function of the larynx is considered the gold-standard assessment in both adult and paediatric voice disorders.^{7,36,146} In some cases, endoscopy should be performed under general anaesthetic, such as when making a differential diagnosis of vocal fold immobility or paralysis; however, mucosal wave during phonation cannot be viewed under these conditions.¹⁴⁷ Therefore, initial evaluation should be performed while the child is conscious and able to follow commands to initiate and sustain phonation, to reveal the movement and function of the vocal folds.^{36,148-150} Evaluation of the larynx via flexible transnasal or rigid transoral endoscopy visualises the gross anatomy of the larynx, and stroboscopy will facilitate assessment of mucosal wave and glottic closure.^{36,44,146} Rigid transoral endoscopy is not well tolerated by young children due to the size of the scope and the posture required to conduct the examination, and the development of flexible fibreoptic endoscopy technology made laryngeal imaging in the awake child possible.¹⁴⁶ However, the literature regarding the tolerance of children to such examinations is mixed, with a recent study concluding that it is problematic in young children, in comparison to earlier research, where full compliance was recorded.^{146,151,152}

While visualisation of the larynx during phonation under stroboscopic conditions remains ideal, the invasive nature of the procedure has led to interest in non-invasive

assessment methods such as laryngeal ultrasound. This method has been shown to identify the presence of laryngeal lesions, but differential diagnosis has so far remained elusive.²⁷ Therefore, despite the difficulties with compliance and discomfort, stroboscopic evaluation of the larynx during phonation remains the current tool for diagnosis of laryngeal pathology, as it is the only method by which to visualise the larynx and differentially diagnose the majority of laryngeal pathologies at the present time. It is recommended that all children with a history of intubation undergo visualisation of the larynx to facilitate accurate diagnosis of any injury and for treatment planning purposes.²⁹

5.1.2 Acoustic assessment

Objective assessment of voice refers to acoustic, computerised analysis of the speech signal.¹⁷ Acoustic assessments are objective, whereas perceptual assessments can be biased.¹⁵³ They are more sensitive to change and thus suitable to measure subtle changes over time or in response to intervention.²

Acoustic analysis of voice remains debated. There are a number of computer programmes available for this purpose, yet the results they yield do not correlate strongly.¹⁵⁴ Thus, consistency of conditions such as recording materials and procedures, calculation methods and use of computer analysis software is imperative. Acoustic analysis of highly aperiodic voices is unreliable but many dysphonic voices are highly aperiodic, particularly those with moderate to severe deviance.¹⁵³

Despite these difficulties, acoustic assessment of voice quality is desirable. Single acoustic measures are correlated with perceptual attributes and are thought to directly reflect the underlying dysfunction of the vocal folds: for example, perturbation measures jitter and shimmer are perceived subjectively as roughness, while a decreased harmonics-to-noise ratio is perceived as breathiness or turbulence.¹⁵⁵ Maximum phonation time is said to reflect underlying pulmonary capacity and the ratio between production of voiced and voiceless consonants can differentially diagnose vocal hyperfunction.⁴⁴ Consideration of these factors in isolation describes the nature of symptoms but does not indicate the presence or severity of dysphonia.

Traditionally, acoustic analysis has been conducted on sustained vowels, as they are the only speaking task on which it is possible to calculate perturbation measures.¹⁵⁶

However, as sustained vowels are not representative of conversational speech, their ecological validity is questionable.¹⁵⁷ Further, listeners tend to under- or overestimate dysphonia severity when using each measure alone and correlation between the ratings is poor.^{158,159} Therefore, objective assessment of the presence and severity of dysphonia should include both sustained vowels and connected speech.

There are a number of objective assessments of dysphonia severity.^{160,161} However, to date, the only validated assessments which include both speaking tasks are the AVQI and the CSID.^{2,5} However, only the AVQI is available to users at no cost.¹⁶² It is reliable, correlates with perceptual assessments of dysphonia severity, is sensitive to change and is therefore suitable as an assessment and therapy outcome measure.^{2,163} The AVQI has also been found to have diagnostic accuracy, with appropriate sensitivity and specificity, in a paediatric population.¹⁴⁰

5.1.3 Perceptual assessment

Perceptual evaluation of dysphonia refers to the subjective rating of voice quality by a trained listener. It is essential in the assessment and treatment of voice disorders, as individuals seek treatment because their voices sound different or abnormal and wish them to return to an aesthetically pleasing state.¹⁶⁴ A summary of the most commonly-used perceptual assessment measures is presented in Table 2.

There are some methodological difficulties associated with the use of perceptual assessments. Administration differs across languages, therefore cross-linguistic robustness is debatable.¹⁶⁵ Some non-standardised measures have been developed for use in research but information is limited and replication is not possible.¹³¹ The GRBAS has been the preferred assessment measure: adopted for its clinical utility and as a minimum standard for perceptual voice assessment.¹⁶⁵ Despite the recommendation that the GRBAS be a minimum standard of auditory-perceptual evaluation, in many published papers it is the only recorded such evaluation.

The most widely-used perceptual evaluation scale had previously been the GRBAS.³ However, the CAPE-V is now regularly used as a perceptual assessment measure in research and clinical practice, in preference to the GRBAS, as it is standardised and more comprehensive.^{30,31,166-168} However, there are some difficulties with the CAPE-V measure. Correlation of a detailed perceptual assessment measure (such as the CAPE-V)

with another measure such as the GRBAS, which is not considered a comprehensive assessment of the parameters of voice, is questionable. The standard established by the GRBAS, against which the CAPE-V is compared, could be considered to be inadequate thus raising concerns about the validity of the CAPE-V. Further, the GRBAS is a Likert scale, whereas the CAPE-V is a visual analogue scale.^{3,4} Whilst good correlations have been shown between the two methods of perceptual evaluation¹⁶⁹, differences in evaluation arising from the scoring methodology cannot be excluded.

This serves to highlight the difficulties associated with auditory-perceptual evaluation of voice disorders. It is considered a gold standard assessment of voice quality, as voice quality is primarily perceptual in nature.¹³² There is significant variability in perception, within and without listeners: any assessment method that is subject to inconsistent judgement must be utilised with caution. Users must ensure that their judgements are as consistent and bias-free as possible, by using perceptual anchors, undergoing regular training and/or calculating inter- and intra-rater reliability of their judgements.¹⁷⁰ Further, the CAPE-V has specific scoring and task instructions, in contrast to the GRBAS: this increases reliability through standardised administration of the measure.⁴ Thus, it can be considered the most appropriate perceptual assessment measure available for use in research and clinical practice, and includes more detailed assessment than the minimum standard set out by the GRBAS.

Table 5.1. Comparison of perceptual voice assessment measures.

Feature	Measure			
	GRBAS ³	CAPE-V ⁴	Vocal Profile Analysis Scheme ¹⁶⁵	Buffalo Voice Profile ²⁵
Degree of subjectivity	High. Stimulus materials specified but required sample short. Disagreement about interpretation of parameters and inconsistent use thereof. ^{4,170,171}	Low; standardised administration and scoring instructions. ⁴	Low; baseline for each parameter rated explicitly stated. ¹⁶⁵	Moderate; scoring instructions available but stimulus materials not specified. Baseline definitions of acceptable quality absent. ²⁵
Scoring method	4-point equal-appearing interval scale.	Visual analogue scale; improved sensitivity.	6-point equal-appearing interval scale.	7-point equal-appearing interval scale.
Comprehensiveness	Low; minimum standard for perceptual voice assessment. ¹⁴⁴	High; developed as a comprehensive assessment by expert consensus. ⁴	High; includes features of anatomy, physiology and voice quality. ¹⁷²	High; 12 features of voice quality and laryngeal functioning are rated. ²⁵
Research utility	Outcome measure in large number of studies; validation measure for new methodologies. ^{2,140,173-175}	Recent publication; emerging use as a research outcome measure (c.f. GRBAS). ^{5,166,168}	No studies identified using VPAS as a voice outcome measure.	Few studies report on BVP as outcome measure. ¹⁷⁶
Clinical utility	High; quick to administer and easy to score. ¹⁶⁵	Recent publication but uptake appears to be high.	High; most common measure in UK. ¹⁶⁵	High; widely used in UK and North America. ^{165,177}
Other	Some major perceptual attributes not accounted for (e.g., pitch, consistency, volume). Limited evaluation may not contribute to differential diagnosis.	Raters prompted to comment on less common features of voice; aids in differential diagnosis. Reliability established. ^{173,178}		

5.1.4 Quality of life

Quality of life measures evaluate patient perceptions of the impact of their health condition on activity participation and limitation. Inclusion of quality of life measures into assessment practices has been associated with better patient outcomes, improvement in communication between clinicians and patients and identification of latent symptoms such as psychological pathology, anxiety and distress.¹⁷⁹

Parent-proxy has been used to describe paediatric health conditions: however, discordance between parent and child attitudes has been found.^{35,179,180} Several parental reports of paediatric dysphonia symptoms have been developed (e.g., the Pediatric Voice Outcomes Survey¹⁸¹, the Pediatric Voice-Related Quality of Life¹⁸², the Pediatric Voice Handicap Index⁹), yet child self-report measures are in their infancy and have not yet been validated to a sufficient degree for use in clinical practice.^{35,180} The recently-developed Children's Voice Handicap Index is a child-report measure which has been validated for use in children aged between 8 and 14 years of age: it cannot be used in children under the age of 8 years, who are frequently seen in paediatric voice clinics.¹⁸³

Of the measures applicable to paediatric dysphonia, the pVHI is the most appropriate instrument for a number of reasons. It is a short questionnaire that canvasses voice-related symptoms across the physical, social and emotional domains, which assess the impact of dysphonia on activities and participation and informs treatment decisions. It may be sensitive to change and suitable for use as a therapy outcome measure.⁹

Appropriate assessment measures are available for use in paediatric populations in each of the essential areas of assessment of voice disorders: perceptual (CAPE-V), acoustic (AVQI) and quality of life (pVHI). Stroboscopic evaluation of the larynx should also be considered.

5.2 Intervention

Intervention strategies can be categorised as medical, including surgical and pharmacological, or behavioural.^{41,134 184} Behavioural strategies encompass voice therapy that is conducted by a speech pathologist.¹⁸⁵ The focus is on changing behaviour associated with voicing, and the term encompasses vocal hygiene, and direct and indirect techniques.¹⁸⁶ Direct voice therapy focusses on replacement of deviant phonatory strategies with voicing techniques that are compatible with healthy laryngeal

function.¹⁸⁷ Indirect voice therapy targets behaviours associated with voicing, such as breathing, relaxation and lifestyle modification.⁴⁴ Vocal hygiene refers to guidelines to minimise harm to the vocal mechanism during every day speaking contexts.⁷

In many voice disorders, a combination of medical and behavioural strategies is recommended where possible.¹³⁴ For example, surgical treatment of vocal nodules is accompanied by a period of voice therapy to prevent relapse.^{148,175} Medical management is indicated for treating the underlying causes of some dysphonias (e.g., reflux laryngitis).¹⁸⁴ It is currently unclear whether surgical procedures in childhood that damage the developing lamina propria may result in permanent damage to the adult larynx.¹⁴⁹ Therefore, surgery is now considered only necessary either to preserve life when airway management is required or when conservative treatments have failed.^{148,149,187} Whereas surgical excision was once the preferred treatment for nodules, recently recommendations have included a trial of behavioural therapy and a watchful waiting approach.^{134,148}

5.2.1 Common voice therapy techniques used in paediatric dysphonia

Surveys of the practices of speech pathologists working in the area of paediatric dysphonia demonstrate that a number of therapy techniques are currently in use, with varying levels of evidence available.¹⁸⁷ Most speech pathologists working in Australia use a combination of direct and indirect therapy approaches when working with children with vocal nodules.¹⁸⁷ Common indirect approaches include vocal hygiene education, laryngeal relaxation and abdominal breathing exercises.¹⁸⁷ The most frequently used direct therapy approaches include remediating hard glottal attack, the yawn-sigh technique and resonant voice therapy.¹⁸⁷

5.2.2 Evidence for intervention in paediatric dysphonia

There is scant evidence for the effectiveness of behavioural intervention, particularly voice therapy, in paediatric dysphonia. It is commonly held that intervention should be tailored to the individual needs of the child, and will vary depending on the child's age, presentation, the presence of vocally abusive behaviours, insight and motivation to effect change in their vocal symptoms.^{148,175} One difficulty with evaluating the literature pertaining to voice disorders is the lack of consistency of terminology. For example, hyperfunctional voice disorders are also referred to muscle tension dysphonia,

psychogenic voice disorders, non-organic or functional dysphonias.¹⁸⁸ Another is the critical lack of empirical studies into treatment effectiveness.¹⁸⁹

5.2.2.1 Hyperfunctional voice disorders

Three studies have examined the effectiveness of behavioural voice therapy in paediatric hyperfunctional voice disorders. They are limited to a case study and two small-scale studies with intervention groups of between 8 and 16 participants. One study was prospective; the other was reported from retrospective chart review.

A combination of vocal hygiene counselling and body movement therapy based on proprioceptive feedback to the laryngeal musculature has been found to improve subjective, but not objective, symptoms of dysphonia in the Italian language in the prospective study.¹⁹⁰ Factors associated with better outcomes included attitude to therapy, regular attendance and completion of home exercises. However, while vocal hygiene counselling is commonly used in the treatment of hyperfunctional voice disorders in the Anglophonic nations, there is no literature on the body movement therapy and its application to voice disorders in the English language.³⁶

A therapy protocol consisting of developing insight into the presence of and factors associated with dysphonia, relaxation of the musculature of the larynx and neck and using easy onset voicing to decrease hard glottal attack was effective in a small sample of children as determined from retrospective chart review.¹⁹¹ There were inconsistencies in outcome measurements and therapy delivery, in the nature, frequency and duration of therapy.

Laryngeal electromyography (EMG) has been used to provide biofeedback about tension in the laryngeal musculature, with reduction in laryngeal muscle tension demonstrated in a single child with a diagnosis of hyperfunctional voice disorder and a history of non-responsiveness to traditional voice therapy techniques.¹⁹² EMG is a non-invasive technique where weak electrical currents delivered via dermal patches are used to stimulate or monitor muscular contractions. It has been applied to treat neuromuscular and localised muscular disorders in both adults and paediatrics.¹⁴⁹ As a consequence of such treatment, voice quality and aerodynamic measures were improved, with effects maintained six months post-treatment. However, a literature search revealed

no other publications pertaining to therapeutic use of laryngeal EMG in paediatrics, although abundant literature is available for its application in adult voice disorders.¹⁹³

One study investigated the effects of family therapy on voice quality.¹⁹⁴ The participants were children who had nodules or a voice disorder of functional origin, and improvements in voice quality were demonstrated when psychological treatment focussing on family of origin issues was administered to the family unit.¹⁹⁴ However, the treatment model assumes underlying familial dysfunction, which may not be present for all children with dysphonia.

Laryngeal hyperfunction is hypothesised to be responsible for the development of the majority of paediatric voice disorders, yet there is little evidence regarding treatment efficacy, despite the view that hyperfunctional voice disorders will not self-resolve, in the absence of treatment.^{15,18,188} Hyperfunctional use of the larynx can result in the development of vocal fold nodules, among other benign vocal fold lesions.^{22,188} Thus, the literature pertaining to treatment of that condition must also be examined.

5.2.2.2 *Vocal fold nodules*

While vocal fold nodules are the most common paediatric voice disorder, there is little experimental evidence of treatment efficacy. A number of reviews and expert opinion reports are available, and there is consensus regarding an initial conservative approach, consisting of vocal hygiene counselling, counselling to reduce vocally abusive behaviours and direct voice therapy techniques, with this therapy described as the “cornerstone intervention”.^{41,148,195} The available opinion spans some four decades, suggesting that this view is persistent in the otolaryngological community.

Vocal hygiene counselling alone has been found to be ineffective in the management of vocal fold nodules in paediatrics, in contrast to adults.^{22,134,196} Whilst phonosurgery has been shown to have immediate improvements in voice symptoms, there are no follow-up data on recurrence of symptoms.¹³⁴ It is hypothesised that surgical excision of vocal fold nodules, while resulting in short-term improvement in voice symptoms, does not address the underlying cause and should be accompanied by voice therapy to maximise long-term outcomes.¹⁴⁸ Therefore, in studies investigating the efficacy of surgery alone, follow-up data is essential to facilitate conclusions about voice symptoms in the long

term. Therefore, the literature on voice therapy could provide insight into the effectiveness of intervention strategies.

Voice therapy consisting of a mix of a vocal hygiene component and counselling to decrease vocally abusive behaviours, diaphragmatic breathing techniques, relaxation, stretching exercises, the accent method of therapy and resonant voice therapy has been shown to decrease symptoms of dysphonia on both perceptual and acoustic measures.¹⁷⁵ The vocal hygiene and reduction in vocally abusive behaviour component of the study was well-described. The following behaviours were targeted: adequate and frequent hydration of the mucosa of the vocal tract, avoidance of speaking above background noise, changing posture by ceasing activity and facing a conversation partner, reduction in frequency of speaking during physical exertion and illness, facilitating decreased effort of speaking by allowing sufficient time for relaxation and play, and caregiver provision of specific, verbal and non-verbal feedback to the child throughout the behaviour modification programme.¹⁷⁵ Informal assessment of the frequency of these behaviours took place at each therapy session; most participants decreased vocally abusive behaviours by the second session, although 16 required two more sessions to successfully comply with this aspect of therapy.¹⁷⁵ More detailed reporting of the reduction in undesirable behaviours, in the form of a behaviour checklist or other frequency tally, would facilitate objective analysis of the effectiveness of this component. The available experimental evidence cautiously supports the inclusion of vocal hygiene education into voice therapy protocols and sufficient detail is provided for replication in future studies.

Additionally, voice therapy targeting the three voicing techniques of “voice presence and awareness”, “phonation duration” and “vocal attack”, delivered by a clinician with supplemental biofeedback from a specialised computer programme, has been shown to decrease voice symptoms on acoustic and perceptual measures, as well as resolve vocal nodules at follow-up six months’ post-treatment.¹⁹⁷ Whilst effectiveness of both treatments was demonstrated in prospective observational studies, the treatments were either not described in sufficient detail or were administered via computer software package that has been discontinued, therefore replication in either a research or clinical setting is impossible.¹⁹⁸ In addition, although one study included assessment data from normophonic children as case controls, the controls were not offered a therapy-like condition and a placebo effect cannot be excluded.¹⁹⁷

The analysis of all previous efficacy studies identified that one repeated difficulty with replicating the findings reported in the literature is the lack of detail of treatment methodologies. There is emphasis on the requirement to tailor therapy to the needs, preferences and behaviour of individual patients.^{41,148} Such responsiveness to individual needs may lead to increased compliance, better rapport and greater levels of trust between clinician and patient. However, if treatment methodologies are inconsistent, conclusions about their contribution to improvement in symptoms cannot be drawn as the presence of confounding variables cannot be excluded.

In the treatment of vocal fold nodules, evidence from two experimental studies and one retrospective chart review provides some evidence that voice therapy is effective at improving voice quality and reducing the appearance of vocal fold nodules.^{27,134,175,197} Vocal hygiene counselling targeting reduction of vocally abusive behaviours is seen as essential, and has been described in sufficient detail for replication in future studies.¹⁷⁵ Both indirect and direct therapies were effective, and should be included in any treatment battery. However, there is a need to investigate and describe the specific components of the therapies that were most effective in the resolution of symptoms.

5.2.2.3 *Laryngopharyngeal reflux*

Laryngopharyngeal reflux occurs when refluxed gastric contents spill into the oro- or nasopharynx and into the laryngeal vestibule.¹⁸⁴ It is a recently-recognised condition and has been found to be present in up to 56% of children with hoarseness and can co-occur with vocal fold nodules.¹⁹⁹ It is hypothesised in such cases, that the inflammatory response of the laryngeal mucosa to the acidity of the refluxate predisposes the early oedematous change indicated in the development of vocal fold nodules, and may be more common in children than previously thought.¹⁹⁹

Laryngopharyngeal reflux is a phenomenon related to, yet separate from, gastrooesophageal reflux, where refluxate is confined to the oesophagus and oral cavity.²⁰⁰ There is little evidence for the management of laryngopharyngeal reflux in paediatric dysphonia. Treatment with medication alone, voice therapy alone and a combination of the two interventions yielded similar results on retrospective chart review; however, the voice therapy was not described in sufficient detail to reproduce.¹⁹⁹ Consensus expert opinion suggests that lifestyle and positional

modification, medication, voice therapy and surgery can be considered in children, and that the preferred treatment strategy depends on the severity of the symptoms.^{184,199}

5.2.2.4 Voice therapy as an adjunct to surgical intervention

Adverse voice outcomes have been reported as a result of a number of laryngeal surgical procedures, including techniques associated with laryngotracheal reconstruction, such as anterior costal cartilage graft, cricothyroid resection and posterior division of the cricoid.^{39,201,202} Whilst there is expert opinion available that supports the use of voice therapy in other dysphonias and as an adjunct to surgical therapy to maximise voice outcomes, there are no experimental studies pertaining to this issue available in the literature.¹⁴⁸

Positive outcomes from voice therapy have been reported as part of larger case series and retrospective studies. Voice therapy was found to improve voice quality in a small population of children who had undergone laser arytenoidectomy for bilateral vocal fold paralysis.²⁰³ Due to the nature of the underlying health condition, there was no control group available for comparison.²⁰³ However, the voice therapy was not described in detail in the literature, nor were outcome measures reported; thus it is unclear which therapy techniques were administered and whether any biases were present in evaluation of outcomes. Children who undergo laryngotracheal reconstruction have been found to have dysphonia; it is not clear whether this relates solely to the procedure or whether there is a correlation with pre-operative laryngeal status.²⁰⁴ Behavioural voice therapy has either been recommended on basic scientific principles, or has been described as having occurred.^{39,204} However, there has been no research into its efficacy in this population to date.

5.2.2.5 Management of intubation-induced dysphonia

Currently, the literature is limited to case studies and case series (see **Chapters 8 and 9** for work published as part of this thesis).^{126,142,205} Success of surgical management was varied, and the use of behavioural voice therapy has yielded inconsistent results.

Therefore, there is a need for well-designed research into treatment efficacy in paediatric voice disorders, where treatment is described in sufficient detail to determine which aspects of treatment have contributed to therapeutic outcomes, allow replication of results in future studies and contribute to clinical therapy techniques.

5.2.3 Factors influencing treatment outcomes

Voice therapy is not well described in the literature. However, correlations between factors associated with treatment and better voice outcomes have been reported.

5.2.3.1 Dosage

An association between treatment frequency and more positive outcomes has been reported. Attendance for greater than seven sessions was associated with better voice outcomes, identified by factor analysis from retrospective chart review.¹³⁴ However, its utility is limited as it is unclear whether the influencing variable is attendance, or attendance associated with a particular therapy technique.

Frequency or dosage is an essential part of any treatment, and it is imperative that it be described in detail. Data from the two prospective observational studies reported in the paediatric voice literature shows that eight sessions are required to achieve change in voice symptoms.^{134,175,197} The length of each session was described in only one study, as consisting of 45 minutes.¹⁹⁷ The timing and frequency of therapy is relevant and further investigation is warranted.

5.2.3.2 Patient compliance

Associations between patient behaviour and positive voice outcomes have been observed. Attendance in one paediatric intervention study was 100%: the authors had cautioned participants that failure to attend would exclude them from participation in the study.¹⁹⁷ While removing participation as a confounding variable, this condition may have decreased the ecological validity of the results as it is questionable whether perfect attendance is feasible in a clinical setting. In adult patient groups, non-attendance rates of 44% have been reported.²⁰⁶

Reduction in vocally abusive behaviours was also associated with better therapy outcomes.¹⁷⁵ An issue of objectivity in measurement of behaviour change has been identified above. However, if an association between patient behaviour change and improvement in dysphonia symptoms is demonstrated, further research into the factors that facilitate behaviour change is warranted.

5.2.4 Lessons from the adult literature

Whilst there are a number of factors suggestive of different approaches to adult and paediatric dysphonia, the absence of literature pertaining to paediatrics specifically is problematic. Despite several studies extrapolating findings from adult studies, research in the paediatric population is still lacking, and further trials are required. This is particularly important, as clinicians are ethically-bound to treat individuals who present to them with pathology and request intervention.

5.3 Concluding remarks

Assessment of paediatric voice disorders should combine perceptual, acoustic and quality-of-life measures. A number of perceptual and quality-of-life measures have been shown to be reliable and valid in paediatric dysphonia. However, the external validity of the AVQI has yet to be established. Further, there is no standardised, objective outcome measure that is sensitive to therapeutic change in a paediatric population. The ideal measurement is the AVQI, which has been found to accurately discriminate between dysphonic and normal voices and correlate with dysphonia severity in a paediatric population. The responsiveness of the AVQI to change in children with dysphonia could be measured as an adjunct to an intervention trial, should the trial be sufficiently powered.

Chapter 6

Dysphonia in preterm children: Assessing incidence and response to treatment

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6.1 Abstract

Background: Mild dysphonia in childhood is surprisingly common, yet moderate to severe dysphonia is rare. The latter has been associated with complex medical conditions and congenital abnormalities. Intubation injury has also been documented as a cause of childhood dysphonia. Children born very preterm may be intubated as part of the intensive care administered in the perinatal and neonatal period, yet there are few studies investigating dysphonia in this population. This study will be the first to: use an objective acoustic voice assessment in a paediatric study, document the incidence of dysphonia in very preterm children at school age, and conduct a controlled trial of behavioural voice therapy in this population.

Design: This study will consist of three phases: assessment of voice quality and its impact on quality of life in up to 200 children born at less than 32 weeks gestation; assessment of the nature and extent of laryngeal pathology in children with moderate to severe dysphonia; and a non-blinded, randomised controlled trial of behavioural voice therapy in children with moderate to severe dysphonia.

Discussion: This study will be the first to use clinical assessment to examine the voice quality of very preterm children, and to use fiberoptic endoscopic evaluation of laryngeal function to determine the nature and extent of any laryngeal pathology in such children. Those participants with significant voice difficulties will be randomised to receive treatment immediately or after the eight week assessment.

Trial registration: This study is registered on the Australian New Zealand Clinical Trials Registry (ACTRN12613001015730/ACTRN12613001012763).

6.2 Introduction

Dysphonia is defined as deviance in the sound quality of the voice produced during speech. An individual's voice is considered dysphonic when it differs perceptually from norms associated with gender, age, stature and culture, or when it impedes the activities of daily living.¹¹

Mild dysphonia in childhood is common. The true incidence is debated but rates between 0.12% and 40% have been reported in otherwise typically-developing children.^{21,23,129,207} One large-scale study reported an incidence of 11%.²⁰

Communication behaviours frequently seen in children, such as shouting, making noises in play and prolonged voice use at elevated volumes place strain on the vocal mechanism and cause superficial mucosal injury, resulting in hoarseness.^{25,26} Such hoarseness usually resolves with changes to the vocal mechanism associated with adolescence and the maturation of communication behaviour in adolescence and adulthood.²² More severe forms of dysphonia in childhood are rare, and causative conditions include juvenile recurrent respiratory papillomatosis, vocal fold paralysis, glottic webs and intubation injury.^{28,68,208}

Dysphonia has adverse effects on academic, social and employment outcomes.^{52,137,209,210} Children with dysphonia are evaluated negatively, in comparison to their normophonic peers, on characteristics such as physical appearance and personality traits.^{54,135,210} Thus, dysphonia can have a significant impact on quality of life.

Tracheal intubation has been associated with laryngeal injury in neonates, and resultant dysphonia in children born very preterm has been reported in case study series.^{13,64,117} Many children born very preterm require resuscitation and ventilator support in the neonatal period.^{73,74} Dysphonia associated with emergency intubation in extremely preterm, extremely low birthweight infants at twelve months corrected age has been reported.¹³¹ Our laboratory has published a pilot study into dysphonia at school age in children born extremely preterm, who were born at less than 25 weeks gestation and intubated, and demonstrated that there is a strong association between intubation variables and voice outcomes.¹²⁹ The requirement to initiate endotracheal intubation to relieve respiratory distress syndrome and to administer surfactant is universal at less than 25 weeks gestation in Western Australia, and decreases with increasing gestational

age. By 32 weeks in our series, fewer than 25% of children are intubated, usually briefly for surfactant administration, and fewer than 2% require a second intubation. Thus, there is a need to investigate the long-term voice outcomes of preterm infants across a wider range of gestational ages, as they may also be considered at high risk of developing dysphonia.

A three-pronged approach to the assessment of the presence and severity of dysphonia, consisting of objective, perceptual and quality of life measures, is considered best practice.¹⁴⁴ Objective assessment refers to acoustic, computerised analysis of the speech signal.¹⁷ Greater accuracy in identification, differential diagnosis and severity judgements is achieved when objective and perceptual methods are used in combination.^{145, 2, 153} However, few composite objective measures have been validated for use in a paediatric population. The AVQI is an index score of the presence and severity of dysphonia calculated from acoustic parameters of the voice signal. It has been found to have diagnostic accuracy, with appropriate sensitivity and specificity, in a paediatric population in a pilot study in our laboratory.¹⁴⁰ However, the responsiveness of the AVQI to therapeutic change in children has yet to be investigated.

6.3 Overall aims of the study

The overall aims of the study are to assess:

1. The presence, severity and impact on quality-of-life of dysphonia for each participant group and to compare the incidence at each gestational age and intubation frequency (Phase I).
2. The nature, extent and severity of laryngeal pathology in a sample of children born very preterm, at school age (Phase II).
3. The effect of behavioural voice treatment on very preterm children's AVQI scores, G scores, CAPE-V results and pVHI scores, in comparison those who receive no treatment (Phase III).

6.4 Methods

This study will address the aims by:

- i) assessing the voice quality of up to 200 very preterm children, investigate its relationship to demographic and medical variables and use the AVQI to assess the presence of dysphonia based on acoustic parameters of the voice (Phase I Assessment);
- ii) documenting the nature and extent of laryngeal pathology in the subgroup of very preterm children with moderate to severe dysphonia (Phase II Videostroboscopy); and
- iii) determining the effect of behavioural voice therapy on the voice quality of Phase II participants (Phase III Intervention).

6.4.1 Phase I Assessment

Specific aims

1. The factors associated with increased odds ratios of the presence and severity of dysphonia.
2. The correlation between the AVQI and perceptual evaluations of dysphonia severity and to determine whether the threshold for pathology in children of 3.46 found in the pilot study is applicable to this larger population.

Participants

A total of up to 200 participants will be recruited. Eligible participants were born at less than 32 weeks gestation and hospitalised in the Neonatal Intensive Care Unit (NICU) at King Edward Memorial Hospital, the sole tertiary perinatal centre in Western Australia. Participants will be aged between 5 and 12 years at the time of assessment, to ensure compliance with assessment tasks. Selection will be stratified by intubation frequency and gestational age from a total of 1851 NICU discharges <32w over the study period, with random case selection within strata based on a medical record number algorithm, having excluded those children with a known disability likely to preclude successful assessment and/or who are resident greater than 200km from the study centre. The families of 391 children were approached to take part in the study. Figure 6.1 depicts the flow of participants through the study phases.

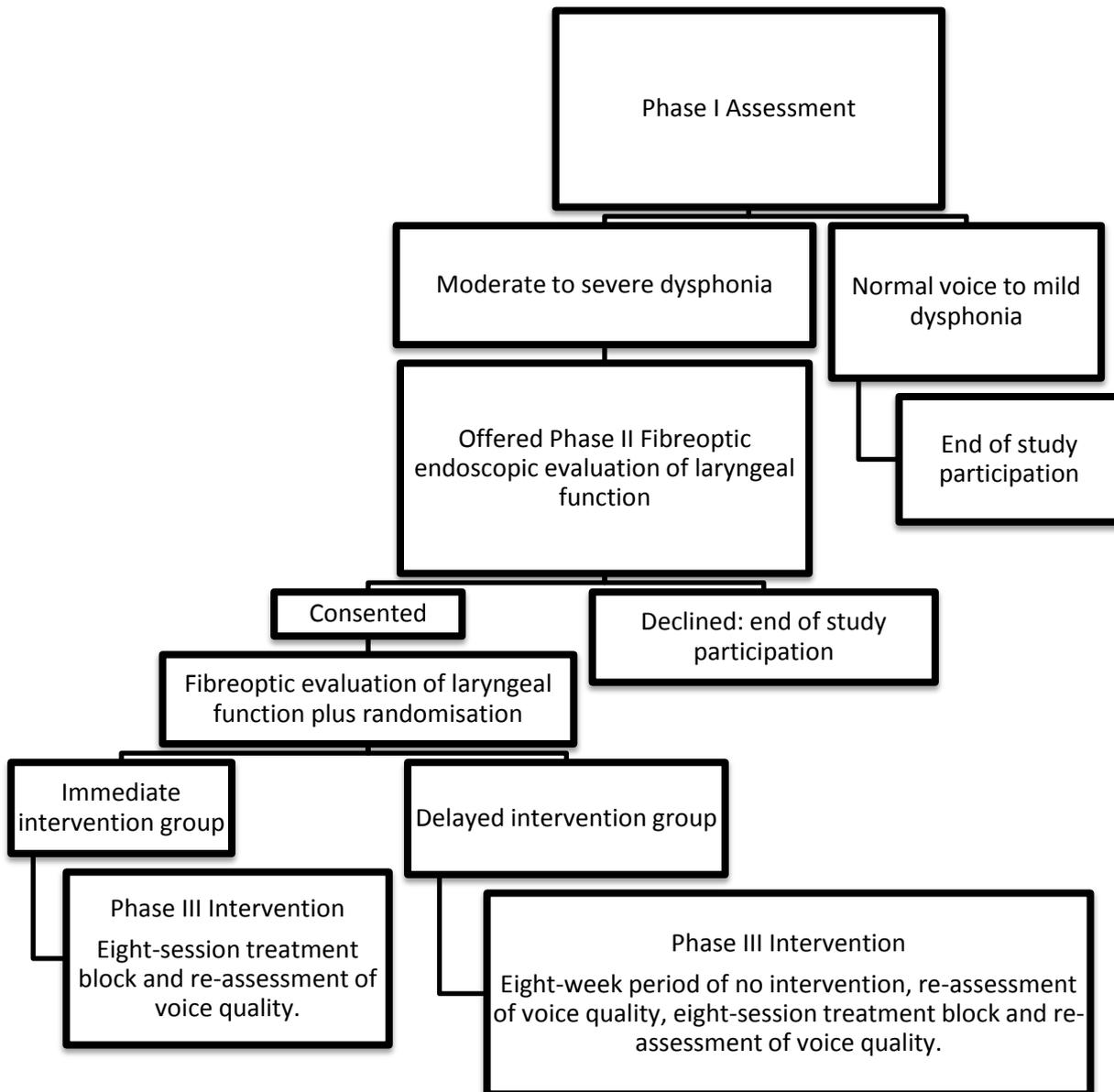


Figure 6.1 Flowchart depicting participant progression through the study phases.

Data from children born at ≤ 24 weeks gestation were collected in the previous pilot study and will be included in the data analysis for this study.¹²⁹ Increasing gestational age typically results in increased survival rates and decreased intubation frequency, thus it is not possible for each group to have equal sample sizes. Equivalence will be retained where possible. Table 6.1 contains the proposed sample sizes for each group.

Table 6.1. Proposed sample sizes from available cases for Phase I – Assessment.

Gestational Age (weeks)	≤23*	24-25	26-27	28-29	30-32
Proposed Total Sample Size	38#	40	40	40	40
Number of Intubations					
0	0	1	13	17	19
1-2	25	19	13	18	19
3+	13	20	14	5	2

*Indicates data already collected. #Number of survivors.

Clinical Assessment

Overall Dysphonia Ratings

The clinical assessments will be conducted by a speech pathologist with post-graduate experience in the assessment and treatment of paediatric voice disorders and will consist of:

- GRBAS (Grade, Roughness, Breathiness, Aesthenia, Strain scale): The GRBAS is a four-point perceptual rating scale that rates five main aspects of voice quality³
- Consensus Auditory Perceptual Evaluation of Voice (CAPE-V): The CAPE-V is a perceptual rating scale including finer subjective aspects of voice quality, volume, pitch and resonance. The CAPE-V will be administered in exact accordance with the published, recommended administration instructions.^{211,4}
- Acoustic Voice Quality Index (AVQI): The AVQI score will be used as the acoustic measurement, with scores meeting or exceeding the threshold for pathology in children considered disordered.¹⁴⁰ The AVQI will be calculated in exact accordance with the procedure described by Maryn et al.²
- Pediatric Voice Handicap Index (pVHI): This short questionnaire canvasses voice-related symptoms potentially affecting quality of life, across the physical, social and emotional domains.⁹ It is completed by the child's caregiver.

Inter-rater reliability will be conducted on a randomly-selected 20 (i.e. > 10%) of voice samples by a second speech pathologist with post-graduate experience in paediatric voice disorders. Intra-rater reliability will similarly be conducted,

on 20 of randomly-selected voice samples, for both raters. The test-retest reliability of the AVQI will be conducted on 20 randomly-selected voice samples.

Questionnaire assessment

- Growing and Changing Questionnaire (GCQ): The GCQ is an assessment of physical changes associated with the onset of puberty.⁶
- Socioeconomic status: This will be ascertained via a questionnaire including such factors as parental educational attendance and qualifications, income, employment status and housing status.

Retrospective chart review

Medical charts will be reviewed and coded for the following information (where recorded in sufficient detail): gender, gestational age, mode of delivery, total duration of intubation, frequency of reintubation, tube size relative to body weight, oxygen requirements during admission and at discharge, duration of hospitalisation, medication at discharge, incidence of re-presentation and readmission, other medical diagnoses including pulmonary disease and any other neurodevelopmental diagnoses subsequent to discharge.

Statistical Analysis

Statistical analyses will be conducted using SPSS v21.0 statistical software (SPSS Inc, Chicago, IL). All hypotheses are two-tailed and p-values of <0.05 will be considered statistically significant. Depending on data normality, demographic and voice characteristics will be summarised using means and standard deviations or medians, interquartile ranges and ranges. Categorical data will be summarised using frequency distributions. Univariate analysis of continuous data will be conducted using the independent samples t-test in the case of normal data distribution, or the Mann-Whitney test. The Chi square test will be used to analyse categorical data. Multivariable logistic regression will be conducted to assess the influence of demographic and intubation characteristics on the severity of dysphonia. Significant factors will be summarised using odds ratios (OR) and 95% confidence intervals (CI). Inter-rater and intra-rater reliability will be assessed using the intraclass correlation coefficient (ICC) and strength

of agreement for ordinal data using weighted kappa statistics. The diagnostic precision of the AVQI for discriminating between normal and dysphonic voices will be determined using receiver operator curve (ROC) analysis.^{2,140}

6.4.2 Phase II Videostroboscopy

Specific aims

1. To determine the physiological findings associated with the presence, nature and severity of laryngeal pathology.

Participants

Children from the study population who present with moderate to severe dysphonia, according to the severity classification of the CAPE-V, will be offered a videostroboscopic assessment of the larynx, and subsequent treatment (see Phase III). An ENT surgeon will carry out the endoscopic studies with assistance from the assessing and treating speech pathologist. Should the ENT surgeon identify pathology that may respond to surgical intervention, those participants will be offered follow-up consultation and treatment at Princess Margaret Hospital following Phase III of the trial. This is consistent with current ENT practice, where a period of behavioural voice therapy is trialled prior to surgical intervention.

Statistical Analysis

Depending on data normality, demographic and voice characteristics will be summarised using means and standard deviations or medians, interquartile ranges and ranges. Frequency tabulations of laryngeal pathology will be summarised, and for qualitative analysis a chi square test will be used to analyse categorical data. Multivariable logistic regression will be conducted to assess the influence of demographic and intubation characteristics on the presence, nature and severity of laryngeal pathology. Relevant demographic characteristics include: gender, birth weight and gestational age. Relevant intubation characteristics include: duration of intubation, frequency of reintubation and tube-size to body weight ratio. Significant factors will be summarised using odds ratios (OR) and 95% confidence intervals (CI). Cases with no intubation data available will not be included in this analysis. Cases with

missing data will be treated as missing cases and excluded from the relevant portion of the analysis.

6.4.3 Phase III Intervention

Specific aims

1. To determine whether a behavioural voice therapy programme results in changes in voice quality of very preterm children.
2. To determine whether the AVQI score is sensitive to changes in voice quality post-intervention.

Participants

See Phase II – participants above.

Randomisation

Eligible children who consent to Phase II of the study will be randomised to the immediate treatment or delayed treatment/comparison group.

Intervention procedures

Each participant in the treatment group will receive eight sessions of behavioural voice therapy, consisting of one 45-minute session per week for eight weeks. The therapy protocol consists of:

- vocal hygiene counselling, which instructs the voice user in ways to maintain the health of the vocal tract;¹⁷⁵
- indirect therapy techniques, which help the voice user to modify behaviours associated with the voice, such as breathing and laryngeal relaxation;¹⁸⁶ and
- direct voice therapy techniques, which train the voice user to initiate and sustain voicing in ways which do not cause trauma to the larynx and/or vocal tract.⁴⁴

The intervention protocol has been developed to address hyperfunctional voicing behaviour in this cohort. It is hypothesised, based on previous clinical experience, that very preterm children with laryngeal pathology adopt hyperfunctional compensatory voicing behaviours from an early age.

Reassessment of voice quality

Each participant from the comparison and intervention groups will undergo a repeat assessment, in exact accordance with the procedures described in Phase I, with the exception of the GCQ and socioeconomic questionnaire. Reassessment of voice quality will occur following the final session of behavioural voice therapy.

Statistical analysis

An intention to treat analysis will be adopted, to account for non-compliance and variation in the delivery of the therapy protocol due to participant illness or unavailability.²¹² This will facilitate a pragmatic analysis of the feasibility of the treatment in a clinical setting. The number of treatment sessions attended and a subjective patient report of compliance with therapy (completion of home practice) will be controlled for in the final analysis.

Depending on data normality, either the independent groups t-test (parametric) or Mann-Whitney *U* Test (non-parametric) will be used to compare differences between the treatment and control groups on the overall severity rating of the CAPE-V, the primary outcome, collected at the final assessment (following the treatment period). The G score, AVQI score and pVHI score will be used as secondary measures. Alterations in voice characteristics will be determined by calculating any changes in the baseline assessment results compared to the final assessment results for each participant using a related t-test or sign test, depending on data normality.

A standardised change score analysis will be used to determine the responsiveness of the AVQI to change. The correlations between the standardised change scores of the AVQI and the G score and the AVQI and the overall severity rating on the CAPE-V will be determined using a Pearson correlation coefficient. A moderate-to-high correlation between the scores will be considered indicative of the responsiveness to change of the AVQI score. This analysis is in accordance with that described by Maryn and colleagues.¹⁶³

Power calculation and sample size

As this study is the first to investigate long-term voice outcomes in children born very preterm, it is impossible to calculate power based on the sample sizes of similar studies.

There are no previous studies into systematic laryngeal assessments in school-aged preterm children. Data from the pilot study of extremely preterm children demonstrated the presence of moderate to severe dysphonia in 58% of the children assessed^{129,213}; however this incidence cannot be applied to this population for several reasons. Firstly, the participants in the pilot phase were all born at less than 25 weeks gestation. The response rate for the pilot study was <50% and selection bias cannot be excluded. Additionally, the presence of moderate to severe dysphonia was predicted by greater than five intubations; this condition is applicable to fewer children at later gestational ages.

Therefore, the number of participants who will present with moderate to severe dysphonia is presently unknown. We anticipate at least 30 children will participate in Phases II and III. Phase III will be the first study into the effectiveness of voice therapy to include children with dysphonia as a comparison group (c.f. Lee and Son, 2005¹⁹¹; Tezcaner and colleagues, 2009¹⁷⁵; and Valadez and colleagues, 2012¹⁹⁷).

6.5 Trial status

Ethics approval for both the pilot phase and this study was obtained from the Ethics Committee of Princess Margaret Hospital. The Ethics Committee of the University of Western Australia has approved this study. This study is being carried out in accordance with *The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans*. Participation in the study is under informed consent from the parent or caregiver, and assent from the child where applicable.

All three phases of the study are underway.

6.6 Discussion

The intervention trial will be conducted as a randomised, non-blinded between subjects design. Participants will be assigned to receive intervention immediately or after a delay. Voice quality will be re-assessed prior to commencement of therapy in the delayed intervention group. The pre-treatment scores of the delayed intervention group will be compared to the post-treatment scores of the immediate intervention group, to assess the effectiveness of behavioural voice therapy.

This will be the first such study in the literature and will contribute to our understanding of the factors increasing the risk of dysphonia in children born very preterm. This may facilitate early intervention to improve voice outcomes. Any responsiveness to therapy will also inform models of care to ascertain whether voice care should be routinely, prospectively offered to children born very preterm. Additionally, the information regarding the diagnostic accuracy and responsiveness to therapeutic change of the AVQI will be applicable to a wider cohort of children with dysphonia and it has the potential to be used as both an assessment and outcome measure.

6.7 Funding

This study is being funded by a Telethon grant, which is administered by the Women and Infants Research Foundation.

Chapter 7

An observational study of voice difficulties in school-aged children following very preterm birth

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7.1 Abstract

Background and objective

Very preterm children may be at risk of dysphonia. Risk factors previously identified in children born extremely preterm include female gender, multiple intubations, complicated intubation and very low birthweight. This study sought to identify the incidence of dysphonia in very preterm compared with term children, at school age.

Methods

Children born between 23 and 32 weeks gestation were included in this prospective observational study. Participants were randomly selected from a sample stratified by gestational age and number of intubations. A term-born reference group of children was recruited to provide an estimate of the incidence of dysphonia in this community. All participants were aged between 5 and 12 years at the time of assessment. Clinical voice assessments were conducted by a speech pathologist, and a diagnosis of dysphonia was made based on perceptual judgement of the presence and severity of disturbance to the voice. Retrospective chart review identified medical and demographic characteristics.

Results

178 preterm and 98 term participants were assessed. The incidence of dysphonia in the preterm cohort was 61.2%, with 31.5% presenting with dysphonia of greater than mild in severity. Female gender, gestational age, and duration of intubation were significantly associated with dysphonia although some preterm children with dysphonia had never been intubated. The incidence of dysphonia in the term-born cohort was 30.5%.

Conclusion

Significant voice abnormalities were observed in children born at up to 32 weeks gestation. Intubation was a major contributing factor. Further research is needed into factors associated with adverse outcomes in girls and children without a history of intubation.

7.2 Introduction

Dysphonia refers to a disruption in voice quality, i.e., the sound produced as exhaled air sets the vocal folds into vibratory motion for speech production. A voice is considered dysphonic when it differs from norms for age, gender, culture and/or stature, or impedes participation in academic, social or employment activities.⁷

Dysphonia following preterm birth is a newly-reported clinical entity. Early case reports linked dysphonia in preterm infants with invasive ventilation via endotracheal tube (ETT).¹³ Our laboratory has demonstrated an increased risk of adverse voice outcomes in females and those who experienced greater than 5 episodes of intubation in children born at <25 weeks gestation.¹²⁹ Other studies have identified further risk factors, including birth weight of less than 1,000 grams, birth at less than 27 weeks gestation, emergency versus elective intubation procedure and surgical ligation of patent ductus arteriosus (PDA).^{111,129,131} All participants in these studies were born extremely preterm, yet later-born preterm children may also be vulnerable to these risk factors. Infants born at up to 32 weeks gestation (i.e., born very preterm) may require invasive ventilation, albeit with decreasing frequency as gestational age increases.²¹⁴ Therefore, very preterm children may also be at risk of dysphonia, although research investigating this hypothesis is lacking in the literature.

The majority of studies to date have focussed on intubation of preterm infants, yet factors other than intubation are known to affect voice quality. Firstly, respiration for phonation may be compromised by chronic lung disease, which is a potential consequence of preterm birth.⁷³ Secondly, dysphonia has been reported in adults with a clinically significant PDA, which was not treated with surgical ligation, following extreme preterm birth.¹¹¹ The link between surgical ligation and voice disturbance arising from damage to the left recurrent laryngeal nerve is established, yet the causal mechanisms of dysphonia associated with clinically significant, persistent PDA have yet to be explored.¹¹¹ Thirdly, hyperfunctional use of the vocal mechanism is a common cause of dysphonia in childhood.¹⁹⁷ Such use of the vocal mechanism to compensate for underlying laryngeal pathology has been documented in preterm children, yet there are no studies investigating the magnitude of the problem in this population.⁶⁹ In order to further explore non-intubation related risk factors for long-term voice difficulties, inclusion of a sample of very preterm children who were not intubated is essential.

We sought to replicate our previous findings in extremely preterm children, and expand the investigation to include those children potentially at risk of adverse voice outcomes, by recruiting a new cohort of preterm children in the expanded gestational age range of 23-32 weeks. This study aimed to evaluate voice quality in a sample of very preterm children and compared this with term children, at school age.

7.3 Patients and Methods

The study was approved by the Princess Margaret Hospital Human Research Ethics Committee and the University of Western Australia Human Research Ethics Office. The trial is registered with the Australia and New Zealand Clinical Trials Registry (ACTRN12613001015730), as it formed the first phase of a three-phase study, the final phase of which was an intervention trial. The study design has been described elsewhere and is unchanged (**Chapter 6**).¹³⁹ A summary of the study design is provided below.

7.3.1 Participants

Preterm participants were recruited from discharge records at King Edward Memorial Hospital and were born between 23 and 32 weeks gestation between 2001 and 2007. Exclusion criteria were distant residence (>200km from metropolitan Perth) and known disability likely to preclude successful assessment. Participants were randomly selected, according to medical record number, following stratification into groups based on gestational age and number of intubations. A term-born reference group of 95 children, aged between 5 years and 3 months and 12 years and 11 months at the time of assessment, was recruited via community volunteers. Recruitment criteria included no history of or known risk factors for voice difficulties, no general anaesthetic within the previous fortnight and no current upper respiratory tract infection and were ascertained on telephone interview with a parent or caregiver prior to recruitment. No member of the reference group presented with concerns regarding voice quality. Thirty eight term-born children were recruited in a previous study by our laboratory and the remainder were prospectively recruited for this study. Written, informed consent was obtained from each participant's parent or caregiver, with child assent collected where appropriate. This research was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

7.3.2 Clinical assessment

Clinical assessment consisted of the administration of a perceptual rating scale, the Consensus-Auditory Perceptual Evaluation of Voice⁴, and an objective, acoustic assessment, the Acoustic Voice Quality Index.^{2,140} Caregivers were asked to complete a quality-of-life measure on behalf of their child, the Pediatric Voice Handicap Index.⁹ Retrospective chart review was used to record demographic variables and intubation characteristics. Gender, gestational age, birth weight, number of intubations, duration of intubation and endotracheal tube (ETT) size were available. Recording of procedural complications and operator experience during intubations were inconsistent and therefore not included in the analysis. Small for gestational age (SGA) status, tube size to body weight ratio (the diameter of the ETT divided by the infant's body weight in kilograms at the time of procedure) and birth weight ratio (actual birth weight divided by predicted birth weight; predicted birth weight is based on maternal and fetal factors resulting in increased individualisation of this outcome measure compared to birth weight alone)²¹⁵ were calculated for each participant. Puberty status was elicited via the caregiver-reported Growing and Changing Questionnaire, where participants were classified into "pre-pubertal" or "going through puberty" based on the Tanner stages.⁶

7.3.3 Data analysis

All data were analysed using SPSS for Windows version 22 (SPSS Inc.; Chicago, IL). Some data were not normally distributed. Logarithmic and square root transformation did not change the normality of the distribution. It was judged that the sample size was sufficient to use parametric tests to analyse the variables and stepwise logistic regression to determine the best fit in the multivariable model.

Rater reliability was assessed using a random sample of 44 voices, which were de-identified. Ratings were conducted by an independent speech pathologist with postgraduate experience in the assessment and treatment of paediatric voice disorders, and the first author. Ratings were conducted over two sessions, at which consensus training consisting of perceptual assessment of two samples in each category, previously agreed to represent normal, mild, moderate and severely dysphonic voices. A two-way, mixed, consistency single measures ICC was calculated using SPSS, and weighted kappa statistics with VassarStats (Richard Lowry, PhD; Poughkeepsie, NY).

7.4 Results

There were 2420 children born at ≤ 32 weeks gestation, admitted to the Neonatal Intensive Care Unit (NICU) and subsequently discharged during the target recruitment period. After excluding children with a known disability likely to preclude successful assessment and those resident greater than 200 kilometres from the study centre, potential participants were stratified according to gestational age and intubation frequency (0, 1, 2 or 3+ intubations). The families of 391 children were invited to participate in the study, and a total of 178 children successfully participated.

The overall incidence of dysphonia in the preterm participants was 61.2%, whereas the incidence in term-born children was 30.5%. Dysphonia incidence and gestational age can be seen in Table 7.1. Demographic characteristics of the preterm and term groups can be seen in Table 7.2.

Table 7.1. Dysphonia incidence in preterm and term-born groups.

	Term	23	24	25	26	27	28	29	30	31	32	Preterm
Normal	66 69.5%	0	8 32.0%	4 17.4%	6 25.0%	8 42.1%	5 27.8%	13 65.0%	13 65.0%	8 53.3%	4 80.0%	69 38.8%
Disordered	29 30.5%	9 100%	17 68.0%	19 82.6%	18 75.0%	11 57.9%	13 73.2%	7 35.0%	7 35.0%	7 46.7%	1 20.0%	109 61.2%
<i>Mild</i>	21 22.1%	1 11.1%	2 8.0%	6 26.1%	9 37.5%	8 42.1%	10 55.6%	5 25.0%	6 30.0%	5 33.3%	1 20.0%	53 29.8%
<i>Moderate</i>	8 8.4%	5 55.6%	9 36.0%	9 39.1%	8 33.3%	3 15.8%	3 16.7%	2 10.0%	1 5.0%	2 13.3%	0	42 23.6%
<i>Severe</i>	0	3 33.3%	6 24.0%	4 17.4%	1 4.2%	0	0	0	0	0	0	14 7.9%

Table 7.2. Demographic characteristics of preterm and term-born groups.

	Preterm	Term-born
Gender	M = 55.1%; n=98 F = 44.9%; n=80	M=56.8%; n=54 F=43.2%; n=41
Age (yrs) (median, IQR)	7.67; 6.42-9.83	8.5; 7.0-10.58
Dysphonia	61.2%; n=109	30.5%; n=29
Significant dysphonia	31.5%; n=56	8.4%; n=8

M=male, F=female, IQR=interquartile range. Significant dysphonia = dysphonia greater than mild in severity.

Univariable analysis, which can be seen in Table 7.3, showed a proportional relationship between gender, number of intubations, duration of intubation, maximum tube size, tube size to body weight ratio and increased severity of dysphonia. There was an inverse relationship between gestational age and dysphonia severity. Birth weight,

birth weight ratio and SGA status were not significantly associated with dysphonia severity.

Table 7.3. Univariable analysis of demographic variables and intubation characteristics

Variable	Mean	SD	Range	<i>p</i> value
Gender (%)	55.1 (male)			<.001
Small for gestational age (%)	9.0 (SGA)			.423
Gestational age (w)	27.17	2.56	23 - 32	<.001
Birth weight	1027.44	360.40	455 - 2240	.302
Birth weight ratio	.97	.15	.54 – 1.32	.407
Total number of intubations	2.54	2.44	0 - 11	<.001
Total duration of intubation	13.66	18.08	0 - 87	<.001
Maximum tube size (mm) (where used)			2.0 – 4.0	.005
Maximum tube size to body weight ratio	2.48	1.59	0 – 5.71	<.001

In the multivariable analysis using stepwise regression, gender ($p = .009$), gestational age ($p = .010$) and total duration of intubation ($p < .001$) were significantly associated with poor voice outcomes. Females demonstrated higher incidence of dysphonia than males, although there were no statistically significant differences between males and females on any other variable in the study, as can be seen in Table 7.4. There was an inverse relationship between gestational age and dysphonia severity. Intubation for longer durations was associated with increased dysphonia severity. There was no significant relationship between total number of intubations ($p = .287$), maximum tube size to body weight ratio ($p = .428$) and maximum tube size ($p = .571$). Our region has very low PDA ligation rates and of the 178 very preterm children, only four had a PDA ligation, three of whom had a transcatheter PDA closure and one required a transthoracic procedure.

Table 7.4. Analysis of demographic variables, intubation characteristics and gender of preterm children.

Variable	Male	Female	<i>p</i> value
	Mean (SD)/ n (%)	Mean (SD)/ n (%)	
Gender	98 (55.1%)	80 (44.9%)	
Small for gestational age	10 (10.2%)	6 (7.5%)	.533
Gestational age	27.46 (2.57)	26.81 (2.53)	.091
Birth weight	1072.35 (380.70)	927.44 (327.87)	.066
Birth weight ratio	.98 (.16)	.96 (.14)	.410
Total number of intubations	2.40 (2.41)	2.73 (2.51)	.378
Total duration of intubation	11.87 (17.05)	15.85 (19.15)	.144
Maximum tube size			.830
Not intubated	24 (24.5%)	16 (22.5%)	
2.0	1 (1%)	0 (0%)	
2.5	24 (24.5%)	25 (31.3%)	
3.0	48 (49.0%)	34 (42.5%)	
3.5	1 (0.6%)	3 (1.7%)	
Maximum tube size to body weight ratio	2.28 (1.51)	2.72 (1.67)	.069

7.4.1 Non-intubated children

Children born preterm who were never intubated were included in the study and a proportion did present with dysphonia: 14 children (35%) presented with mild dysphonia and 3 (7.5%) presented with moderate dysphonia. Severe dysphonia was not observed in this group. A summary of the univariable analysis of demographic variables of non-intubated preterm children can be seen in Table 7.5. As no significantly influencing variables were identified, multiple regression was not performed.

Table 7.5. Demographic characteristics of preterm children who were not intubated.

Variable	Mean/n	SD/%	Range	<i>p</i> value
Gender	24 male 16 female	24.5% 20.0%		.858
Small for gestational age	2	5.0%		.743
Gestational age	29.38	1.69	26 - 32	.716
Birth weight	1258.50	332.58	685 - 2010	.147
Birth weight ratio	.96	.14	.67 – 1.22	.377

There was a statistically significant difference in the incidence of dysphonia between children who were and were not intubated, $p = .002$.

7.4.2 Gender

Gender distribution of term-born participants (males = 57.7%) was similar to that in the preterm group (males = 55.1%). However, there were no gender differences in the incidence of dysphonia in the term-born reference group, $p = .908$.

In the preterm cohort, female gender was identified as significantly influencing the likelihood of dysphonia in the multivariable model above. Information regarding pubertal status of preterm participants is summarised in Table 7.6. Males were more likely to present with dysphonia prior to the onset of puberty, $p = .046$. There was no significant relationship between pubertal status and presence of dysphonia in females, $p > .05$.

Table 7.6. Puberty status and dysphonia count data, by gender.

		Puberty status				Total
		Pre-pubertal		Going through puberty		
		Normal	Dysphonic	Normal	Dysphonic	
Gender	Male	28 (42.4%)	38 (57.6%)	13 (68.4%)	6 (31.6%)	85
	Female	19 (27.9%)	49 (72.1%)	1 (25.0%)	3 (75.0%)	72
Total		47	87	14	9	157
		134		23		

7.4.3 Rater reliability

The single-measures ICC between raters for the CAPE-V severity score was .76 (95% CI = .60 - .86), with a weighed kappa of .63, indicating a moderate to good level of agreement between raters. The ICC within raters was .65 (95%CI = .44 - .79), with a weighted kappa of .57, indicating a fair to good level of intrarater agreement. These results indicate that the CAPE-V severity score assigned upon initial assessment is an acceptable indicator of the presence and severity of dysphonia in this cohort.

7.5 Discussion

Mild dysphonia, generally relating to sustained and enthusiastic use of the voice, is common in childhood.²¹ More severe voice disorders are rare in children, representing less than 2% of cases referred for voice evaluation.²⁸ In our term-born cohort, the incidence of dysphonia was 30.5%. This figure reflects the large number of term-born,

otherwise healthy children, who use their voices frequently and inefficiently in childhood. This leads to mild disruption of the vocal signal, perceived as hoarseness. Maturation in communication behaviour and pubertal changes to the structure and function of the larynx in adolescence are associated with the resolution of childhood dysphonia in many cases.^{22,34}

Our data confirm that the majority of voice disorders seen in term-born children are of mild severity and no term-born child in our cohort presented with a severe dysphonia. Our data demonstrates that the incidence of voice disorder beyond that which would be expected in otherwise healthy children was present in our cohort in children born at 32 weeks gestation and under. While non-intubated study participants also presented with dysphonia, incidence of dysphonia was significantly greater in children who were intubated. Thus, intubation appears to be a major factor contributing to voice problems in this population. This is not a surprising finding, as intubation may be associated with gross structural laryngeal damage in preterm children(**Chapter 8**).²¹⁶ Further, the histological structure of the infant vocal fold mucosa may also be damaged in the neonatal period, potentially disrupting the process of differentiation from the single-layered lamina propria present in newborns to the trilayered structure found in adults.

Greater than five episodes of intubation and complicated procedure have been previously associated with dysphonia in extremely preterm children.^{129,131} In this very preterm cohort, factors significantly associated with adverse voice outcomes in the multivariable model were female gender, gestational age and total duration of intubation. To the authors' knowledge, this is the first such finding in a cohort of very preterm children (≤ 32 weeks) at school age. Duration of intubation has been associated with greater laryngeal injury in post-mortem studies following preterm birth, and is correlated with deeper and more permanent ulceration to the laryngeal mucosa and growth of tissue around the introduced structure.^{82,112} Data from this study indicates that such laryngeal damage may translate to poorer functional voice outcomes (**Chapters 8 and 9**).^{142,216} Surgical ligation of PDA has been associated with adverse voice outcomes in extremely preterm children in some series.¹¹¹ However, in this preterm cohort, one child underwent the procedure, yet presented with a normal voice. Therefore, surgical ligation of PDA is not a major factor associated with voice outcomes in this study.

These data also suggest an association between factors unrelated to intubation and voice quality. The major, non-intubation related finding is the susceptibility of females to more severe dysphonia in comparison to males. This is the second such report in the literature, as we have previously showed this gender difference in our study of extremely preterm infants (<25 weeks) and this finding remains true for this extended preterm population¹²⁹ There were no significant differences between males and females on any demographic characteristic or intubation variable, suggesting that sex- or gender-related factors may underlie this increased risk. One possible explanatory variable is sex or thyroid hormones, both of which are associated with voice changes due to their influence on the composition of the vocal fold mucosa.²¹⁷ In females, hormones may result in interstitial fluid loss from the superior lamina propria, thus altering its vibratory characteristics and thus the perceptual properties of the vocal signal.²¹⁷ In this cohort, males going through puberty were less likely to present with dysphonia, but no such relationship was observed in girls, which may have been due to the small sample size of girls going through puberty. However, in term-born children, completion of puberty is associated with a high likelihood of resolution of typical childhood voice problems, more so in males than females.²² However, these results, if replicated, may suggest that preterm girls may be less likely to experience improvement in voice quality with puberty, similar to their term-born counterparts without structural laryngeal damage. These features require larger numbers of cases in future studies, ideally via a longitudinal study, as it may also elucidate the mechanisms underlying persistence of typical childhood voice problems in term-born females following completion of maturation.

Several children who were not intubated did present with moderate dysphonia beyond what would be expected in term-born children, yet none of the demographic variables investigated in this study was found to have a significant association with dysphonia severity in that sub-group of children. These children's voice difficulties may be associated with other factors which were not explored in this study. Preterm infants are at increased risk of iatrogenic pharyngo-oesophageal injury than their term-born counterparts, suggesting susceptibility of the anatomy to medical intervention such as intubation, feeding tubes and oral suctioning.²¹⁸ Given the universal use of orogastric feeding tubes in the very preterm population, we were not able to evaluate the possible role of such tubes in preterm dysphonia in either intubated or non-intubated children.

The relationship between premature birth and vocal fold mucosa is not well understood. The composition of vocal fold mucosa contributes to the mass and tension of the vocal folds, which is reflected in voice quality. At birth, the composition of the vocal fold mucosa is a single layer of epithelium, with a high concentration of hyaluronic acid, whereas in adults, the structure is trilayered.³⁷ Differentiation commences in the second or third month of life, but it is not yet clear whether this process is triggered by gestation to term, or exposure to oxygen ex-utero.³⁷ Therefore, changes to the histology of the vocal fold mucosa could be associated with prematurity, or with the altered gaseous environment of CPAP in comparison to unassisted breathing in room air. Other long-term sequelae of very preterm birth include bronchopulmonary dysplasia persisting into adulthood, which will limit the vital capacity available for phonatory support.²¹⁹ Children with chronic lung problems may be prescribed inhaled corticosteroids, of which dysphonia is a side effect.²²⁰ Bronchopulmonary dysplasia has been associated with voice-related impairments in quality-of-life in preterm children, via caregiver report, although this finding has yet to be correlated with voice quality as measured by clinical assessment.⁹⁵

This study had several limitations. The scope of this study was to investigate the influence of demographic variables and intubation characteristics on functional voice outcomes in very preterm children born at ≤ 32 weeks gestation. Visualisation of laryngeal structures via laryngostroboscopy was not performed as part of this clinical assessment. Whilst there is an imperfect correlation between laryngeal pathology and voice quality, laryngeal imaging would elucidate the mechanisms underlying the disruption to voice quality. Additionally, the demographic variables investigated in this study did not include data pertaining to co-morbid health conditions associated with voice production, as described above. Investigation into such factors in children with and without a history of intubation may provide further information about risk factors associated with long-term voice difficulties in very preterm children.

7.6 Conclusion

The incidence of dysphonia in very preterm children is higher than that of their term-born counterparts. Female gender, gestational age and total duration of intubation increased the likelihood of voice difficulties at school age. A proportion of very preterm children without an intubation history also presented with dysphonia, which is the first

such report in the literature. No significant association between voice quality and the demographic variables investigated in this study was identified in children who were never intubated. Further research is needed to elucidate the factors associated with adverse outcomes for females and children without a history of intubation.

Children born at up to 32 weeks gestation may be at risk of significant dysphonia at school age. Routine screening for voice difficulties could be included in neonatal follow-up programmes for such children.

7.7 Acknowledgements

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Chapter 8

Laryngeal pathology at school age following very preterm birth

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8.1 Abstract

Introduction: Intubation injury resulting in laryngeal pathology is recognised as a possible complication of preterm birth, yet few published studies have examined such pathology and its relation to voice outcomes. This study reports on the results of prospective laryngeal function examinations of a cohort of very preterm children, all of whom presented with significant dysphonia at school age.

Materials and methods: The laryngeal pathology of 20 very preterm children, born between 23 and 29 weeks gestation, was examined under halogen and stroboscopic conditions. Laryngeal structure and function were assessed using a rigid laryngoscope or a flexible nasendoscope. The approach was selected based on the age and/or likely compliance of the child.

Results: Nineteen children were found to have structural laryngeal pathology. Fourteen children presented with a chink to the posterior glottis and all demonstrated at least a mild degree of supraglottic hyperfunction. Other common findings were arytenoid prolapse and vocal fold immobility. More isolated findings included posterior scar band, vocal fold atrophy, arytenoid oedema and growth on the vocal folds. One child who presented with structural laryngeal pathology was never intubated.

Discussion: Supraglottic hyperfunction was common to all participants, regardless of the nature and extent of underlying structural laryngeal pathology. Posterior glottic chink was the most common pattern of incomplete vocal fold closure. These data support the hypothesis that very preterm children adopt supraglottic tightening to compensate for underlying laryngeal pathology. The mechanism underlying laryngeal damage in the child who was not intubated is unclear.

Conclusions: Voice quality of very preterm children is affected by both laryngeal structure and function. A trial of behavioural voice treatment is recommended to evaluate any therapeutic response in this population.

8.2 Introduction

Dysphonia is defined as disruption in voice quality, and can affect individuals across the lifespan.²²¹ Dysphonia may arise from organic causes, or maladaptive use of the vocal mechanism, or both. Individuals with organic dysphonia may adopt maladaptive compensatory voicing strategies and while maladaptive use of the voice can result in structural changes to the larynx, both of which result in further impairments to voice quality.^{222,223}

Advances in imaging technology have led to increased and more accurate diagnosis of laryngeal pathology.⁷⁹ Laryngeal damage has been identified as a potential complication of endotracheal intubation following preterm birth (**Chapter 2**).¹³³ Potential causes of structural injury include: initial placement of the endotracheal tube, movement of the tube in situ, infection and tissue growth around the tube.⁶⁴ Serious, long-term laryngeal complications of prolonged endotracheal intubation in infancy include: subglottic stenosis, acquired subglottic cysts, posterior glottic furrow, vocal fold scarring, cricoarytenoid joint fixation and traumatic vocal fold avulsion.^{13,29,69,82,115,126} Moderate to severe airway abnormalities post-extubation were identified in up to 23.7% of preterm infants, and following intubation for as little as 24 hours.^{79,115}

Dysphonia has been reported in preterm children, and associated with frequency of intubation, female gender, birth weight, gestational age and emergency intubation.^{111,129,131} Dysphonia in adulthood, associated with left vocal cord paralysis following surgical ligation of patent ductus arteriosus in extreme prematurity, has also been documented.¹¹¹ Children with laryngeal injury following neonatal intubation may adopt compensatory supraglottic hyperfunction, which is known to cause further laryngeal damage beyond the initial injury, with associated disturbances in voice quality.^{69,126} However, the majority of studies of laryngeal pathology pertain to infants with few reports of voice quality. This is problematic for several reasons. Long-term voice outcomes cannot be extrapolated or predicted from infant cries due to physiological differences in infant larynges.²²⁴ Fibrosis and stenosis can develop up to twelve months post-extubation and thus may not be reflected in voice quality in infancy.²⁹ Finally, lack of standardised reports of voice quality may result in underestimation of the true morbidity of dysphonia in this population. Whilst the

correlation between laryngeal pathology and functional voice outcomes is imperfect, an understanding of the nature and extent of laryngeal pathology in preterm children will elucidate the mechanisms underlying disordered voice production in this population.

8.2.1 Aims and hypotheses of this study

It is hypothesised that very preterm children who undergo endotracheal intubation in the neonatal period are at high risk of long-term laryngeal injury, and that such injury will be associated with dysphonia severity. Further, it is hypothesised that very preterm children with laryngeal injury are more likely to adapt maladaptive strategies to initiate and sustain phonation, which will manifest as supraglottic hyperfunction resulting in a strained vocal quality.

The aim of the study was to determine the nature and extent of laryngeal pathology in this cohort. Prospective examination of the laryngeal structure and function of a cohort of very preterm children at school age with moderate to severe dysphonia was conducted.

8.3 Materials and methods

The study design and methodology has been described elsewhere and is unchanged (**Chapter 6**).¹³⁹ A brief summary of participant characteristics and assessment methodologies is set out below.

8.3.1 Participants

Two hundred and fifty children underwent clinical voice assessment to determine the incidence, presentation and severity of dysphonia in very preterm children across two studies (**Chapter 7**).^{129,225} Participants were recruited from a total of 1,851 NICU discharges born at ≤ 32 weeks gestation and were aged between 4 years and 11 months and 15 years and 10 months at the time of initial assessment. Each study was approved by the Princess Margaret Hospital Human Research Ethics Committee. The pilot study investigated voice quality in children born at < 25 weeks gestation. Due to the small number of children, all NICU discharges were invited to participate. The second study investigated voice outcomes in children born at ≥ 32 weeks gestation, who were stratified according to gestational age and number of intubations recorded on their NICU discharge summary. After exclusion of children with known disabilities likely to

preclude successful assessment and those residing >200kms from the study centre, participants were randomly selected.

Across the two incidence studies, ninety four participants presented with dysphonia that was greater than mild in severity. Three were lost to contact between the study phases; 35 declined further assessment as their parents were not concerned about their child's voice quality. The families of 25 children refused nasendoscopic evaluation. The families of 31 children consented and 20 children have undergone the procedure, with an additional 2 refusals at the time of procedure and one unsuccessful attempt due to the small stature of the child.

8.3.2 Clinical assessments

Each participant underwent a clinical voice assessment by a speech pathologist with post-graduate experience in the assessment and treatment of paediatric voice disorders. The assessment consisted of a perceptual evaluation with the Consensus Auditory Perceptual Evaluation of Voice (CAPE-V)⁴, acoustic analysis of the voice signal with the Acoustic Voice Quality Index (AVQI)¹⁶³ and a caregiver-proxy quality of life report, the Pediatric Voice Handicap Index⁹. The CAPE-V is rated by a trained listener, on a visual analogue scale, where 0 represents normal voice and 90 represents severe dysphonia. A severity score of greater than 0 is considered dysphonic, with increasing score reflecting increased severity of disturbance to the voice. The AVQI is a new, objective assessment measure and is presently used for discriminating normal from dysphonic voices in children. The threshold for pathology of the AVQI in paediatric voice is 3.46, with a higher score representing greater disruption in the voice signal.¹⁴⁰ On the pVHI, children with normal voices score ≤ 2 .

8.3.3 Laryngeal assessments

Participants were aged between 6 years and 6 months and 17 years and one month at the time of laryngeal examination. Oral (rigid) approach or nasal (flexible) approach was selected by the administering otorhinolaryngologist based on the age and likely compliance of the participant, in consultation with the family where appropriate. Co-phenylcaine was administered via the nares bilaterally prior to the introduction of the scope into the respiratory tract. Task instructions were administered by a speech pathologist with post-graduate experience in the assessment and treatment of paediatric

voice disorders. Speech targets were elicited to facilitate completion of the Stroboscopy Evaluation Rating Form (SERF) and included sustained phonation of a close-front vowel at comfortable pitch and loudness, at maximum loudness, at lowest and highest pitch, ascending and descending pitch glides, rote speech and inhalation phonation¹⁰.

All participation was carried out under informed caregiver consent and child assent where appropriate. This research was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

8.4 Results

Participant medical, demographic and voice characteristics are described in Table 8.1. Thirteen participants were female. Whilst participation in this study was voluntary, the larger number of female participants reflects the higher incidence of dysphonia found in females in this cohort¹²⁹. Variables included were those with a demonstrated link to dysphonia following preterm birth. One participant underwent PDA ligation reflecting the rare occurrence of this procedure in very preterm infants in this region. All participants experienced enteral feeding via nasogastric tube. A comparison of characteristics of participating and non-participating children is presented in Table 8.2.

A summary of laryngeal findings for each participant can be seen in Table 8.3. It can be seen that each participant presented with both structural laryngeal pathology and supraglottic hyperfunction. Count data for laryngeal diagnoses are set out in Table 4. It can be seen that glottic incompetence was the most common structural laryngeal pathology observed. Figure 8.1 shows the breakdown of glottic closure patterns. Images of each participant's larynx during phonation and at rest can be seen in the supplementary material in Figure 8.2.

In order to assess reliability of perceptual judgements, a sample of voice recordings were de-identified and rated by an independent speech pathologist with postgraduate experience in the assessment and treatment of paediatric voice disorders. The average ICC between raters for the CAPE-V severity score was .648 (95% CI .360-.806), with a weighed kappa of .36, indicating a fair level of agreement between raters. The de-identified samples were also re-rated by the first author. The average ICC within raters was .752 (95%CI .590-.856), with a weighted kappa of .56, indicating a moderate to good level of intrarater agreement. These results indicate that the CAPE-V score was a

reliable measure of dysphonia severity in this cohort. Further, Pearson's correlation coefficient between the CAPE-V severity scores and the AVQI scores was .647, indicating a moderate correlation which was considered acceptable given the small sample size of the study cohort.

Table 8.1. Demographic, medical and voice characteristics of extremely preterm children, who underwent endoscopic evaluation of laryngeal structure and function at school age.

Case	Gender	GA	BW (g)	Number of intubations	Duration of intubation (days)	CAPE-V severity	AVQI score
1.	M	25	650	4	28	50	6.60
2.	F	25	640	10	47	90	5.65
3.	F	23	560	16	69	50	6.62
4.	F	24	565	9	90	66	6.42
5.	F	24	755	5	35	50	7.20
6.	F	24	585	7	64	50	4.98
7.	F	24	685	6	49	50	3.43
8.	F	23	630	6	41	50	6.85
9.	F	24	550	8	57	74	6.16
10.	M	24	685	5	43	30	4.32
11.	M	23	705	7	65	50	3.75
12.	F	23	460	9	81	90	7.77
13.	M	24	570	3	41	70	5.09
14.	F	24	570	4	31	70	7.36
15.	M	24	600	10	69	50	5.21
16.	F	23	665	9	92	70	5.24
17.	M	23	470	8	66	80	3.16
18.	F	23	630	7	50	50	3.78
19.	M	29	1335	0#	0	50	5.49
20.	F	28	1010	0#	0	50	3.92

nasal CPAP only respiratory support

GA = gestational age, BW = birth weight, CAPE-V = Consensus Auditory Perceptual Evaluation of Voice⁴, AVQI = Acoustic Voice Quality Index¹⁶³

Table 8.2. Characteristics of participating versus non-participating very preterm children.

Characteristic	Participating n = 23 M (SD) or # (%)	Non-participating n=71	<i>p</i> value
Gender			
M	9 (24%)	28 (76%)	.94
F	14 (25%)	42 (75%)	
CA	9.75 (2.94)	8.86 (2.62)	.21
BW (grams)	671.96 (239.83)	751.76 (255.67)	.18
GA (weeks)	24.35 (1.72)	24.38 (1.34)	.93
Number of intubations	6.39 (3.68)	4.90 (2.02)	.07
Duration of intubation (days)	48.39 (25.72)	34.24 (16.88)	.02
Maximum tube size to bodyweight ratio	4.02 (1.75)	3.96 (.84)	.85
Maximum tube size	2.58 (1.06)	2.79 (.46)	.21
GRBAS Grade	2.09 (.42)	2.03 (.52)	.59
GRBAS Mean G score	1.77 (.43)	1.56 (.43)	.05
AVQI score	5.34 (1.06)	5.14 (1.26)	.48
pVHI score	39.09 (20.88)	25.15 (18.38)	.01

CA = chronological age; BW = birthweight; GA = gestational age; GRBAS = Grade, Roughness, Breathiness, Aesthenia and Strain scale; AVQI = Acoustic Voice Quality Index; pVHI = Pediatric Voice Handicap Index.

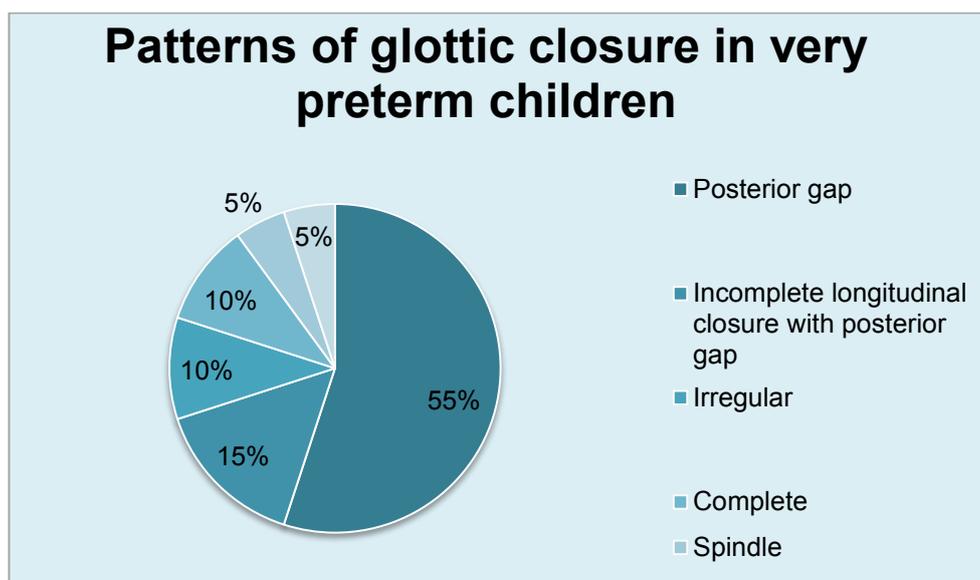


Figure 8.1. Patterns of glottic closure in very preterm children.

Table 8.3. Laryngeal pathology of very preterm children, who underwent endoscopic evaluation of laryngeal structure and function at school age.

Number	Vocal cords	Tissue changes	Supraglottic compression	Phase closure	Arytenoid status	Comments
1.			Moderate in both planes		Oedematous	
2.	Decreased mucosal wave	Bilateral nodules.	Moderate in both planes, impeding assessment of mucosal wave		Left prolapse	
3.			Severe in both planes, impeding assessment of mucosal wave	Breathy	Bilateral prolapse L>R Stiff left CAJ	
4.	Right VC atrophy and stiffness		Moderate anteroposterior constriction, moderate right and mild left mediolateral constriction		Stiff right CAJ	Interarytenoid scar band Underwent surgical ligation of PDA. Approach by posterolateral thoracotomy via fourth intercostal space.
5.	Right VC atrophy	Cyst right VC	Severe compression in both planes, impeding assessment of mucosal wave			
6.	Impaired mucosal wave and atrophy of right VC		Severe compression in both planes, impeding assessment of mucosal wave			
7.	Right VC atrophy with divot		Severe supraglottic constriction in both planes			Right supraglottic cyst
8.	Left VC atrophy, immobility		Moderate anteroposterior supraglottic hyperfunction, mild to moderate mediolateral compression.	Breathy	Hyperfunctioning right arytenoid	
9.	Mild right VC atrophy		Inconsistent, mild to moderate mediolateral and posterior	Breathy		
10.			Severe hyperfunction in all planes impeding assessment of mucosal wave			
11.	Left VC atrophy with immobility		Mild in both planes			Mucous on VCs+++ Possible early reflux changes (oedematous interarytenoid mucosa)
12.	Atrophy and decreased mucosal wave of right VC		Mild mediolateral compression with severe anteroposterior compression	Breathy	Mild right prolapse	Larynx rotated to posture and unequal extralaryngeal tension. Resistant to re-posturing
13.	Right VC atrophy		Severe, right-sided mediolateral compression, moderate anteroposterior compression		Hyperfunctioning right arytenoid	Mucous anterior commissure
14.	Left VC atrophy with absent mucosal wave	Left VC cysts x 2	Severe mediolateral	Breathy		
15.	Reduced amplitude and mucosal wave		Moderate mediolateral and severe posterior	Normal		
16.			Moderate anteroposterior and mild mediolateral.		Right arytenoid prolapse	Irregular epiglottis with tissue deviated to left
17.		Possible nodules bilaterally.	Severe supraglottic constriction in both planes, impeding assessment of mucosal wave		Oedematous	Laryngitis
18.			Severe compression in both planes, impeding assessment of mucosal wave		Oedematous	
19.	Oedematous VCs bilaterally	Left VC cyst Sulcus left VC.	Mild mediolateral compression			Was not intubated.
20.		Bilateral VC nodules.	Mild mediolateral and moderate posterior	Pressed		Was not intubated.

VC = vocal cord, CAJ = cricoarytenoid joint, PDA = patent ductus arteriosus

8.5 Discussion

There was considerable heterogeneity of clinical presentations in this cohort, which reflects the individual nature of the children's health status and medical care. Intubation and ventilation were common characteristics in the cohort, yet factors such as duration and number of re-intubations were varied. Further, long-term health outcomes were varied among the cohort. Many children presented with persistent chronic lung disease and were prescribed corticosteroids: both factors may affect voice quality. Investigation of respiratory health was outside the scope of this study, but could be considered for further investigation.

Characteristics of participants were compared with children who were eligible for inclusion but declined. Demographic variables were equivalent between groups. Some differences in intubation characteristics were observed between the groups, yet comparison of voice characteristics demonstrated that both groups experienced a similar degree of disturbance to voice quality and its impact on quality of life. Whilst the difference in CAPE-V severity score between the groups trended toward statistical significance, both scores represented a moderate voice disturbance on perceptual assessment. The results therefore suggest clinical equivalence in voice disruption across the cohort.

8.5.1 Structural laryngeal pathology

Laryngeal damage associated with medical intervention in the neonatal period resulted in disruptions to voice quality at school age in this cohort of very preterm children. All underwent mechanical ventilation following birth, with endotracheal intubation administered in eighteen of the children. During the first month of life, the infant vocal fold mucosa is comprised of a single layer, high in concentration of hyaluronic acid.^{37,226} Layers of the lamina propria begin to emerge after the second month of life⁴³. Vocal fold injury sustained in this period may persist in the long term and disrupt differentiation of the trilaminar structure, which continues throughout childhood⁴³. Whether preterm birth itself may interrupt this process is currently unknown. Arytenoid subluxation is hypothesised to have occurred during tube placement, and was associated with hypermobility and CAJ stiffness in this cohort.²²⁷ Glottic incompetence was common among this cohort, with posterior gap accounting for the majority of cases. It is proposed that this phenomenon arises due to erosion of the vocal process from

placement of the endotracheal tube in the posterior portion of the glottis. Posterior glottic incompetence is common in adult female speakers, yet was observed in nineteen participants, beyond the expected level in term-born, non-intubated speakers. Incomplete longitudinal closure was associated with vocal fold atrophy, where observed.

The absence of intubation granuloma and significant subglottic stenosis was not a surprising finding. These conditions are commonly reported following prolonged intubation. Both intubation granuloma and subglottic stenosis may affect airway patency to such a degree as to warrant surgical intervention. It is likely that severe cases would have been treated early in life, upon identification of airway limitations. Yet, any degree of subglottic stenosis may result in increased phonation pressure threshold, facilitating over-activation of the supraglottic musculature on initiation of phonation. Intubation granuloma may, depending on location, result in irregular vocal cord vibration and/or incomplete closure. Thus it can be seen that less severe cases may manifest only in disordered voice production, without airway compromise. To the authors' knowledge, this cohort forms the largest sample of very preterm children to undergo laryngeal examination at school age. However, conclusions about the absence of these pathologies in this cohort may not generalise to the entire very preterm population.

The finding of right vocal cord paralysis in the female participant who underwent surgical ligation of PDA was unexpected. However, the left-sided approach to the ductus was confirmed on retrospective chart review suggesting that the recurrent laryngeal nerve was spared during the procedure and the structural laryngeal damage was most likely to have been sustained during intubation. Such cases rarely occur in children, but have been reported in the literature.²²⁸ Therefore, in this cohort, surgical ligation of PDA was not linked to dysphonia in any participant. Whilst PDA ligation has been associated with poor long-term voice outcomes in extremely preterm children in some series, it is apparent that intubation is the major significant risk factor for structural laryngeal damage in our cohort.

8 5.2 Effects of laryngeal pathology on voice quality

The vocal parameter of roughness reflects the acoustic perception of variation in pitch and/or amplitude in the voice signal, caused by irregular vocal fold vibration. Potential causes of irregular vibration observed in this cohort were vocal cord growths, including

cysts and nodules, vocal fold atrophy and immobility. One or more of these pathologies was identified in three quarters of the children. Incomplete glottic closure, regardless of closure pattern, was associated with audible excess air escape during phonation in this cohort.

Each participant presented with a degree of supraglottic hyperfunction, which manifested as strained voice quality. It is hypothesised that this behaviour resulted in a higher degree of disturbance in the voice signal than would be expected from the structural laryngeal pathology alone. In six cases, supraglottic tightening was such that mucosal wave was unable to be assessed due to obscuration of the vocal folds during phonation. Vocal hyperfunction is common in childhood.¹⁹⁷ Many term-born, otherwise healthy children develop mild dysphonia as the result of overuse of the voice, e.g., sustained use of the voice, voice use at loud volumes. Such behaviour may be amenable to voice therapy.^{175,190,191,197} It is currently unclear whether voice therapy would have any effect on the voice quality of children whose vocal hyperfunction is secondary to underlying structural pathology, such as the very preterm participants in this study. However, given the potentially significant impact of dysphonia on the quality of life of affected children, a trial of behavioural voice therapy in such cases is warranted.

8.5.3 Laryngeal findings in non-intubated children

Three children who were never intubated presented with moderate dysphonia and consented to laryngeal examination. One child withdrew consent immediately prior to the procedure. Structural laryngeal injuries were identified in the male child who underwent examination. Hoarseness was observed at a developmental review at the corrected age of two years, suggesting that dysphonia arose early in life. There were no other indicators of potential laryngeal injury: thus, the cause of his voice difficulty is unclear. The female child presented with primary muscle tension dysphonia, with no other overt signs of laryngeal pathology. Similarly, there were no other indicators of potential laryngeal injury. Severely hyperfunctional voice use may be the sole cause of her dysphonia, as evidenced by pressed phonation, supraglottic hyperfunction and bilateral vocal fold nodules. However, in the case of the male, supraglottic hyperfunction is less likely to have had a causative relationship with the structural laryngeal pathology observed. He presented with a large posterior glottic gap and sulcus vocalis. The converse is a more likely explanation, with over use of the supralaryngeal musculature

representing an attempt to achieve vocal cord closure during phonation, in the presence of the glottic gap. Both children presented with hyaline membrane disease in the neonatal period and were treated with nasal CPAP using Hudson prongs. In the absence of any other indicators, and given the history of persistent dysphonia, it is hypothesised that CPAP treatment may be a contributing factor. Alternatively, nasogastric tube syndrome has been reported as a source of laryngeal damage in some infants, although as yet, there are no reports of long-term laryngeal outcomes in such children.²²⁹ Further investigation is warranted, although this phenomenon appears to be rare.

The structural pathology and hyperfunctional use of the larynx in this cohort were reflected in clinical assessments of vocal quality. It can be seen that laryngeal injury sustained following very preterm birth persists into school age. Yet, it is not known whether there is any spontaneous recovery. Some of the participants in this study had undergone previous laryngeal evaluation, either with awake nasendoscopy or laryngoscopy under general anaesthetic. These evaluations were carried out at multiple institutions by a number of practitioners and the results were therefore not available to the authors of this study. Based on parent report, it appears that some children may experience changes to the larynx. For example, the mother of case 8 reported that previous investigations had identified a “completely flaccid” left vocal cord in her daughter. However, at the age of fifteen, on participation in this study, the mobility of the left vocal cord was impaired, not absent. Whilst this observation is based on parent report rather than clinical assessment results, it was not isolated in the cohort. A longitudinal study of laryngeal structure and function in very preterm children would elucidate the nature and extent of any spontaneous recovery.

8.6 Conclusion

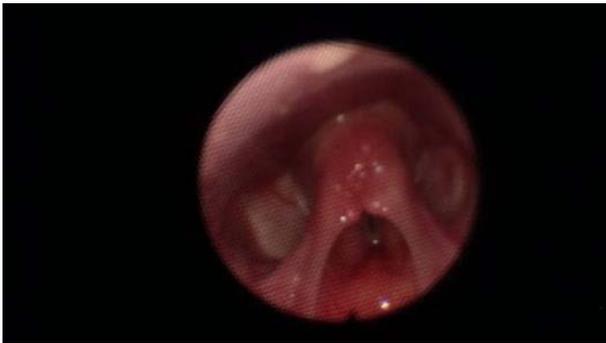
Structural laryngeal pathology was observed in school-aged very preterm children with significant voice abnormalities. Most of the participants presented with roughness, breathiness and strain audible in their voices. Intubation was a major contributing factor, yet two study participants were not intubated. Regardless of underlying laryngeal pathology, each child adopted compensatory supraglottic tightening behaviours during phonation. Investigation of the efficacy of treatment for dysphonia related to preterm birth is recommended.

8.7 Acknowledgements

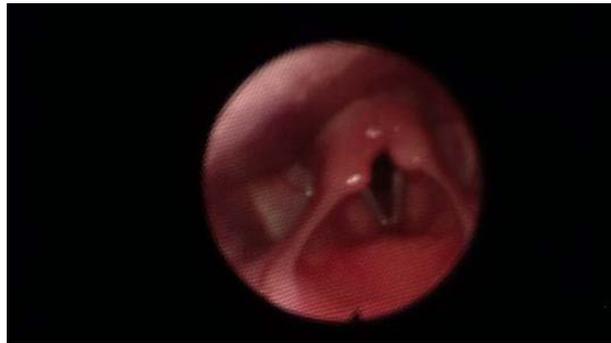
The authors acknowledge research funding from Telethon and the Women and Infants Research Foundation. The first author is the recipient of an Australian Postgraduate Award.

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Figure 8.2 Supplementary Material.



Case 1 During phonation



Case 1 At rest



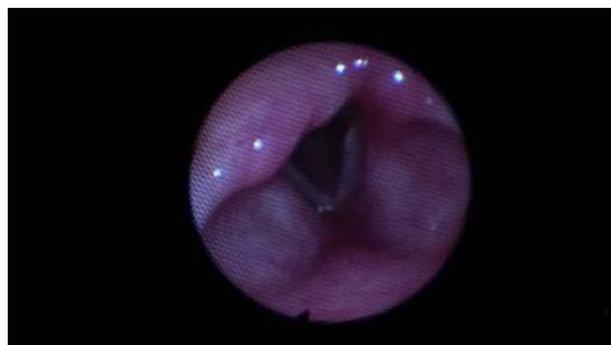
Case 2 During phonation



Case 2 At rest



Case 3 During phonation



Case 3 At rest



Case 4 During phonation



Case 4 At rest



Case 5 During phonation



Case 5 At rest



Case 6 During phonation



Case 6 At rest



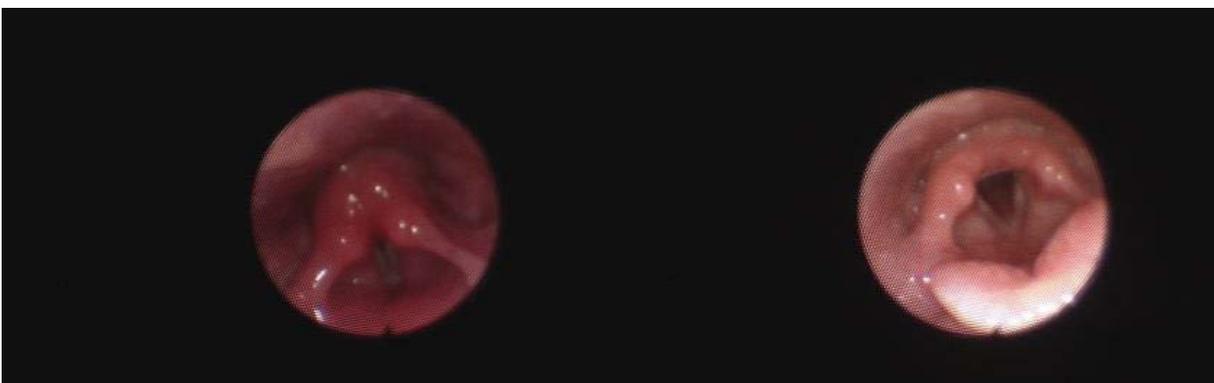
Case 7 During phonation

Case 7 At rest



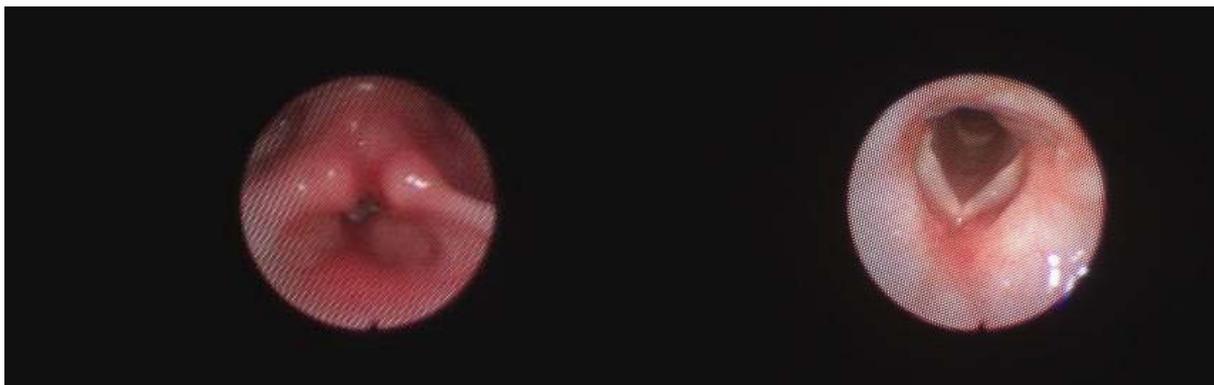
Case 8 During phonation

Case 8 At rest



Case 9 During phonation

Case 9 At rest



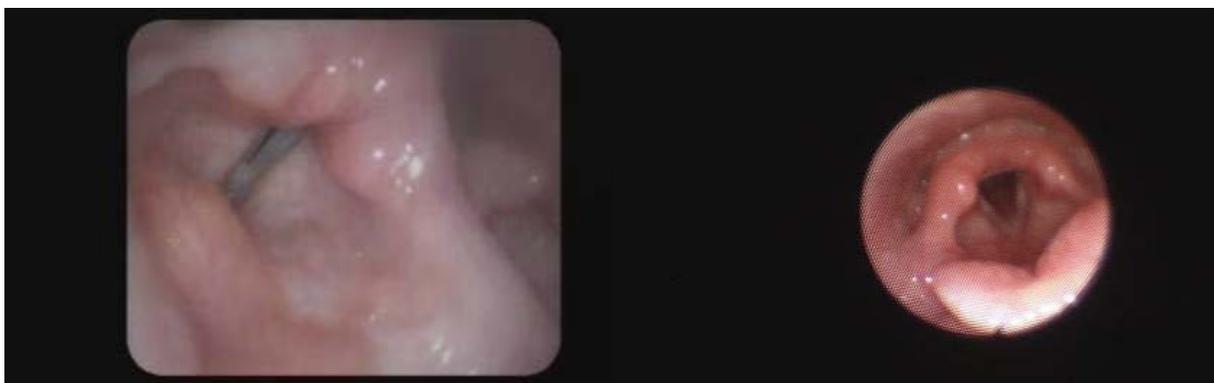
Case 10 During phonation

Case 10 At rest



Case 11 During phonation

Case 11 At rest



Case 12 During phonation

Case 12 At rest



Case 13 During phonation



Case 13 At rest



Case 14 During phonation



Case 14 At rest



Case 15 During phonation



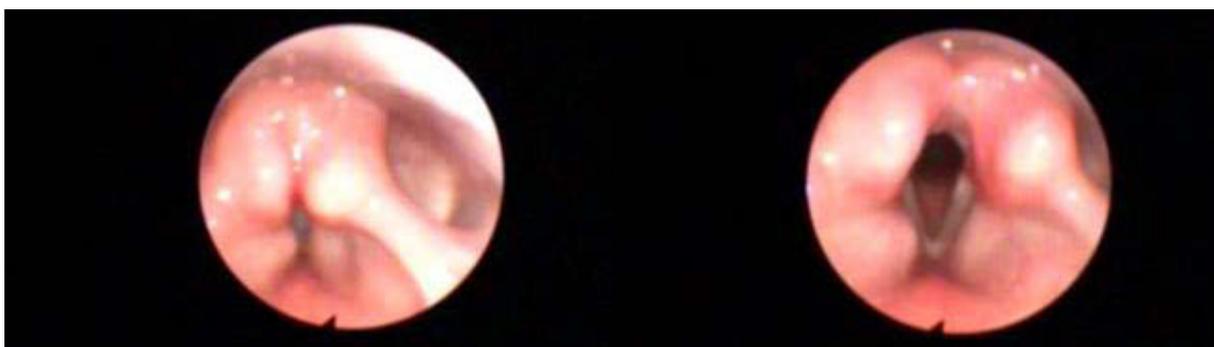
Case 15 At rest



Case 16 During phonation



Case 16 At rest



Case 17 During phonation

Case 17 At rest



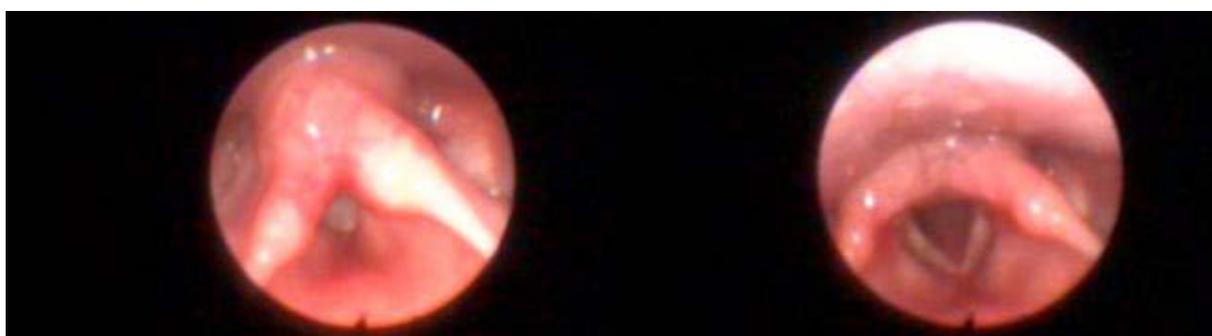
Case 18 During phonation

Case 18 At rest



Case 19 During phonation

Case 19 At rest



Case 20 During phonation

Case 20 At rest

Chapter 9

Intubation-Related Dysphonia Following Extreme Preterm Birth: Case Studies in Behavioural Voice Intervention

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9.1 Abstract

Many more children than ever before survive and thrive following preterm birth.²¹⁹ To date, research has focussed on medical, developmental, neurological, and behavioural outcomes. As the number of surviving children increases and survivors reach school age and beyond, it has become apparent that many children experience difficulties with voice production (Chapter 7).^{129,225} Following preterm birth, endotracheal intubation may be necessary to deliver surfactant or relieve respiratory distress during the neonatal period⁷³. Intubation injury to the larynx and resultant dysphonia are well described in the literature (Chapter 8).^{69,216} This article presents a brief review of the literature relevant to intubation-related injury following preterm birth and two case studies of voice outcomes following a trial of behavioural voice therapy in extremely preterm children who were intubated.

9.2 Introduction

In the majority of studies published regarding neonatal intubation injury in preterm children, the primary focus is laryngeal pathology affecting airway patency.⁷⁹

Dysphonia associated with intubation injury has been reported in children born at up to 36 weeks gestation, yet few studies describe its treatment.^{13,69,71,79,126,130} Dysphonia in childhood is now recognised to have potentially significant adverse effects on quality of life⁹, thus the focus of research pertaining to neonatal intubation injury has recently expanded to include long-term voice outcomes (**Chapter 7**).^{129,131,225}

However, this area of research is still in its infancy and consistent reporting of outcomes is yet to be achieved. Further, in many reports, while dysphonia was described as a symptom of laryngeal pathology, its treatment was not described.^{13,71,115} Further studies are required to identify the prevalence of dysphonia, along with an exploration of the appropriate treatment approaches.

9.3 Aetiology of Intubation-Related Dysphonia in Preterm Children

The only large-scale studies that reported intubation-related voice outcomes refer to children born extremely preterm.^{129,131} Dysphonia in infancy has been linked with birth weight of < 1,000 grams, birth at < 27 weeks gestation, and emergency intubation.¹³¹ In school-aged children, female gender and number of re-intubations was strongly associated with adverse voice outcomes.¹²⁹ These findings indicate that intubation is a factor that strongly influences voice outcomes in extremely preterm children, but more research is needed to better understand the exact conditions under which the risk of developing persistent dysphonia increases. To date, none of these findings have been replicated. There is also evidence that some children may adopt hyperfunctional voicing strategies to compensate for underlying laryngeal injury.⁶⁹

The mechanisms of dysphonia following preterm birth are not yet well understood. In those children with a history of very preterm birth and dysphonia evaluated by our pediatric otorhinolaryngology service, we have found a variety of pathologies, including vocal fold scarring, cysts, stenosis, sulcus vocalis, arytenoid dislocation, and cord paralysis. However the numbers are not large at present and we are currently conducting studies to gain a better understanding of the nature and frequency of the underlying pathologies. Other, non-intubation-related causes of dysphonia may occur in preterm

children. Surgical ligation of patent ductus arteriosus may cause paralysis of the left vocal cord that persists into adulthood, in which dysphonia may result.¹¹¹ Pulmonary disease is common in preterm children but, while caregivers of preterm children with bronchopulmonary dysplasia report more voice-related quality of life restrictions than those without, any link with functional voice outcomes has yet to be explored.^{94,95} There are no reports in the literature of any causal or correlated factors pertaining to medical co-morbidities.

9.4 Treatment of Intubation-Related Dysphonia in Preterm Children

Some intubation-related laryngeal pathology, such as posterior glottic furrow and incomplete vocal fold closure, may be amendable to surgical intervention.^{69,126} Many experts recommend behavioural voice therapy as an adjunct to such management or as a precursor to surgical intervention in cases where invasive intervention prior to puberty is contraindicated.^{69,230} Yet specific therapy techniques are not well described in the literature. Of the literature that reported dysphonia as a symptom of preterm intubation-injury, two studies described voice outcomes following treatment. One case study reported surgical management only,¹²⁶ while the other case series reported behavioural voice intervention.⁶⁹ Behavioural management recommended for incomplete approximation of the vocal folds included promoting firm glottal onsets, deconstriction exercises, and targeting increased vocal loudness. A therapeutic focus on improving breath support for voice was reported to result in decreased inspiratory phonation and a reduction in muscular tension during voice production. Specific detail of the therapy activities was not described.

One exception is impairment in vocal loudness. Compensatory strategies such as environmental changes in the school and voice amplification systems were used for children with soft, weak voices.⁶⁹ This may be beneficial for increasing communication effectiveness but will not lead to alterations in voice quality. Thus, there is need to investigate the effectiveness of specific treatment strategies in intubation-related dysphonia in preterm children, and to provide sufficient description for replication in clinical practice.

9.5 Case Presentations

The case studies were recruited as part of a large-scale study of the incidence of dysphonia in very preterm children and response to intervention (**Chapters 6 and 7**).^{139,163} The research hypothesis regarding aetiology of dysphonia in this cohort was that of structural laryngeal damage following intubation in the Neonatal Intensive Care Unit (NICU) accompanied by compensatory, hyperfunctional supraglottic compression during voice production. Pre- and post-intervention assessments consisted of subjective evaluation with the Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V),⁴ objective assessment of the voice signal with the Acoustic Voice Quality Index (AVQI),¹⁴⁰ and a caregiver-proxy quality-of-life report, the Pediatric Voice Handicap Index (pVHI).⁹ The therapy protocol consisted of vocal hygiene counselling for the child and their caregiver, instruction in diaphragm-driven breathing and breath support for speech, laryngeal relaxation via the yawn-sigh and silent giggle manoeuvres, easy-onset phonation, and resonant voice therapy.

9.5.1 Case 1

A 10-year-old female, born at 25 weeks gestation weighing 640 grams, was recruited. She was intubated 8 times for a total duration of 52 days. One difficult intubation was noted in the medical record. She presented with severe dysphonia and endoscopic evaluation of laryngeal function and voice therapy were indicated. Both she and her caregiver reported significant, longstanding concerns with her voice. Her complaints included being the subject of teasing at school because her voice “sounded like a boy”, and her caregiver reported concerns at the physical limitations imposed by the voice, as well as emotional consequences of being subjected to teasing. Endoscopic evaluation was performed at age 11 and revealed left arytenoid prolapse with decreased vocal fold mobility. There was a posterior chink between the vocal cords and vocal nodules bilaterally. Voice therapy was recommended. Significant supraglottic compression was observed in the anterior-posterior and mediolateral planes (Figures 9.1 and 9.1a). She attended eight sessions of voice therapy and was fully compliant with home practice. Following voice therapy, arytenoid prolapse persisted, but improved vocal fold closure and mucosal wave were noted bilaterally. Vocal nodules had completely resolved. Pre- and post-intervention voice data can be seen in Table 9.1. Subjectively, her caregiver reported that she was able to use her “new voice” approximately half of the time and

was continuing to increase its use in everyday situations as the therapy strategies became habituated. She also reported “losing her voice” following a concert just prior to her final clinical evaluation, but used the strategies learned in therapy to regain her voice. Prior to therapy, her caregiver stated that she had little knowledge of the factors underlying the disturbances in voice quality, other than the “tubes” having caused the problem. Following endoscopy, both demonstrated insight into the nature and symptoms of the structural laryngeal pathology observed. At the conclusion of therapy, both demonstrated understanding of the impact of dysfunctional voicing behaviours on voice and the ability to use techniques learned in therapy to maintain acceptable voice quality.

9.5.2 Case 2

A 6-year-old male born at 25 weeks gestation weighing 650 grams was recruited. He was intubated four times for a total duration of 28 days. He presented with moderate dysphonia, and his caregiver requested endoscopic evaluation of laryngeal function and voice therapy. She reported that he had cried at birth, prior to resuscitation, and that her perception was of a normal, infant cry. She reported that her significant concerns with his voice quality had arisen upon hearing his infant cries following NICU discharge, which she perceived were hoarse. She reported a strong belief that his dysphonia had arisen as a result of intubation, and that his voice quality had remained consistently impaired. Endoscopic evaluation revealed arytenoid prolapse bilaterally with supraglottic tightening. There were signs of reflux changes, including arytenoid oedema. Vocal folds were scarred and oedematous bilaterally (Figure 9.2). Anti-reflux medication was prescribed. He attended eight sessions of voice therapy and his caregiver reported that he was not compliant with home practice activities, despite her best efforts to encourage him. Follow-up endoscopic evaluation was not performed. Pre- and post-intervention data can be seen in Table 9.1. Subjectively, his caregiver reported that she felt equipped to support him to continue to develop his voice skills on an ongoing basis. She reported understanding of voice misuse behaviours, e.g., the supraglottic tightening, its effect on voice quality and implementation of voice therapy techniques to decrease such behaviours.

Table 9.1. Voice assessment scores pre- and post-intervention

Case	Pre CAPE-V score	Post CAPE-V score	Pre AVQI score	Post AVQI score	Pre pVHI score	Post pVHI score
1	90	50	5.37	4.12	45	33
2	50	41	6.60	6.09	27	25



Figure 9.1. Case 1 prior to therapy. Endoscopy image shows arytenoid prolapse and significant mediolateral supraglottic hyperfunction.



Figure 9.1a. Endoscopy image shows right vocal fold oedema, arytenoid prolapse and left vocal fold atrophy.



Figure 9.2. Case 2 prior to therapy. Endoscopy image shows antero-posterior supraglottic hyperfunction, vocal cord oedema and scarring and arytenoid oedema and prolapse.

9.6 Discussion

Both children in the aforementioned case studies experienced a decrease in dysphonia severity, from severe to moderate in one case and from moderate to mild-to-moderate in the other. Observable laryngeal pathology was reduced in the child who underwent follow-up endoscopic evaluation. Neither child experienced a complete resolution of dysphonia, suggesting that behavioural voice therapy alone may not be sufficient to normalise voice quality in extremely preterm children.

The main persisting subjective complaint for both children was lack of power to the voice. The decrease in supraglottic activity during phonation may have been a contributing factor. Increases in volume may have been achieved by supraglottic tightening and subsequent increased vocal fold approximation. Decreases in supraglottic activity were associated with decreased strained quality to the voice and increased intelligibility. Intervention targeting increasing vocal loudness while maintaining minimal laryngeal effort, such as twang, could be trialled with this population.

The female patient achieved better outcomes than the male patient. It is hypothesised that this may have been influenced by the difference in age. The female was observed to participate fully in therapy and autonomously complete home practice, whereas the male was not able to participate in home practice without full support from his caregiver, in the form of reminders and joint participation in activities. Further, the male participated in numerous extracurricular activities, leaving less time available for practice for each activity. A placebo effect from therapy cannot be excluded. Both children and their caregivers reported that they enjoyed participating in therapy and

wanted their voices to improve. Further, medical perspectives regarding likely permanence of developmental sequelae following extreme preterm birth may have led to hypervigilance to any developmental input on the part of the parents, who may therefore have been over-receptive to the prospect of any positive change. However, both patients experienced a decrease in their Acoustic Voice Quality Index score, indicative of increased regularity of the voice signal.

9.7 Conclusion

Behavioural voice therapy resulted in improvements in voice quality in two children with an intubation-related laryngeal pathology, to varying degrees, yet did not completely resolve symptoms of dysphonia. Further research in a larger sample of children is warranted to determine whether behavioural voice therapy is effective in the extremely preterm population.

Chapter 10

A randomised, controlled trial of behavioural voice therapy for dysphonia related to prematurity of birth

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10.1 Abstract

Objectives/hypothesis

Dysphonia is a potential complication of preterm birth. It is hypothesised that preterm children sustain iatrogenic laryngeal damage during medical intervention in the neonatal period. Further, many preterm children may engage in compensatory maladaptive behaviours to initiate and sustain phonation. Voice disturbances are known to persist into the school years. This pilot study aimed to evaluate the effects of a behavioural voice therapy protocol on voice quality in school-aged children with dysphonia related to premature birth.

Methods

Twenty seven very preterm (VP) children (born at 23-29 weeks gestation) with dysphonia were identified from a larger study and consented to laryngeal examination and randomisation to an immediate intervention group ($n=7$) or a delayed-intervention, waiting list control group ($n=14$). Following analysis of the immediate intervention and waiting list control data, secondary analysis was conducted on the pooled intervention data of both groups. Six participants did not complete the trial.

Results

Statistically significant improvements in voice quality, as measured on perceptual assessment, were seen following both the control ($n = 14$) ($p = .026$) and the secondary analysis of the intervention ($n = 21$) ($p = .026$) data. However, this was not reflected in caregiver-proxy reports of quality of life.

Conclusions

Behavioural voice therapy was associated with improvements in voice quality in some VP children and some improved spontaneously. Further research is needed to identify the facilitators of and barriers to success of therapy, as well as to identify those children who may experience spontaneous improvements in voice quality.

10.2 Introduction

Dysphonia is a potential long-term outcome of very preterm (VP) birth.¹³³ Disturbances in voice quality in VP children are thought to result from structural laryngeal damage - sustained primarily during neonatal intubation - and compensatory tightening of the supraglottic musculature during voice use, also referred to as secondary muscle tension dysphonia.¹³⁸ Dysphonia in childhood has been associated with academic and social disadvantage, as well as negative evaluations from peers and adults.^{56,57}

Developmental, medical and behavioural outcomes following preterm birth continue to improve.²¹⁹ Greater numbers of children survive to adulthood following preterm birth and many of those live independently, successfully compete in the open workforce and experience quality of life similar to that of their term-born peers.²³¹ For many VP children, dysphonia may be the only significant, long-term consequence of their preterm birth. It is estimated that approximately one-third of the workforce in developed countries require the use of the voice.⁵⁸ Further, voice problems are also associated with absenteeism in non-voice related occupations, albeit with less frequency.²³² Thus it can be seen that disturbance to voice quality associated with preterm birth may also result in occupational disadvantage in adulthood.

The prognosis for dysphonia in VP children is uncertain. As a recently reported entity, research has focussed on incidence, pathology and presentation. In the absence of intervention, dysphonia in preterm children is persistent.²³³ The results of surgical intervention have been reported in case reports and series, and show that surgery is effective in improving voice quality in pathologies such as posterior glottis furrow and posterior glottis diastasis, where structural laryngeal anomalies were approximated to a more typical anatomical position.^{69,234} However, the effect of such intervention on the behavioural characteristics contributing to voice disturbance is unclear. Voicing behaviours are a learned phenomenon, and expert opinion suggests that in cases of paediatric hyperfunctional voice use, surgical intervention alone may not result in changes to behaviour.¹⁴⁸

Behavioural voice therapy refers to intervention aiming to modify behaviour associated with voicing to promote efficient phonation.³⁶ The effectiveness of behavioural intervention has been demonstrated in children with primary muscle tension dysphonia (for example, Lee & Son and Mackiewicz and colleagues).^{34,191} Such intervention is thought to decrease symptoms of vocal hyperfunction, primarily strained voice quality.³⁶ It can be hypothesised that behavioural voice therapy may improve voice quality in VP children who experience secondary muscle tension dysphonia. However, there have been no investigations of the effects of behavioural voice therapy in preterm children.

This pilot study aims to evaluate the effects of behavioural voice therapy on the voice quality of preterm children with significant voice abnormalities.

10.3 Methods

The study methodology has been described elsewhere and is unchanged.¹³⁹ This delayed-intervention, randomised controlled trial formed the third phase in an exploratory study of the prevalence, presentation, influencing factors and response to treatment of voice disorders in VP children. A summary of the participant characteristics and a description of the treatment protocol are provided below.

10.3.1 Participants

A total of 2,420 children born at ≤ 32 weeks gestation were admitted to and subsequently discharged from the Neonatal Intensive Care Unit (NICU) of the study centre in metropolitan Perth, Western Australia, between 2001 and 2007. Children were excluded if they were diagnosed with a known disability likely to preclude participation in assessment tasks or residence greater than 200km from the study centre. The remaining eligible participants were stratified into groups, based on gestational age and number of intubations recorded on the NICU discharge summary, and then randomly selected. The families of 391 children were approached, and 179 assessments were completed. Details of the participants in the second, laryngeal phase of the investigation have been published elsewhere.¹³⁸ Briefly, those who presented with moderate to severe dysphonia were invited to undergo laryngoscopy and participate in intervention. Each participant therefore in this phase presented with moderate or severe dysphonia and consented to laryngoscopy. Laryngoscopic findings from all participants showed primary, structural pathology of a heterogeneous nature, with supraglottic hyperfunction of the laryngeal musculature which was hypothesised to be compensatory in nature. The most common structural pathology in this cohort was glottic incompetence. Vocal fold immobility and atrophy were also observed. In addition, a number of participants had vocal cord irregularities such as nodules, pseudocysts and sulci.

Participants in the intervention trial were born between 23 and 29 weeks gestation. The flow of participants through the study phases can be seen in Figure 1. The age of participants at the commencement of intervention ranged from 6 years 9 months to 17 years 2 months.

10.3.2 Clinical assessment

A clinical assessment was completed prior to and immediately following the treatment administration. Clinical assessment consisted of: subjective evaluation of voice quality with the Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V);⁴ objective assessment with the Acoustic Voice Quality Index (AVQI)² and the caregiver-reported quality of life instrument the Pediatric Voice Handicap Index (pVHI).⁹ The CAPE-V was considered the primary outcome measure. Due to the subjective nature of the CAPE-V, the mean of two blinded ratings was used for statistical analysis. The pVHI and AVQI were considered secondary outcome measures. Although the AVQI has demonstrated its diagnostic accuracy in discriminating between normal and dysphonic

children's voices, its responsiveness to therapeutic change is yet to be established in paediatrics.^{2,140}

10.3.3 Recruitment

Participants were recruited for initial clinical assessment between February 2011 and July 2013. Figure 1 depicts participant flow through the study phases, with reasons for discontinuations where relevant. Recruitment ceased when the predicted number of participants had been reached for the phase I clinical assessments. Following establishment of eligibility, recruitment for the laryngeal examination and behavioural intervention trial took place between February 2013 and August 2014. Recruitment ceased when all eligible participants had been successfully contacted, or after three attempts had failed to contact them. Twenty six participants were randomised to phase III of the study, of whom 21 completed the trial (immediate intervention group N = 7, control group N = 14). Figure 2 depicts the randomisation and progression of participants through this phase of the study.

10.3.4 Randomisation

Participants were randomised to the intervention or waiting list control groups by a colleague with no professional connection to this study. Randomisation occurred via opaque envelopes on the day of the laryngeal examination and was conducted by an individual external to the study group. Blocking was used in the case of two sets of twin participants. Due to the nature of the study, blinding to group was not possible.

10.3.5 Treatment protocol

The intervention consisted of eight, one-hour sessions, delivered a minimum of one week apart. Treatment was delivered by a single speech pathologist, with postgraduate experience in assessment and treatment of paediatric voice disorders. The treatment period commenced in March 2013 and ended in April 2015.

Treatment tasks were standard across participants, although explanations and specific prompts were individualised, depending on the cognitive skills of the participant and their mastery of the task. A description of the treatment tasks, being the session by session treatment protocol, is provided in Table 10.7 (Appendix). All treatment sessions took place in the Children's Clinical Research Facility at Princess Margaret Hospital in Perth, Western Australia, or at participants' homes when participants were physically unable to attend the study centre.

10.3.6 Sample size

Being a pilot study, prior calculation of sample size with reference to other studies was not possible, due to the lack of relevant, similar reports in the literature. The sample size for this trial was determined by: the sample size for the first phase of the investigation; the number of children meeting eligibility criteria for further participation and the consent of the participants and their families (see Figure 10.1).

10.3.7 Rater reliability

All voice samples were rated online by the first author as part of participants' clinical assessments, and for feedback to participants and their families. To determine the reliability of the perceptual rating scale, the CAPE-V, all voice samples were de-identified and rated independently by a speech pathologist with postgraduate experience in the assessment and treatment of paediatric voice disorders and re-rated by the first author. At the commencement of each of the joint rating sessions, raters listened to two voice samples at each level of severity, selected by previous consensus, to establish an external reference standard. To overcome any potential biases associated with the perceptual aspect of the assessment, the mean of the two blinded ratings was used as the dysphonia severity score for the purposes of data analysis.

A two-way, mixed, average measures ICC was calculated. The ICC between raters for the CAPE-V severity score was .77(95% CI = .61 -.86), with a weighed kappa of .51, indicating a moderate to good level of agreement between raters. Therefore, the mean of the two blinded ratings was an acceptable indicator of dysphonia severity in this cohort.

10.3.8 Statistical analysis

Data were summarised using means and standard deviations. All data analysis was conducted using SPSS for Windows (v. 21: SPSS Inc, Chicago, IL). Due to the ordinal nature of the data, non-parametric tests were used for data analysis. A Mann Whitney *U* test was used to compare voice quality between the intervention and control groups at baseline assessment. Figure 10.2 contains a depiction of the statistical analysis of intervention and control data. The first analysis was conducted on the intervention and control groups. After the control period, the control group underwent intervention. The second analysis was of the pooled intervention data and the post-intervention data of the control group. Wilcoxon signed rank tests were used for the first and second analyses. To facilitate consideration of clinical significance of changes, descriptive statistics were used to describe the data.

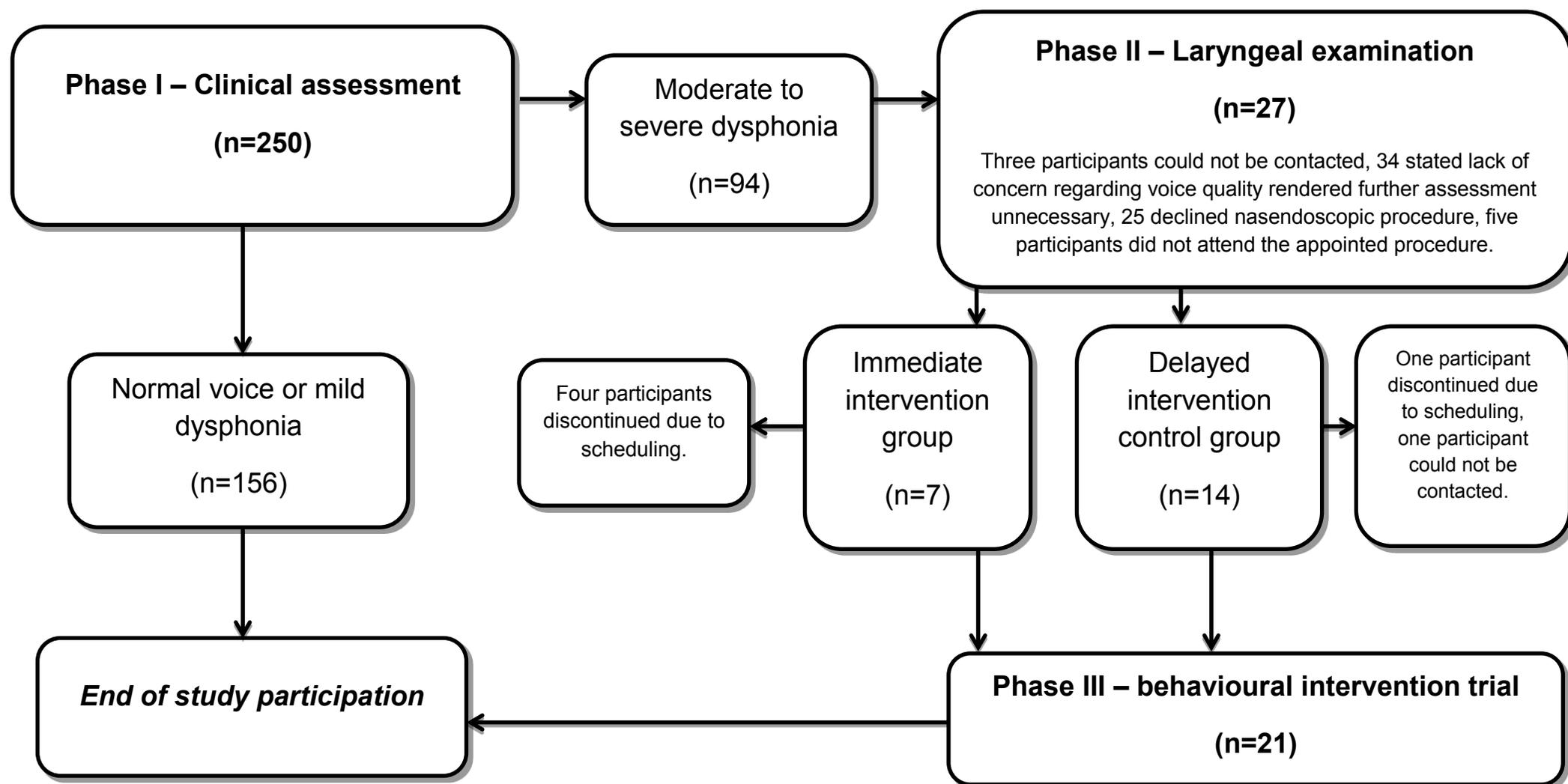


Figure 10.1. Participant flow through study phases.

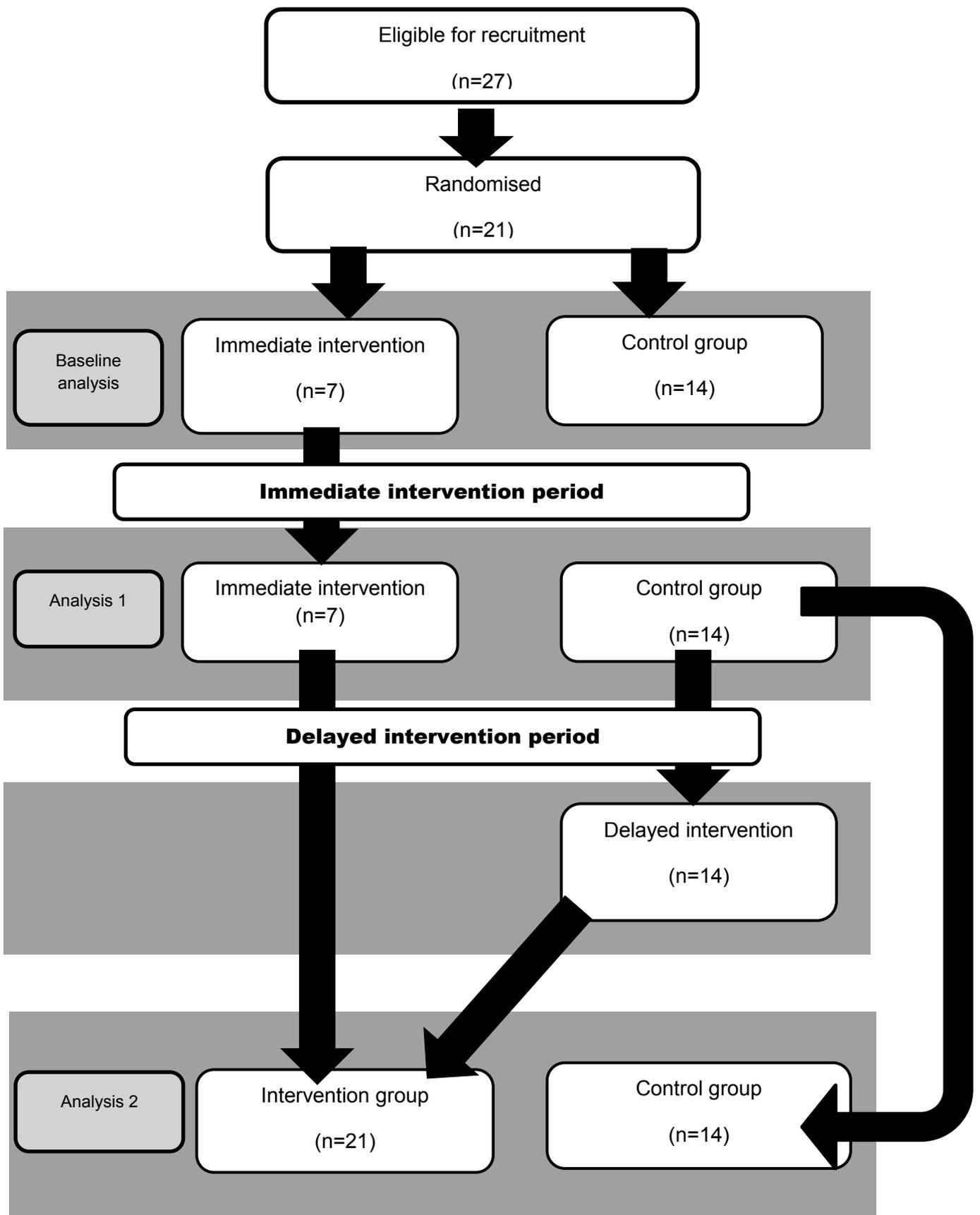


Figure 10.2. Randomisation and analysis of intervention and control groups.

10.4 Results

10.4.1 Baseline analysis

Only those participants with moderate to severe dysphonia who consented to laryngoscopy were eligible for participation in this intervention trial. Independent samples t-tests were used for baseline analyses, as normality assumptions were not violated in this data set. Due to the self-selective nature of the inclusion criteria of the study, a comparison of the voice, medical and demographic characteristics of participating versus non-participating children was performed, and can be seen in Table 10.1. No differences in sex, age, birth weight or gestational age were found between the groups. Whilst the number of intubations and duration of intubation trended towards statistical significance, this did not translate to poorer functional voice outcomes, as CAPE-V severity score and AVQI score were equivalent across the groups.

The baseline characteristics of the intervention and control groups are presented in Table 10.2. Equivalence across the groups was seen in all measures, confirming success of randomisation and less likelihood of bias.

Table 10.1. Voice, demographic and medical characteristics of participating and non-participating cases.

	Study cases (consented to laryngoscopy) (n=27)	Non-participating cases (did not consent to laryngoscopy) (n=65)	<i>p</i>
Sex (male)	11 (40.7%)	26 (40.0%)	.947
Chronological age (years)	9.24 (2.99)	9.02 (2.62)	.747
CAPE-V severity score	58.30 (18.41)	54.11 (16.87)	.314
AVQI score	5.17 (1.09)	5.21 (1.26)	.880
pVHI total score	35.26 (21.37)	25.92 (18.71)	.056
Birth weight (g)	697 (236)	746 (259)	.383
Gestational age (weeks)	24.37 (1.59)	24.38 (1.37)	.990
Number of intubations	6.19 (3.45)	4.89 (2.06)	.078
Duration of intubation (days)	45.19 (25.35)	34.70 (17.05)	.057

Table 10.2. Baseline data of intervention and control groups.

	Immediate intervention group (n=7) n (%) / M (SD)	Delayed intervention control group (n=14) n (%) / M (SD)	<i>p</i>
Sex (male)	2 (28.6%)	7 (50%)	.350
Age	9.21 (2.87)	8.48 (2.72)	.590
CAPE-V severity score	65.14 (16.08)	55.64 (20.53)	.264
AVQI score	5.49 (1.38)	5.11 (1.16)	.549
pVHI score	45.43 (24.83)	27.36 (15.17)	.114
Birth weight (g)	612 (88)	759 (245)	.062
Gestational age (weeks)	23.86 (.90)	24.86 (1.99)	.130
Duration of intubation (days)	50.71 (16.35)	34.79 (31.51)	.144
Number of intubations	7.57 (4.07)	4.40 (2.83)	.098

CAPE-V = Consensus Auditory-Perceptual Evaluation of Voice. AVQI = Acoustic Voice Quality Index, pVHI = Pediatric Voice Handicap Index.

10.4.2 Intervention data

10.4.2.1 Intervention group

The intervention group did not experience a statistically significant improvement in voice quality on any measure following the intervention period (as defined in Figure 2). A comparison of changes in voice quality between the intervention and control groups can be seen in Table 10.3. Descriptive data, and comparison of within-group pre- and post-intervention voice quality, can be seen in Table 10.4.

Table 10.3. Comparison of changes in voice quality between the intervention and control groups (analysis 1).*

	Treatment group change (n=7) M (SD)	Control group Change (n=14) M (SD)	<i>p</i> value
CAPE-V severity score	-14.05 (31.16)	-13.15 (19.26)	.913
AVQI score	-.66 (1.61)	.11 (1.04)	.636
pVHI total score	-2.28 (17.09)	2.77 (10.67)	.438

CAPE-V = Consensus Auditory-Perceptual Evaluation of Voice. AVQI = Acoustic Voice Quality Index, pVHI = Pediatric Voice Handicap Index. *Negative values signify improvement.

Table 10.4. Descriptive changes in dysphonia severity following intervention period (analysis 1).

	Treatment (n=7)			Control (n=14)		
	Pre-intervention	Post-intervention	<i>p</i> value	Initial assessment	Follow-up assessment	<i>p</i> value
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
	Range	Range		Range	Range	
CAPE-V severity score	62.87 (16.72) 34.00-80.00	48.82 (24.20) 20.00-84.5	.310	61.50 (13.50) 31.50-85.00	48.36 (26.08) 5.00-86.25	.026
AVQI score	5.85 (.84) 4.61-7.14	5.19 (1.18) 3.16-6.58	.398	4.84 (1.18) 2.64-7.33	4.96 (1.38) 2.93-7.58	.875
pVHI total score	47.28 (22.26) 25.00-90.00	45.00 (17.50) 23.00-66.00	.752	28.54 (14.18) 11.00-54.00	31.71 (15.12) 13.00-60.00	.362

CAPE-V = Consensus Auditory-Perceptual Evaluation of Voice. AVQI = Acoustic Voice Quality Index, pVHI = Pediatric Voice Handicap Index. * Negative values signify improvement.

10.4.2.2 Control group

Dysphonia severity, as measured by the CAPE-V severity score, was significantly improved in the control group without any specific treatment, with a medium effect size of -0.35. However, there was no such difference in AVQI score. Similarly, the difference on pVHI score between the initial and follow-up assessments was not statistically significant. No participant presented with a perceptually normal voice following the control period, but two male participants, both going through puberty, who initially presented with moderate dysphonia experienced a decrease in severity to mild dysphonia, defined as a CAPE-V severity score of ≤ 2 . The range of change in each measure of dysphonia severity can be seen in Table 10.4.

10.4.2.3 Secondary analysis of pooled intervention data

Due to the small sample size, a decision was made a priori to pool the pre- and post-intervention data from the intervention and control groups, to increase statistical power, as described in Figure 10.2 (analysis 2). Dysphonia severity, as measured by the CAPE-V severity score, was significantly lower following the intervention period, $p = .026$ representing a medium effect size of -0.35. The AVQI trended towards, but did not reach statistical significance, p representing a small to medium effect size, -0.26. However, the difference on pVHI score following the intervention period was not

statistically significant. Two other participants presented with a perceptually normal voice following the intervention period, and a further six with mild dysphonia, defined as a CAPE-V severity score of ≤ 20 . Neither of the participants who presented with mild dysphonia following the control period presented with a normal voice following intervention. The range of change in each measure of dysphonia severity can be seen in Table 10.5.

Table 10.5. Comparison of changes in voice quality between the intervention and control groups (analysis 2).*

	Treatment group change (n=21) M (SD)	Control group Change (n=14) M (SD)	<i>p</i> value
CAPE-V severity score	-15.01 (25.91)	-13.15 (19.26)	.960
AVQI score	-.38 (1.49)	.11 (1.04)	.222
pVHI total score	-1.84 (12.65)	2.77 (10.67)	.223

CAPE-V = Consensus Auditory-Perceptual Evaluation of Voice. AVQI = Acoustic Voice Quality Index, pVHI = Pediatric Voice Handicap Index. *Negative values signify improvement.

Table 10.6. Descriptive changes in dysphonia severity following intervention period (analysis 2).

	Treatment (n=21)		<i>p</i> value	Control (n=14)		<i>p</i> value
	Pre-intervention Mean (SD) Range	Post-intervention Mean (SD) Range		Initial assessment Mean (SD) Range	Follow-up assessment Mean (SD) Range	
CAPE-V severity score	53.20 (23.98) 5.00-86.25	38.19 (26.17) 0.00-84.50	.026	61.50 (13.50) 31.50-85.00	48.36 (26.08) 5.00-86.25	.026
AVQI score	5.26 (1.28) 2.93-7.58	4.88 (1.56) 1.77-7.49	.099	4.84 (1.18) 2.64-7.33	4.96 (1.38) 2.93-7.58	.875
pVHI total score	36.90 (18.81) 13.00-90.00	37.47 (13.74) 19.00-66.00	.602	28.54 (14.18) 11.00-54.00	31.71 (15.12) 13.00-60.00	.362

CAPE-V = Consensus Auditory-Perceptual Evaluation of Voice. AVQI = Acoustic Voice Quality Index, pVHI = Pediatric Voice Handicap Index.

10.5 Discussion

Dysphonia is a recognised potential complication of very preterm (VP) birth. To date, the course of voice disturbance in such children is unknown.²³³ This is the first published trial of behavioural voice therapy in very preterm children. This study demonstrated that improvements in voice quality were seen, on both objective and subjective measures of dysphonia severity, for some children over time without intervention and others following behavioural intervention. Thus, both spontaneous and interventional recovery can be seen.

Following the initial treatment period, there was no change in dysphonia severity. However, inspection of descriptive data revealed decreases in voice disturbance as measured by the CAPE-V severity score and the AVQI and improvements in quality of life as measured by the pVHI. At the end of the treatment period, the secondary analysis of pooled data demonstrated a reduction in CAPE-V severity and AVQI score, from moderate to severe dysphonia prior to intervention, to moderate dysphonia following completion of the treatment protocol suggesting some improvement in voice quality. However, the clinical significance of this change across the group is unknown. These data suggest that the initial intervention results may have been a function of the small sample size. The unequal sample size is noted and is unfortunate; however, it is a function of participation and the randomisation process.

It was informally noted in two of the male control participants that puberty may have occurred in the control period. Puberty in males is associated with both maturational changes in voice quality, and resolution of dysphonia in some cases of childhood voice disorders.^{22,230} These factors may have been associated with spontaneous improvements in voice quality. Yet pubertal change was not formally assessed within this trial, so this remains a tentative hypothesis.

Further, although the perceptual scores of dysphonia severity were lower in the control group, the objective AVQI score did not show similar change, suggesting that perceptual improvements in voice quality were not reflected by increased regularity in the voice signal. No control participant presented with a normal voice following the control period. However, two participants did present with change to mild dysphonia, as measured by a CAPE-V severity score of ≤ 20 . Therefore, further investigation into the nature and extent of spontaneous improvement in voice quality in preterm children is recommended, with particular emphasis on identifying those children who may be more likely to experience such change.

It is hypothesised that the behavioural voice intervention resulted in decreases in constriction of the supraglottic musculature during phonation. Individuals with primary laryngeal pathology may adopt tightening of the supraglottic musculature during phonation in an attempt to compensate for vocal hypofunction caused by structural laryngeal abnormalities. Behavioural intervention is unlikely to have been effective in changing intubation-related laryngeal pathologies such as arytenoid subluxation, posterior glottic insufficiency or vocal fold immobility. Yet, changes in voicing behaviour may have occurred and resulted in increased regularity of the vocal signal.

Yet, group means masked significant individual variability in this cohort, with some individuals achieving acceptable voice outcomes following intervention, while others experienced minimal-to-no change. The secondary analysis demonstrated that two participants (who had been randomised to the delayed intervention group and presented with no change in voice quality during the waiting period) presented with normal voices following intervention, and a further three presented with mild dysphonia (as measured by a CAPE-V score of ≤ 20). While post-intervention voice quality remained in the moderate range, a further three participants experienced a change in CAPE-V scores of ≥ 15 . The two participants who presented with mild dysphonia following the control period continued to present with mild dysphonia and were therefore not responsive to intervention. The factors which contributed to greater improvements in voice quality are presently unknown. Further research to elucidate these factors will facilitate better therapeutic outcomes for affected children.

Observing a correlation between individual participant laryngeal pathology and therapy outcomes is difficult in this study. Due to the individual heterogeneous presentation of structure and function of the vocal mechanism, coupled with the universal nature of the intervention, statistical correlations could not be performed. A study with a larger sample size or a study targeting particular laryngeal pathologies may be able to achieve

this in future. However, adopting a universal therapy protocol may have increased the ecological validity of the intervention. A clinical caseload of children with dysphonia seeking treatment is likely to be heterogeneous, and the study population will reflect this. In a clinical context, therapy would be more individualised, to address both the perceptual characteristics of the voice signal and the underlying laryngeal pathology.

The findings pertinent to quality of life are less clear. Some participants reported increased impact of dysphonia on quality of life following intervention. Anecdotally, a number of caregivers reported that participating in the therapy process had increased their awareness of the difficulties faced by their children. During the therapy process, some participants disclosed, for the first time, having been subjected to past or current teasing relevant for their voice quality. Many caregivers reported that their child's voice was relatively un concerning, given the many medical obstacles related to premature birth already encountered. It is clear that the relationship between voice and quality of life in these participants is complex, and that participating in intervention may have highlighted an ongoing problem of which caregivers were unaware.

10.5.1 Limitations of this study

This protocol was piloted on a small cohort. The sample size limitation was due to the low response rate of families who consented to the laryngeal examination, and a tendency toward those born at earlier gestational age. Further, a response bias cannot be excluded due to the self-selection of participants. Future studies may improve response rates by instituting multi-centre trials, or recruiting from specialist, tertiary voice centres to identify and include treatment-seeking individuals.

10.5.2 Strengths and generalisability

This pilot study is the first, to the authors' knowledge, to investigate the effects of behavioural voice therapy in a randomised trial in preterm children. Comparison of treatment outcomes was facilitated by the inclusion of a control group, with baseline voice, medical and demographics characteristics equivalent to the intervention group.

Comparison of baseline data demonstrated that the children who consented to laryngoscopy and participated in the trial were representative of the cohort. There was a trend towards lower pVHI scores in the non-participating group, suggesting that families perceived their children's voices to have fewer adverse consequences on their quality of life. This may have influenced their decision regarding participation.

Previous studies have described the use of behavioural voice intervention in cases of childhood primary muscle tension dysphonia.^{34,134,175,190,191,197,235} This study provides some evidence in support of the use of behavioural voice therapy to decrease symptoms of compensatory hyperfunction in some cases of childhood vocal hypofunction. The heterogeneous nature of the underlying laryngeal pathologies observed in this study may lead to cautious generalisation of these results to term-born children with intubation injury, or children with laryngeal conditions unrelated to preterm birth where vocal hyperfunction is known to be present.

10.6 Conclusions

This pilot study demonstrated that behavioural voice therapy improves voice quality in some very preterm children with observed structural laryngeal pathology and secondary vocal hyperfunction. It is hypothesised that therapy activities resulted in decreased supraglottic constriction, improved breath support and increased regularity of vocal fold vibration, which was reflected in increased regularity of the voice signal. However, due to the inconsistent response to intervention, these findings are inconclusive.

10.7 Other information

This study is registered with Australian and New Zealand Clinical Trials Registry (ACTRN12613001012763). The trial protocol can be accessed at <http://dx.doi.org/10.1016/j.cct.2013.12.004>. This study was funded by Telethon and the Women and Infants Research Foundation. The first author is the recipient of an Australian Postgraduate Award.

Table 10.7 Treatment tasks for behavioural voice intervention protocol.

<i>Therapy</i>	Task information
<i>Information provision</i>	<ul style="list-style-type: none"> Diagrams and photographs were used in conjunction with clinician demonstration to describe respiratory, laryngeal and resonance systems.
<i>Abdominal breathing</i>	<ul style="list-style-type: none"> Guided self-assessment of tidal breathing patterns was conducted. Place one hand on abdomen and one on chest to feel movement: abdominal movement should be greater.²⁵ Imagery and other cues were used to demonstrate and promote abdominal breathing.²³⁶ Attention was focused on the expiration phase of the breathing cycle, with exhalation released as a barely-audible sigh.²³⁶
<i>Abdominal breathing plus speech</i>	<ul style="list-style-type: none"> /s/ and /ʃ/ were produced on exhalation in a rhythmic fashion, beginning with longer, slower pulses, moving to shorter, sharper pulses.⁴⁴ A prolonged, voiced bilabial fricative was produced.²³⁷
<i>Relaxation exercises</i>	<ul style="list-style-type: none"> Yawn-sigh: participants were instructed to inhale deeply, triggering a yawn if possible.²³⁸ Exhalation was silent, to minimise constriction. Easy onset phonation: participants produced /h/ on exhalation, and were instructed to feel the easy onset of phonation and transition to a vowel without introducing tension into the vocal folds.¹⁹¹ Silent giggle: a laugh was triggered. Participants were then instructed to “take the sound away” or “don’t make a noise”.²³⁹ Participants were instructed to “freeze” in the middle of the laugh and attend to the kinaesthetic sensation hypothesised to be associated with retracted ventricular folds.
Resonant voice/forward focus resonance	<ul style="list-style-type: none"> Forward focus resonance was described as effortless or easy phonation, with no muscle tightness in the voice box. Participants were instructed to “throw” their voice forwards to make the front of their face “buzz”.²⁴⁰ Participants’ focus was directed to sensory and auditory feedback to facilitate correct production.²⁴¹ Participants produced a hum with an easy voice, feeling vibration in the face, rather than the throat or the back of the mouth.²⁴² Increases and decreases in pitch were introduced.²⁴² Tasks were structured in a hierarchy to promote skill acquisition, commencing with short phrases containing nasal consonants then structured and semi-structured speech tasks and automatic speech.²⁴¹⁻²⁴³

Chapter 11

External validity of the Acoustic Voice Quality Index in the paediatric voice clinic

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11.1 Abstract

Objective: The Acoustic Voice Quality Index (AVQI) is an objective, composite score of dysphonia severity based on a speech sample consisting of a sustained vowel and connected speech. Including both speaking tasks results in improved ecological validity in comparison to measures based on either task alone. In an initial investigation into the diagnostic accuracy of the AVQI in paediatric voice, it was found to have appropriate sensitivity and specificity in the study cohort. This study aimed to measure the external cross-validity of the Acoustic Voice Quality Index in paediatric voice by replicating the initial study with a larger sample of children.

Methods: One hundred and seventy nine participants born at ≤ 32 weeks gestation were recruited to undergo a voice assessment. Voice recordings were sub-sampled from each severity category and forty four voice samples randomly selected for inclusion in this study. Signal to noise ratios (SNR) were calculated for each sustained vowel and connected speech sample. Each participant's AVQI score was calculated on a standardised voice sample consisting of a sustained vowel and continuous speech, in exact accordance with the procedure described elsewhere.

Results: The AVQI was strongly correlated with perceptual impressions of dysphonia severity according to the GRBAS scale. The threshold for pathology in this sample of 3.24 showed appropriate sensitivity, specificity and accuracy, with good likelihood ratios. The mean SNR for voiced segments extracted from connected speech was 26.44dB and for vowels 27.67dB (SPL).

Conclusions: The AVQI retained its diagnostic utility in an independent cohort of children with a wider distribution of voice disturbances. Similar results were found to the initial validation study in children, suggesting that it has acceptable external validity. In this study, the mean SNR of the voice samples was < 30 dB, suggesting that the AVQI is a useful tool in clinical settings, where background noise levels are higher than in experimental settings. The AVQI may be considered a suitable acoustic assessment in the evaluation of childhood voice disorders.

11.2 Introduction

Voice disorders affect individuals across the lifespan, affecting social, academic and employment participation.^{53,54,56} Yet there is limited research attention to paediatric populations compared to adults.¹⁸⁹ This is relevant, as paediatric and adult voices should be considered separate clinical entities due to structural differences of the larynx and vocal tract.^{36,37} These differences lead to variations in aspects of voice quality such as pitch, roughness and breathiness.^{8,41} Voice assessment tools and outcome measures need to be developed and validated in either or both populations to ensure that they are sensitive enough to detect the differences in voice quality produced by adult and child speakers, and should therefore be normed on appropriate populations.

To accurately measure voice disturbance, assessments must be reliable and valid.²⁴⁴ A three-pronged assessment approach is considered best practice when evaluating voice quality.¹⁴³ A subjective, perceptual evaluation is essential as individuals seek assistance for voice problems because their voices sound different to the norm.¹⁴⁴ An acoustic analysis of the voice signal is objective and non-invasive. It is less subject to clinician bias and more sensitive to minute, but potentially clinically significant, changes in voice quality than the human ear and should therefore be included in any test battery to supplement perceptual assessments.¹⁴⁵ Finally, a quality of life measure is necessary to measure any restrictions imposed by an individual's voice on their activities, participation and well-being.¹⁴⁴

A number of subjective, perceptual assessment tools have been validated for use in children (e.g, the Grade, Roughness, Breathiness, Aesthenia and Strain scale, the Consensus Auditory Perceptual Evaluation of Voice and the Vocal Profile Analysis).^{3,222,245} Several quality of life questionnaires are also available, including both parent-proxy and child self-report measures (e.g, Pediatric Voice Handicap Index, Pediatric Voice Outcome Survey, Children's Voice Handicap Index-10).^{9,246,247} Further, paediatric norms for some acoustic measures are available.^{248,249} Yet although single acoustic measures reflect underlying vocal pathology, they are poor predictors of overall dysphonia severity.^{5,145} There is a need to investigate combinations of single acoustic parameters to better identify the magnitude of deviance in voice quality, and to provide information about underlying laryngeal functioning. Such measures require independent validation in paediatric populations, separately to adults.

The Acoustic Voice Quality Index (AVQI) is such a measure, consisting of six parameters of the vocal signal, as described by Maryn et al.² The AVQI is unique in acoustic voice analysis because it calculates a composite score of dysphonia severity, based on a speech sample consisting of a prolonged vowel and connected speech.² This approach is said to yield better ecological validity than calculations based on either speaking condition alone.¹⁵⁸ The AVQI has been found to have diagnostic utility in discriminating between normal and dysphonic voices in both adults and children.^{2,140,250}

The concurrent validity of the AVQI in paediatric voice was established by comparing AVQI scores with perceptual assessments, as measured using the GRBAS scale.^{3,140} However, before a measure can be confidently incorporated into clinical practice, it must be replicated in different populations to confirm its generalisability. The initial study validated the AVQI on a large sample of extremely preterm and term-born children, where the distribution of voice quality was not normal.¹⁴⁰ Nonetheless, the AVQI was found to accurately predict the presence and severity of dysphonia in this cohort. However, for appropriate external validity, the AVQI should be investigated in a larger sample of children with a more even distribution of normal and pathological voices.

The external validity of the AVQI in adult Dutch speakers has been established.¹⁶³ However, it is yet to be established in children in the English language. This study reports the external validity of the AVQI in paediatric voice by repeating the initial experiment in a different cohort of children, using the GRBAS as the reference standard.

11.3 Methods

The study design and methodology have been reported elsewhere and are unchanged (**Chapter 6**).¹³⁹ A summary is described below.

11.3.1 Participants

Very preterm participants were prospectively recruited to receive a voice assessment consisting of: the reference standard (GRBAS), the index test (AVQI) and a quality of life report (pVHI). Based on previous research into voice disorders in extremely preterm children, it was hypothesised that this cohort would present with voice quality ranging from normal to severely disordered.¹⁴⁰ Thus, this cohort represented a variety of normophonic and dysphonic voices. The AVQI is unbiased to medical status, and

cognitive and behavioural factors associated with preterm birth that may influence subjective evaluations of voice quality.

Assessments were conducted between October 2012 and June 2013. Participants born between 2001 and 2007 were included and so were aged between 4 and 12 years at the time of assessment. One participant was excluded from the current analysis because of interference in the voice sample precluding calculation of the AVQI. To overcome any self-selection bias, and for practical and financial reasons, 44 of the remaining 178 completed voice assessments were randomly selected for inclusion in this study.

This study was approved by the Princess Margaret Hospital Human Research Ethics Committee and the University of Western Australia Human Research Ethics Office. The trial was registered with the Australia and New Zealand Clinical Trials Registry (ACTRN12613001015730). All voice samples were collected under prior, written, informed consent from the parent or guardian caregiver.

11.3.2 Data collection and analysis

All voice samples were collected using the methodology described by Reynolds et al (Chapter 6).^{139,140} Voice samples were recorded on a Zoom H2 Handy Recorder via a Røde lavalier microphone. The microphone was headset-mounted and placed at a distance of three to four centimetres from the participant's mouth, at a 45° angle. The ambient noise level in the clinic environment was <50dB at all times. The GRBAS (Grade, Roughness, Breathiness, Aesthenia and Strain) scale was used as the reference standard as it is widely used in clinical voice evaluation and research. It is considered to be the minimum standard for perceptual evaluation of voice quality.¹⁶⁵ Samples were prepared and analysed in exact accordance with the procedure described by Maryn et al., using the Praat v5.3.56 (Paul Boersma & David Weenink, Institute of Phonetic Sciences, University of Amsterdam, The Netherlands) and SpeechTools (James Hillenbrand, Western Michigan University, Kalamazoo, MI) programmes to calculate each participant's AVQI score.² Praat was also used to calculate the signal to noise ratio (SNR) of the sustained vowel samples and the extracted, voiced segments of the connected speech sample, by comparing the intensity to that of a standard pause in the reading passage used to elicit the speech sample.

Each voice sample was rated online by the first author, for participant feedback and to mimic typical clinic conditions. The 44 randomly-selected voice samples were then rated independently by a second rater, with extensive postgraduate experience in the assessment and treatment of paediatric voice disorders and again by the first author in two joint rating sessions. An attempt to establish an external reference standard was made at the commencement of the joint rating sessions, by listening to two voice samples from the pilot study at each level of dysphonia severity, as measured by the G score, where severity had previously been agreed. Raters were required to listen to de-identified voice samples consisting of two prolonged vowels, the CAPE-V sentences, “The Bird” story from the Neale Analysis of Reading Ability and a conversation sample, through a desktop computer in a room with an ambient noise level of <50dB.

11.3.3 Statistical methods

Statistical analyses were conducted using SPSS for Windows v19 (SPSS Inc, Chicago IL). Continuous data were described by median, interquartile range and range and categorical data were described using frequency distributions.

For the purpose of the ROC analysis, voices were considered dysphonic if the mean G score was greater than 0.33, indicating that at least one rater considered the voice to be disordered. Data-driven techniques were used to determine the best AVQI cut-off score in this sample by calculating the point closest to (0, 1) on the curve. The methods used were minimising $([1 - \text{sensitivity}]^2 + [1 - \text{specificity}]^2)$, and maximising $[\text{sensitivity} + \text{specificity} - 1]$.

For the purpose of determining reliability of subjective ratings, the intra-class correlation co-efficient and weighted kappa were calculated using SPSS and VassarStats (Richard Lowry, PhD; Poughkeepsie, NY), respectively.

11.4 Results

11.4.1 Population characteristics

Classification according to G score demonstrated that 8 participants had normal voices (mean $G=0$) and 36 participants had dysphonic voices (mean $G \geq 0.33$). Participant demographics, classified according to dysphonic and normal speakers, can be seen in Table 11.1.

Table 11.1. Participant demographics

	Normal voices M (IQR, R)	Dysphonic voices M (IQR, R)
Age	10;3 (8;11 – 11;10, 6; 3 – 12; 1)	7;7 (6;4 – 9;9, 5;3 – 10;8)
Male	5 (62.5%)	20(55.6%)
AVQI score	2.74 (2.29 – 3.17, 2.23 – 3.55)	4.22 (3.27 – 5.28, 1.83 – 6.69)

11.4.2 Rater reliability

The average weighted kappa was 0.49 (95%CI 0.33 – 0.64), indicating moderate agreement beyond that expected by chance.²⁵¹ The average-measures ICC was .857 (95%CI .763 - .917) indicating good agreement among raters. This confirms that the mean-G was a reliable indicator of dysphonia severity in this cohort.

11.4.3 Agreement between GRBAS and AVQI methods of assessment

Agreement between the subjective and objective assessments in discriminating dysphonic voices was 81.1%. The kappa statistic was 0.572 (94%CI 0.23 - 0.82), indicating moderate agreement beyond that expected by chance. . The diagnostic agreement between AVQI scores and G scores can be seen in Table 11.2.

Table 11.2. Dysphonia severity and Acoustic Voice Quality Index score.

		GRBAS (Mean G)		Total
		Normal	Disordered	
AVQI score	Normal	7	7	14
	Disordered	1	29	30
Total		8	36	44

11.4.4 Concurrent validity

The relationship between the AVQI and the mean-G score was determined using Spearman's rank order correlation co-efficient. The correlation indicated a strong, positive linear relationship, confirming the concurrent validity of the AVQI ($r_s = 0.680$, $p < .001$). The relationship between mean-G score and AVQI scores can be seen in Figure 11.1.

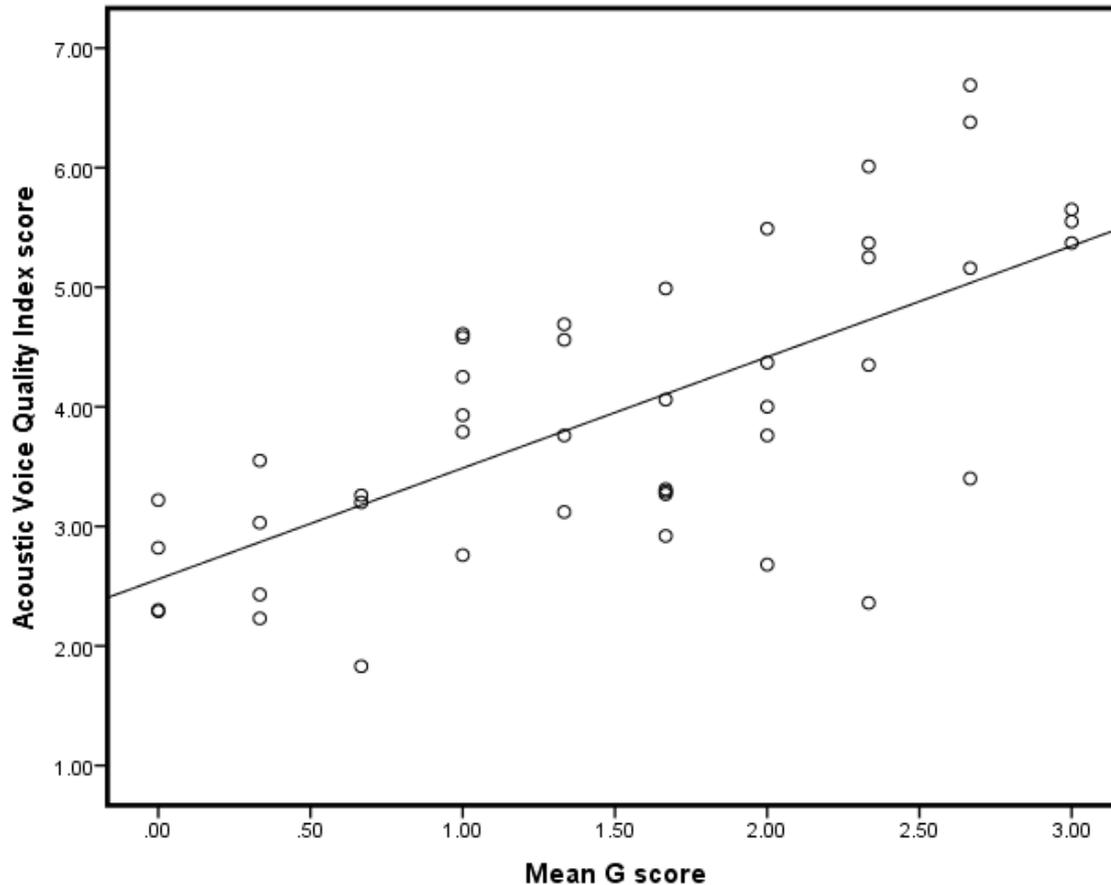


Figure 11.1. Scatterplot and linear regression line depicting the relationship between mean-G score and AVQI score.

11.4.5 Diagnostic precision – ROC curve analysis

The area under the receiver operator curve (AUC), using mean-G as the state variable, was 0.885 (95%CI 0.782 – 0.989, $p < .001$), indicating good discriminatory potential in detecting dysphonic voices. The ROC curve is illustrated in Figure 11.2. A cut-off score of 3.46, as recommended in the pilot study into the diagnostic utility of the AVQI in the paediatric population, was applied to the data and gave the following diagnostic results: sensitivity 87.5%, specificity 66.7%, with LR+2.62 and LR- 0.19.¹⁴⁰ Both data-driven techniques used to determine the ideal threshold for pathology identified the score of 3.24 as the best AVQI cut-off score in this cohort. The score gave the following diagnostic results: sensitivity 87.50%, specificity 80.56%, with LR+ 4.50 and LR- 0.16.

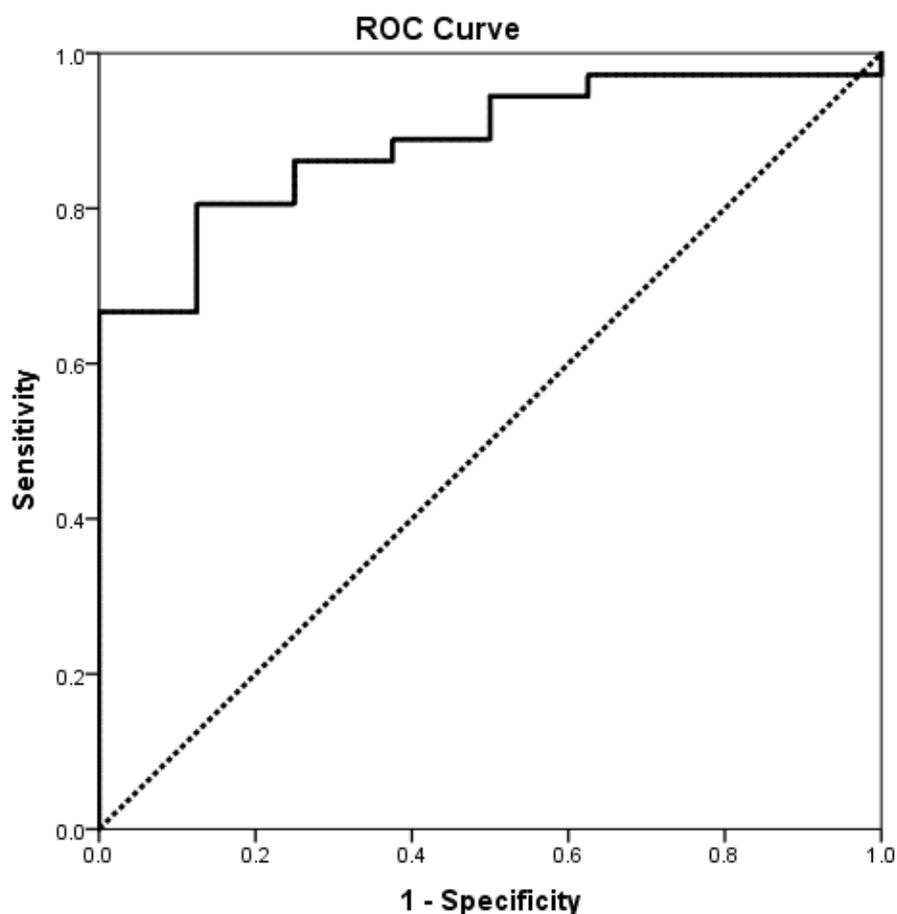


Figure 11.2. ROC graph illustrating the accuracy of the AVQI. The dotted line represents chance-level discrimination between normal and dysphonic voices.

11.5 Discussion

The results of this study confirm the generalisability, robustness and stability of the AVQI in the paediatric population. The AVQI is a measure with appropriate diagnostic accuracy in discriminating between normal and dysphonic voices in children.

As with previous studies, the correlation between mean-G score and AVQI score showed a positive linear relationship, whereby increases in AVQI score are associated with subjective increases in dysphonia severity. Thus, the concurrent validity of the AVQI in paediatric voice is retained in this cohort.

Consensus regarding the use of a three-pronged approach to assessment has been reached due to the requirement for both the perceptual evaluation of voice quality and analysis of the physical properties of the voice signal. An ideal test battery includes objective, subjective and quality-of-life measures. The AVQI is a suitable objective

measure, with excellent ecological validity due to its use of both connected speech and sustained vowel to determine dysphonia severity.

The threshold for pathology found in this study was 3.24, in comparison to 3.46 identified in our laboratory's previous study. The cut-off of 3.24 had appropriate sensitivity and specificity, with fair likelihood ratios. This study had a larger sample size from which voice samples were randomly selected, and a more equal distribution of children with varying degrees of dysphonia severity, which may account for the lower threshold for pathology identified in this population. Further, in an investigation of the AVQI's cross-linguistic robustness, Maryn et al. found AVQI thresholds of 3.29 and 3.25 in each of the English-language sentence stimuli, consistent with the threshold identified in this study.²⁵² Thus, it is recommended that 3.24 be adopted as the threshold for pathology in English-speaking children aged up to 13 years.

As with previous studies, there was disagreement between the diagnoses on the AVQI and the GRBAS. As yet, there is no objective measure with perfect correlation with subjective voice evaluation. Where disagreement exists, perceptual evaluation and child and caregiver perceptions of voice-related quality of life will provide further insight into the nature of any voice difficulty and inform intervention practices. However, the parameters of the AVQI have been shown to reflect underlying laryngeal function and properties of the vocal tract, so examination of these individually may identify any area of sub-optimal functioning.

11.5.1 Limitations

The present study represented part of a larger investigation into voice quality of very preterm children. Mild dysphonia is commonly found in children, affecting 30 to 40% of otherwise typically-developing children.^{21,23} The incidence of mild dysphonia in this cohort, at 37%, is consistent with these reports. Further, severe dysphonia is uncommon in children, yet was present in this cohort. Therefore, results of this study are applicable to the range of children seeking services at paediatric voice clinics.

Due to clinical considerations, the SNR of the voice samples was <30dB in the cohort. Thus, the voice samples do not represent experimental conditions, such as those in our laboratory's pilot study.¹⁴⁰ However, the testing conditions do represent typical, non-

soundproofed clinic settings. Thus, these results demonstrate that the AVQI suitably discriminates between children's normal and dysphonic voices in clinical conditions.

Having established that the AVQI retains its diagnostic utility in a differing cohort and in typical clinic conditions, attention must now turn to its suitability as an outcome measure. The AVQI has shown appropriate sensitivity to therapeutic change in adults; thus this property must be investigated in a paediatric population also.¹⁶³

11.6 Conclusion

The AVQI is an acoustic assessment of voice quality that has been found to have diagnostic sensitivity, specificity and external validity in paediatric voice. The collection procedure is simple and quick and the availability of automated calculation procedures facilitates the AVQI's utility in busy paediatric voice clinics. The AVQI could be incorporated into an assessment protocol evaluating childhood voice disorders, or screening at-risk groups of children.

Chapter 12

General Discussion

This thesis describes several studies that are the first in their field. Key findings are summarised in section 12.1; these findings are discussed in the context of the wider literature in section 12.2. Clinical practice guidelines are detailed in section 12.3 and recommendations for future research are discussed in section 12.4. Concluding remarks are presented in section 12.5.

12.1 Summary and general discussion of key findings

12.1.1 Phase I Prevalence Study

This study, investigating the prevalence of dysphonia in very preterm children, demonstrated that children born at up to and including 32 weeks gestation are at greater risk of developing childhood voice disorders than their term-born peers. Female sex, gestational age and duration of intubation were found to be associated with greater risk of voice disturbance at school age. However, children who were never intubated also presented with a higher prevalence of dysphonia than their term born counterparts.

Further, whilst intubation has been identified as a major risk factor in a number of studies – both large-scale and case study/series – these data suggest that other risks are present. The presence of dysphonia in females and non-intubated children suggests that sex- or gender-related issues, as well as the currently unknown issues related to prematurity, also influence voice quality.

In addition to traditional clinical assessment methodology, this study sought to replicate previous findings of the diagnostic utility of the Acoustic Voice Quality Index (AVQI) in a paediatric population. These data confirm that the AVQI has good potential to discriminate between normal and dysphonic voices in preterm children.

12.1.2 Phase II Laryngeal Examination

This study documented the laryngeal pathology of a subset of children from Phase I, born at up to and including 29 weeks gestation with significant voice difficulties. In this investigation, all children presented with structural laryngeal pathology underlying the disturbance to voice quality. The individual presentations were heterogeneous. Glottic incompetence was common among the cohort. Yet, wide variation in concomitant pathologies was observed, with some individuals presenting with multiple pathologies. Additionally, all participants presented with compensatory, maladaptive use of the vocal

mechanism, resulting in further disturbance to voice quality. Laryngeal pathology was also identified in a child who was never intubated, and the mechanisms by which such damage was sustained are currently unclear.

12.1.3 Phase III Randomised, Controlled Intervention Trial

This study is the first trial of behavioural voice therapy for consenting participants in Phase II - a population of children with known laryngeal pathology affecting voice production. The results were complex. The primary analysis of the intervention (n=7) and control (n=14) groups revealed that there was no effect of intervention on voice quality, but that a reduction in dysphonia severity following the period of no intervention in the control group. To increase statistical power of the trial, the control group underwent intervention. Analysis of the pooled pre- and post-intervention scores (n=21) revealed an overall group effect of the intervention protocol. However, the group mean masked individual variability and it was not possible to identify factors associated with, or barriers to, success of the intervention in individual participants. Approximately one-third of participants had a positive response to voice therapy. However, only two participants presented with a normal voice following intervention; although some participants achieved acceptable voice outcomes and others made functional improvements in their ability to initiate and sustain phonation.

12.2 Significance of the findings in the context of the wider literature

Previous studies have identified numerous risks for dysphonia in extremely preterm children, including female sex, frequency of intubation, birth at <27 weeks gestation, extremely low birth weight, bronchopulmonary dysplasia, emergency intubation procedure and surgical ligation of patent ductus arteriosus.^{111,128,129,131} Yet, these risk factors are not limited to extreme prematurity. This prevalence study (Phase I: Chapter 7) confirms that these risks were associated with poorer functional voice outcomes. A higher than expected prevalence of dysphonia was found in children who were not intubated. Whilst intubation is clearly a major influencing factor, other issues pertaining to neonatal care of the preterm infant, or preterm birth itself, may be associated with the voice difficulties observed in this cohort.

The effect of premature exposure of the vocal folds to air following preterm birth is unknown. It is hypothesised that this may dehydrate the vocal fold mucosa and alter its

vibratory properties, resulting in a rough quality of cries in infancy. In the first month of life, the lamina propria is monolayered and contains a high concentration of hyaluronic acid.³⁷ Differentiation commences in the second or third months of life, and continues until middle childhood. Gross damage to vocal fold mucosa resulting from laryngeal injury, has been reported in the literature and seen in this study (Phase II: Chapter 8).^{69,216} However, subtle damage may also influence long-term voice outcomes, as the differentiation process may be delayed, disrupted or altered.

Respiratory function and voice production are linked, as the production of voice occurs on exhaled air and requires a minimum respiratory capacity and level of control of the airflow through the glottis during speech. Preterm children, particularly those born very preterm prior to the commencement of surfactant production, are at risk of respiratory function difficulties.²⁵³ Decreased vital capacity may result in shorter breath units available for speech. It can be hypothesised that affected children may adopt tightening of the supraglottic musculature in an attempt to regulate airflow through the glottis, resulting in strained voice quality. The link between lung capacity and function and voice production in preterm children has yet to be explored, however.

One further factor that may influence voice production is inhaled corticosteroid use during childhood. Many preterm children are prescribed inhaled corticosteroids, due to the high rate of ongoing respiratory difficulties in this population. Inhaled corticosteroid use has been shown to induce dysphonia in healthy adults with no history of voice disturbance.²⁵⁴ The dysphonia was transient and resolved with cessation of corticosteroid use. However, the effect of long-term use in childhood on voice quality is unclear. It can be hypothesised that, in the preterm population which is already susceptible to voice problems, inhaled corticosteroids may have a significant impact on voice quality.

Damage to the larynx following neonatal intubation in preterm children has been reported in case study and series form. Post-mortem studies have identified significant changes to the gross and fine anatomy of the larynx in such cases.^{64,82} This study demonstrated that laryngeal damage is associated with dysphonia, and that neonatal intubation is not the sole cause of such damage. Case studies report of tightening of the supraglottic musculature during phonation in preterm children with structural laryngeal pathology.⁶⁹ This study is the first to report on the widespread nature of this

phenomenon, affecting the entire study cohort. The results may have implications for non-surgical management of dysphonia in preterm children, prior to completion of puberty.

Behavioural voice therapy has been shown to be effective in children with primary hyperfunctional voice disorders; that is, in children who adopt a posture of supraglottic tightening to initiate and sustain phonation, without underlying structural pathology.^{34,41,134,175,190,191,197,235,255} This study demonstrates that secondary hyperfunctional voicing behaviour in preterm children may be responsive to voice therapy in some cases, irrespective of either the presence or nature of the underlying structural laryngeal pathology.

The AVQI has been demonstrated to have diagnostic accuracy in adults in a number of European languages, and to have suitable sensitivity to change.^{2,163,250,252} Thus, it is suitable as both a diagnostic tool and therapy outcome measure in adults. These data confirm the suitability of the AVQI as an assessment of the presence and severity of dysphonia in children. Further, these data were collected under non-experimental acoustic conditions, characterised by a signal to noise ratio (SNR) of <30dB for the voice samples. Factors underlying the SNR included minor variations in background noise and low voice volume in many of children with dysphonia. These factors are common to the paediatric voice clinic. Thus, these data demonstrate that AVQI retains its diagnostic utility in paediatric dysphonia under clinical conditions.

12.2.1 Strengths and weaknesses of the overall trial.

This is the first trial to investigate the prevalence and severity of voice disorders in a large cohort of preterm children at school age. Assessment at school age, rather than in infancy or adulthood, is ideal as the demands on the vocal system reach their peak with academic requirements and social interactions outside the home environment of a child's early years. Thus, this prevalence reported in this study is likely to be a true representation of the extent of voice problems in this cohort. However, with 178 consenting from the families of 391 children approached, the response rate in this study was 45%. The number of preterm children identified with dysphonia was commensurate with that identified by the term-born reference group in this study. However, a self-selection bias in favour of individuals with concerns about vocal quality cannot be excluded and the prevalence may be overestimated.

Our longitudinal data indicates that voice problems are persistent in preterm children, although our observations are based on retrospective review of existing data in a small sample of children. To be more certain of the present results, a prospective, longitudinal study should be undertaken in a cohort of preterm children with dysphonia, to document the progression of the condition as children progress through adolescence. Our data has demonstrated wide individual variation, therefore, a large sample of children, from both sexes and with varying degrees of dysphonia severity should be included.

The issue of self-selection bias was also present in Phases II and III. A large number of participants eligible for Phase II declined further evaluation, stating that they did not wish to undergo the endoscopy due to its invasive nature. Of the 94 participants eligible, 27 underwent laryngeal examination giving a response rate of 28.7%. Therefore, while the results of Phase II represent the largest report of laryngeal pathology in preterm children in the literature to date, it is possible that the non-participating children may have presented with differing laryngeal pathology and the clinical relevance of this is unclear.

Phase III represented the first, randomised control of behavioural voice therapy in preterm children in the literature. The randomised allocation of participants to a control group in Phase III controlled for individual variation and facilitated comparison of treatment outcomes. Further, it is the only intervention trial in paediatric voice disorders, to our knowledge, to include children with dysphonia as a control group. Phase III demonstrated that behavioural voice therapy is effective for some preterm children, although the sample size was small. Future studies should aim to recruit larger numbers of children, and implement intervention targeted to particular laryngeal pathologies, which could be developed following identification of such pathologies on laryngeal examination.

Finally, the diagnostic utility of the AVQI in the paediatric voice clinic has been demonstrated, by its use under clinical conditions with a lower SNR than required for experimental evaluation. Whilst it was initially anticipated to use the pre- and post-intervention AVQI scores to determine the responsiveness to change of this measure in paediatrics, the SNR and small sample size of Phase III negated this analysis. This study confirms that this experimental voice outcome measure can be utilised in clinical

conditions. However, further research is needed to determine the utility of the AVQI as a therapy outcome measure in childhood dysphonia.

12.3 Guidelines for clinical practice arising from the findings

12.3.1 Clinical assessment

Due to the high prevalence of voice abnormalities noted within our and other studies, it is recommended that practitioners working with childhood voice disorders - including primary care physicians, speech pathologists and otorhinolaryngologists - routinely elicit information regarding prematurity in their initial evaluations and case history-taking. This will allow clinicians to consider the impact of a child's neonatal experience on their presenting voice complaint, and facilitate evaluation and management appropriate to the presentation.

Due to the diagnostic accuracy and efficiency of implementation of this measure found in our studies, it is recommended that the AVQI be used routinely as part of clinical assessment of voice quality in children seeking treatment for voice disturbance. This will provide an objective measure of the disturbance to the voice signal, to supplement auditory-perceptual evaluations of voice quality. The AVQI is freely available to clinicians, whereas the only other validated objective, index measure of dysphonia severity calculated on a prolonged vowel and a sample of continuous speech, the Cesptral Spectral Index of Dysphonia, is commercially available and not within the means of many clinics.⁵

12.3.2 Screening

Due to the high prevalence of dysphonia identified by our and other studies, it is recommended that neonatal follow-programs screen for voice difficulties routinely in very preterm children most at risk of ongoing dysphonia. This will ensure that individual children with voice difficulties are identified early and referred to otorhinolaryngologists and speech pathologists for management in a timely fashion. Further, a screening program for those most at risk would facilitate the development of a pathway of care for preterm children with long-term voice problems. Our data demonstrates that children born at ≤ 31 weeks gestation are at risk, with females, those born extremely preterm (< 28 weeks gestation) and those who were intubated for longer durations being most at risk. Given that extremely preterm children participate in

neonatal follow-up within Western Australia until the age of 5, a voice screen could be included in routine follow up appointments.

In order to determine the presence and severity of dysphonia in preterm children, it is recommended that the AVQI be used as a screening tool, together with a perceptual voice assessment rated by a trained listener and a quality of life questionnaire, to determine whether a preterm child should be referred to Otorhinolaryngology and Speech Pathology for further investigation and management of any voice difficulty. This will ensure that all relevant areas of voice disturbance – perceptual and acoustic – are evaluated, as is any potential impact on the activities of daily living. A clinical assessment consisting of these measures is estimated to take approximately 30 minutes and is thus feasible in terms of clinician time and child attention levels.

12.3.3 Referral

Due to the potential for persistence of voice problems in preterm children, it is recommended that those identified at risk of voice difficulties following screening are referred to speech pathology and otorhinolaryngology for joint management. This will allow thorough assessment of the structural and functional difficulties affecting voice production, and consideration of surgical and behavioural management, where appropriate. Currently, there is no routine referral pathway for preterm children in our catchment area. Individuals who demonstrate concern with their voices are referred to tertiary or community clinics for management, whereas this data supports the establishment of a model of care for preterm children with dysphonia.

Due to the high prevalence of voice problems identified in very preterm children, it is recognised that voice problems may only become apparent following discharge from follow-up services. It is recommended that primary care physicians be alert to the potential for voice problems in their very preterm patients and refer appropriately to otolaryngology and speech pathology services.

12.3.4 Routine laryngeal examination

International best practice guidelines recommend routine laryngeal examination in children with dysphonia. However, due to the high rate of refusal observed in our study (11%), it is recognised that some preterm children may present with anxiety associated with the invasive nature of the endoscopy procedure. Should a preterm child refuse

endoscopy, behavioural intervention may be trialled at the discretion of the managing otorhinolaryngologist, with endoscopy deferred until adolescence, or until consent is given. This course will facilitate management of the behavioural component of dysphonia until the physiological, structural laryngeal pathology can be investigated instrumentally with the potential for surgical management.

12.3.5 Intervention

The intervention trial demonstrated that improvements in dysphonia severity in some children were observed following a waiting period in some children and a trial of behavioural intervention in others. It is therefore recommended that behavioural intervention be routinely trialled, should voice impairment persist following a waiting period, in preterm children with dysphonia who present with concerns about their voice quality or associated limitations on their participation in daily activities. Further, where behavioural issues are identified as contributing to dysphonia severity, surgical intervention may be less successful. If maladaptive voicing behaviour is persistent, secondary pathology may develop, further disrupting voice quality. Therefore, individual responsiveness to intervention may also be diagnostically useful when considering candidacy for phonosurgery at a later stage in the maturation process (e.g., in adolescence).

As a corollary to the above, it is also recommended that very preterm children with dysphonia who undergo behavioural intervention receive follow-up Speech Pathology and Otorhinolaryngology consultation following intervention, to assess the requirement, and possible candidacy, for surgical intervention.

12.4 Recommendations for future research

Areas of future research identified from the prevalence study are the susceptibility of females and those children who were never intubated to dysphonia. It is essential to further investigate the greater incidence in females, as this is the second such finding in the literature. While preliminary data cautiously supports a link between puberty and improvement in voice quality in males, no improvement was observed in females. Further research with a larger sample size of children at various stages of puberty is required to determine the role of puberty in preterm dysphonia. Many of the participants in Phase I of this study will complete puberty within the next five to ten years. A

longitudinal follow-up of this cohort would provide a clear indication of the evolution of dysphonia in preterm children over the course of childhood.

Respiratory difficulties following preterm birth are well-documented. The power, source, filter model of voice requires adequate respiratory capacity to power voice production.^{8,14} It can be hypothesised that respiratory capacity may not be adequate in some preterm children, which may lead to difficulties with voice production such as decreased breath units for speech. Some children may adopt tightening of the laryngeal musculature, to regulate airflow through the glottis, in an attempt to conserve respiratory vital capacity during phonation. This may manifest as strained voice quality. Further, some preterm children in our study were identified with impairments to vocal fold movement. It can be hypothesised that reduced rate and range of movement of the vocal folds may impede airflow through the glottis, resulting in decreased respiratory function. Thus, any link between respiratory function and voice quality should be explored. An ideal trial would include instrumental evaluation of laryngeal and pulmonary structure (e.g., laryngeal endoscopy and chest CT to the level of the supraglottic region), perceptual and acoustic evaluation of voice quality, measures of respiratory capacity and function (e.g. spirometry), as well as exercise tolerance testing. This would facilitate comparison of the association between respiratory structure and function and vocal quality, as well as vocal fold movement on respiration.

The findings in children without a history of intubation require further investigation into the mechanisms underlying the disturbance in voice quality. More importantly, it is essential to identify whether the results of this study represent sampling effect or a more widespread risk for voice difficulties in preterm children than was previously known. Identification of preterm children who were never intubated is possible from hospital discharge records. An observational incidence study, with identical clinical assessment methodology to Phase I of this trial, would identify the nature and severity of any voice problems in such children. Abstraction of data from medical records in such children will be essential to determine whether there are any similarities in clinical presentation or hospital treatment, or both, that may be associated with voice problems.

Laryngeal examination in future studies is essential, to accurately identify and describe structural laryngeal pathology in preterm children. In particular, detailed description of laryngeal pathology in a greater number of children without a history of intubation

would identify whether premature birth interrupts development of the vocal mechanism or whether iatrogenic factors including the possible adverse effects of suction catheters and feeding tubes, in addition to intubation, may be responsible for laryngeal injury.

The responsiveness to therapeutic change of the AVQI in a paediatric population is currently unclear. Trialling its use as a pre- and post-intervention assessment measure would allow comparison of its qualities to a reference standard, and indicate whether it should be adopted as a therapy outcome measure. The availability of this measure to determine responsiveness to change will be useful in reporting outcomes of the management of paediatric voice disorders.

The nature and extent of any spontaneous recovery from neonatal laryngeal injury is unknown, as is whether normal childhood growth of the laryngeal mechanism was disrupted by the neonatal injury in this cohort. This observational study documented the status of the injury at school age, when maximal healing may be presumed to have occurred. However, recent work into laryngeal wound healing in has yielded evidence that scarring may be minimised.^{256,257} It is hypothesised that this may result in improved vocal function, yet it is unclear whether similar effects may be found in a paediatric population.

The inconsistent response of preterm voice problems to behavioural intervention warrants further investigation. At present, it is unclear which preterm children will experience improvements in voice quality following such treatment. Prospective evaluation of factors such as age, gender, motivation, participation and locus of control will assist in formulating future prognoses and individualisation of therapy activities to promote success in greater numbers of children.

12.5 Concluding remarks

This study confirms that very preterm children are at increased risk of dysphonia in comparison to their term-born counterparts. The risk factors identified by this study were female sex, gestational age and duration of intubation. Voice quality in very preterm children is influenced by a combination of structural laryngeal damage, sustained during neonatal intubation in most cases, and tightening of the supraglottic musculature during phonation. Some very preterm children had a favourable response to behavioural voice therapy.

Despite recent medical advances, preterm birth is a persistent phenomenon. At early gestational ages, intubation is inevitable in the care of many infants. The requirement to intubate may never be completely obviated, due to the timing of maturation of respiratory structures in utero. Therefore, it is essential to focus attention on early identification of preterm children with dysphonia and to initiate treatment appropriately, to mitigate the effects of their voice quality on their social, academic, and ultimately employment, participation.

In summary, this study confirms the susceptibility of very preterm children to long-term voice difficulties, documents the nature of the underlying anatomical and functional impairment and provides evidence that some cases may respond to behavioural voice therapy.

“All I have is a voice.” – W.H. Auden

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