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Contents

Weekly Volume 26 Number 12 March 28, 2020

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Basic Study

Case Control Study

Retrospective Cohort Study

Contents

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Volume 26 Number 12 March 28, 2020

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MINIREVIEWS

Oesophageal atresia: The growth gap

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Abstract

Poor growth is an under-recognised yet significant long-term sequelae of oesophageal atresia (OA) repair. Few studies have specifically explored the reasons for growth impairment in this complex cohort. The association between poor growth with younger age and fundoplication appears to have the strongest supportive evidence, highlighting the need for early involvement of a dietitian and speech pathologist, and consideration of optimal medical reflux management prior to referring for anti-reflux surgery. However, it remains difficult to reach conclusions regarding other factors which may negatively influence growth, due to conflicting findings, inconsistent definitions and lack of validated tool utilisation. While swallowing and feeding difficulties are particularly frequent in younger children, their relationship with growth remains unclear. It is possible that these morbidities impact on the diet of children with OA, but detailed analysis of dietary composition and quality, and its relationship with these complications and growth, has not yet been conducted. Another potential area of research in OA is the role of the microbiota in growth and nutrition. While the microbiota has been linked to growth impairment in other paediatric conditions, it is yet to be investigated in OA. Further research is needed to identify the most important contributory factors to poor growth, the role of the intestinal microbiota, and effective interventions to maximise growth and nutritional outcomes in this cohort.

Key words: Oesophageal atresia; Growth; Malnutrition; Feeding difficulty; Dysphagia; Microbiota

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Core tip: Poor growth is an under-recognised yet significant long-term consequence of oesophageal atresia repair. This review highlights that the association between poor growth with younger age and fundoplication in children with oesophageal atresia appears to have the strongest supportive evidence. However, it is difficult to determine the contribution of other factors to growth, such as dysphagia, feeding difficulties, diet, and the microbiota. Early intervention of a dietitian and speech pathologist is warranted, but further research is needed to identify the most important factors related to growth, and effective interventions to maximise the growth outcomes of these children.

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INTRODUCTION

Oesophageal atresia (OA) is a congenital anatomical malformation characterised by discontinuity of the oesophagus as a result of disruptions to foregut separation during embryological development[1,2]. It has a worldwide prevalence of 2.4 to 3.2 per 10000 live births[3-5]. In the majority of cases, there is a fistula between the trachea and oesophagus. Five types of OA have been identified, based on the presence and location of the tracheoesophageal fistula (TOF), including OA without TOF (Type A), OA with proximal TOF (Type B), OA with distal TOF (Type C), OA with proximal and distal TOF (Type D) and TOF without OA (Type E). Type C is most common, occurring in 86% of cases[1]. Associated anomalies and syndromes are present in over 50% of children[5-8].

OA is usually surgically corrected in the first few days of life, and survival rates currently exceed 90% due to advancements in surgical techniques and neonatal intensive care[9]. As a result, the focus has shifted from decreasing mortality to reducing morbidity and improving quality of life[6-8]. Negative sequelae of OA include gastrointestinal complications, such as gastroesophageal reflux disease (GORD), dysphagia, feeding difficulties and oesophageal strictures, respiratory issues such as pulmonary aspiration and respiratory infections, as well as poor growth and neurodevelopmental delays[10-12]. Furthermore, the contribution of altered gastrointestinal or respiratory microbiotas to nutritional status is an emerging area of research[13], which has not yet been studied in this cohort.

The objective of this review is to explore and evaluate the literature on the prevalence of and factors associated with growth impairment in children with OA, to facilitate targeted management of growth and nutritional issues, and the development of interventions to prevent its adverse physical and cognitive consequences.

PREVALENCE OF POOR GROWTH IN CHILDREN WITH OA

Assessing growth and nutrition in paediatric patients involves accurate anthropometric measurements including weight, length/height and weight-for-length/body mass index (BMI). These parameters are plotted on appropriate growth charts, and standard deviation (SD) scores, z scores or percentiles are calculated to determine a child's growth in relation to the reference norm. The World Health Organisation (WHO) has recommended the use of z or SD scores, as they describe growth status more precisely than percentiles[14].

In an international cross-sectional study of 928 children with OA recruited from European support groups, it was reported that children under 18 years had less than average height-for-age (HFA) and weight-for-age (WFA), with a median SD score of -0.41 and -0.63 respectively[15]. Although parent-reported anthropometric data may have compromised the accuracy of the results, poor growth has similarly been described in studies where height and weight were accurately assessed by study investigators at hospital appointments[16-18]. Beucher *et al*[16] retrospectively collected follow-up data from the medical records of 43 children with surgically repaired OA,

reporting a median BMI z score of -0.67. Likewise in 2017, a retrospective study of 75 children aged 0-18 years who were referred to a multidisciplinary OA clinic for follow-up, found a median BMI z score of -0.4[17].

In contrast, growth impairment based on mean weight-for-height (WFH) z scores was not observed in a French prospective follow-up study of 57 children with repaired OA, wherein the mean WFH z score was 0.24[19]. However, the study examined a predominantly older cohort with an age range of 9.5-18.5 years (mean 13.3 years), possibly explaining the better outcomes observed, as growth appears to improve with age. Additionally, only children with OA type C were included, a group observed to have better feeding outcomes and a lower rate of complications than other types of OA[20-22].

The literature has also reported a high prevalence of malnutrition, specifically undernutrition, in children with OA. The WHO defines stunting as HFA < -2SDs, wasting as WFH < -2SDs and underweight as WFA < -2SDs, with a cut-off of -2SDs implying that the baseline prevalence of malnutrition is 2.3%[23]. A 2017 longitudinal follow-up study of 126 children with repaired OA found that stunting was present in 5%-8% and wasting in 3%-12%, depending on age, suggesting that the prevalence of malnutrition in children with OA is higher than expected in the reference population[18]. Interestingly, the authors also investigated distance-to-target-height, where HFA was corrected for individual target height based on parental height measurements. Using this parameter, growth appeared more favourable than using HFA, with only 3%-5% having a distance to target height < -2SDs. Calculating target height is useful for distinguishing children who are growing according to their genetic height potential from those who are chronically malnourished. This confirms the importance of undertaking comprehensive nutritional assessments, including a variety of anthropometric measures, to assess a child's nutritional status in the clinical context.

A retrospective Australian study of 75 OA children similarly noted a relatively high prevalence of malnutrition, wherein 9% had HFA < -2SDs and 18% had WFA < -2SDs[17]. The authors included a "malnourished" category defined as weight-for-length/BMI < -2SDs, which was present in 9% of participants. It has been proposed that BMI-for-age is more effective than WFH in identifying acute malnutrition, as this takes into account the relationship between weight and height as it changes with a child's age[24,25].

While multiple other studies have reported on malnutrition, comparisons are made difficult by the non-uniform definitions of malnutrition in the literature. In addition to the definitions used in the studies above and in other studies[26-29], malnutrition has been defined as growth measurements below the 2.5th[30], 3rd[9,31] or 5th[6,32-34] percentile, or the exact criteria has not been specified[19].

Overall, it is clear that the OA cohort has poorer growth and a higher prevalence of malnutrition compared to the reference population norm. However, there is a need for the development of standardised definitions of poor growth and malnutrition in children with repaired OA, such that accurate prevalence estimates can be determined and comparisons between studies can be made.

FACTORS ASSOCIATED WITH POOR GROWTH IN CHILDREN WITH OA

Age

Table 1[15,17-19,26,28,35-37] summarises the studies which have specifically investigated factors associated with poor growth in OA. One such factor is a child's age. In retrospective and cross-sectional studies, growth in younger children has been described as significantly worse than older children[15,17,26,34]. Poorer growth in infancy and early childhood may be linked to a higher rate of hospitalisations, feeding difficulties, and complications, such as GORD and strictures[17,38].

Longitudinal studies have suggested that growth impairment declines in prevalence with age[27,32,34,38,39], and recent literature has indicated that this may resolve in a "catch-up" growth phenomenon[18,38]. Leibovitch *et al*[38] reported weight and height < 10th percentile in 43.5% and 41.3% of patients aged 0-2 years, compared to just 10% in those aged 16-21 years, with catch-up occurring at around 8 years. These findings are supported by a large prospective cohort study which reported that SD scores for WFA and HFA were below the population norm at infancy, before improving and normalising by 8 and 12 years respectively[18].

Conversely, Presse *et al*[40] and Okuyama *et al*[41] observed that their study population of adolescents and adults with OA were stunted and had a lower mean BMI than the reference population, proposing that normalisation of growth does not

Table 1 Factors associated with poor growth in children with oesophageal atresia

Ref.	Type of study	Population, setting	Growth measures	Significant findings
Andrassy *et al*[26], 1983	Cross-sectional	53 patients, age range 11 mo–31 yr	HFA, WFA, Triceps skin fold, Mid arm circumference SD scores	HFA SD score lower in children < 13 yr of age compared to > 13 yr[a]
Puntis *et al*[28], 1990	Cross-sectional	124 patients, age range 0.5-23 yr	HFA and WFH SD scores	Oesophagostomy group had significantly lower mean WFH[a] and HFA[b] SD score than primary anastomosis group
Legrand *et al*[19], 2012	Retrospective and cross-sectional	57 patients, age range 9.5-18.5 yr	BMI, WFA, HFA and WFH z scores	Lower WFH z score in children with history of GORD compared to those without a history of GORD[a]
Spoel *et al*[35], 2012	Prospective follow up	37 children, age range 6 mo–2 yr	HFA and WFH SD scores	Thoracoscopy group had HFA SD significantly lower than thoracotomy group[b]
				Thoracotomy group had WFH SD significantly lower than thoracoscopy group[b]
Menzies *et al*[17], 2017	Retrospective	75 children, age range 0-16.8 yr	WFA, HFA and weight-for-length/BMI z score	Infants (< 1 yr), those who had undergone fundoplication, were at risk of aspiration and had surgery in the first year of life in addition to OA repair had lower mean BMI z scores[a]
Vergouwe *et al*[18], 2017	Prospective follow-up	126 children, age range 0-12 yr	HFA, WFH and distance to target height SD scores	Results of multivariable linear mixed models showed: HFA SD scores negatively associated with low birthweight[b] and fundoplication[b]
				WFH SD scores negatively associated with low birthweight[a] and fundoplication[b] and positively associated with total number of surgeries[b] and history of pulmonary infections[a]
				Distance to target height SD scores negatively associated with low birthweight[b] and fundoplication[b]
Masuya *et al*[36], 2018	Retrospective	73 children, age range 6 yr 7 mo–24 yr)	HFA, WFA and BMI SD scores	HFA, WFA and BMI-for-age SD scores not associated with associated anomalies and late complications
Mawlana *et al*[37], 2018	Retrospective	57 patients, age range 9.5-18.5 yr	Weight, height, head circumference velocity percentile	45% of children with VACTERL had weight velocity < 10th centile compared to 13% of children without VACTERL[b]
Svoboda *et al*[15], 2018	Cross-sectional	928 patients, age range 1 mo-60 yr	WFA and HFA SD scores	Significantly lower mean score for HFA SD in children < 5 yr than > 5 yr (*P* value not reported)

[a]$P < 0.05$.
[b]$P < 0.01$. OA: Oesophageal atresia; HFA: Height-for-age; SD: Standard deviation; WFA: Weight-for-age; BMI: Body mass index; WFH: Weight-for-height; GORD: Gastro-oesophageal reflux disease; VACTERL: Vertebral anomalies, anal atresia, cardiac anomalies, tracheoesophageal fistula, renal anomalies and limb defects.

necessarily occur with increasing age. It is possible that these results reflect a selection bias, as symptomatic patients may have been more likely to be included due to referrals and ongoing follow-up. Future prospective longitudinal studies should seek to clarify the occurrence of catch-up growth.

Overall, it appears that poor growth is more common in the early years of life.

Intervention is important in these crucial years of development, as malnutrition can lead to later cognitive impairment, poor schooling achievements and increased risk of chronic diseases[42]. Indeed, a recent study demonstrated that at 12 months of age, acutely malnourished children with OA (WFA < 5th percentile) had poorer cognitive development than those who were well-nourished[33], which reinforces the need for early intervention.

Neonatal factors

Low birthweight in children with OA was significantly associated with future poor growth in two large studies[6,18]. In a study investigating the neurodevelopmental outcomes of infants with OA, the associated syndrome VACTERL (vertebral anomalies, anal atresia, cardiac anomalies, tracheoesophageal fistula, renal anomalies and limb defects) was present in 52.9%. Of these children, 45% had weight growth velocity < 10th centile compared to 13% without VACTERL (P < 0.001)[37]. While not tested for statistical significance, it has been noted that a higher proportion of long-gap OA patients had WFA < 3rd percentile compared to patients without a long gap[9]. Low birthweight, VACTERL and long-gap OA are predictors of a complicated clinical course[22,43], which may contribute to growth impairment. However, the relationship between these factors and growth is uncertain, as contradictory results have been obtained. This is likely related to the difference in each study's definition of growth impairment[17,19,26,36]. While further studies using consistent parameters are required to clarify the contribution of these factors to poor growth, it would be worthwhile to longitudinally monitor the growth outcomes of these more complex children.

Surgical factors

Repair of long-gap OA can be achieved through delayed primary anastomosis or oesophageal replacement, often involving formation of a gastrostomy and/or cervical oesophagostomy. To our knowledge, the study by Puntis *et al*[28] was the only one to compare the growth outcomes of children who underwent primary anastomosis with those who had an oesophagostomy. The oesophagostomy group were more likely to be both stunted and wasted, a likely result of prolonged hospitalisation and complications associated with long-gap OA. It would be useful to re-examine these findings in light of new surgical developments in long-gap repair over the last three decades[44], such as the oesophageal growth augmentation technique of Foker[45]. The repair approach has also been associated with growth. Spoel *et al*[35] evaluated the growth and respiratory morbidity of children with OA at 6, 12 and 24 months of age. Interestingly, HFA SD scores were significantly lower in patients with thoracoscopic repair, while WFH SD scores were significantly lower in patients with thoracotomy repair at all timepoints. There were no other differences between the groups in terms of perinatal characteristics or lung function. These results seem to reflect the lack of consensus in the literature regarding the optimal repair approach[46]. The small sample size (n = 14-21 depending on time point) further limits the statistical power of these findings, necessitating larger multi-centre studies to establish the short and long term growth outcomes of these surgical options.

GORD and fundoplication

GORD is a common complication of OA repair, caused by oesophageal dysmotility, oesophageal shortening at the anastomosis, and hiatal hernia, which causes an upward displacement of the gastroesophageal junction[2,47]. A recent meta-analysis found a pooled prevalence of 40.2%[10].

In a 2002 retrospective study with a sample size of 371 patients, a history of GORD was associated with HFA and WFA < 5th percentile[6]. Similarly, despite having a smaller sample size of 81 patients, the study by Legrand *et al*[19] reported that GORD was associated with lower z scores for WFH. GORD may not only result in loss of calories due to vomiting, but can also cause a fear of eating due to pain from reflux[48]. Feeding may also be compromised by reflux-related complications, such as anastomotic stenosis, respiratory disease due to aspiration, and oesophagitis resulting in heartburn and pain[49].

However, the association between growth and GORD is disputed by two recent studies which did not observe a significant relationship[17,18]. This may be due to inconsistencies in the definition of GORD between studies, where each used a different combination of symptom reports, 24hr pH-metry, pH impedance monitoring and upper gastrointestinal endoscopy. Interestingly, studies by Menzies *et al*[17] and Vergouwe *et al*[18] both observed a significant association between fundoplication and poor growth outcomes. This may suggest that it is the complications following fundoplication, such as worsening dysphagia, which may adversely affect nutrition, rather than GORD itself. It has been established that children with OA are more likely to suffer dysphagia post-fundoplication, as fundoplication worsens oesophageal stasis

by increasing resistance to gravity-driven oesophageal clearance in patients with oesophageal dysmotility[50]. The decision to proceed to fundoplication in OA patients therefore needs to made with caution only after optimised medical therapy for GORD has failed.

Respiratory complications

Menzies *et al*[17] observed that children with OA at risk of aspiration were more likely to have lower mean BMI z scores, potentially because aspiration (both direct and reflux-related) contributes to feeding difficulties and respiratory infections[11]. While an association between respiratory infections and growth was not identified, a longitudinal follow-up study surprisingly reported that a history of lower respiratory tract infections and number of surgeries were associated with higher WFH SD scores[18]. The authors speculated that these children were more likely to be exposed to dietary interventions as a result of frequent hospitalisations, suggesting the importance of multidisciplinary care of children with OA.

Dysphagia

Dysphagia refers to difficulty swallowing, often caused by anastomotic strictures and dysmotility, and involving the oral, pharyngeal and/or oesophageal phases of swallowing[51]. There is a wide variability in the reported prevalence of dysphagia in children with OA, ranging between 50%-70% in recent studies[21,51,52]. This can be explained by its non-uniform definition, the differing evaluation methods and the multiple age ranges studied. Commonly, assessment is based on parent- or self-reported symptoms[21,34,53]. In a retrospective chart review of OA patients aged 3-20 years, Cartabuke *et al*[21] assessed symptoms of dysphagia and reported that 72% of patients had dysphagia to solids and 44% to liquids.

Objective dysphagia scales have rarely been used for a more accurate assessment of prevalence and severity[51,54,55]. While no scales have been validated in children with repaired OA, the Dakkak dysphagia symptom scoring system[54,56] has shown a prevalence of 50% in children with OA aged 2 months–10 years, and the Functional Oral Intake Scale[51] has shown a steady decrease in the prevalence of dysphagia, from 61% in children < 1 year to 5% in children aged 12-18 years.

Dysphagia leads to the development of adaptive feeding behaviours in children with OA, such as drinking excessive amounts of fluid to facilitate swallowing, using fingers to "milk" food down, eating slowly, and avoiding textures that are difficult to swallow[17,27,28,38,57]. In two prospective studies conducted 10 years apart, questionnaires about feeding difficulties were completed by over 120 parents of a support group[28,57]. Despite a differing median age of 4.3 and 14 years respectively, patients in both studies avoided tough/bulky foods, commonly meat (37%; 16%), fruits (23%; 9%), and vegetables (12%; 17%), in order to prevent dysphagia and impaction. Other reasons proposed for texture avoidance include chewing disorders and parental concern about feeding skills[17,58].

The high prevalence of these dysphagia-related feeding problems raises concerns that children with OA may have deficiencies in overall energy intake and consumption of macro- and micro-nutrients, which consquently impairs growth[11,17,59]. To date, the literature has not explored the energy and nutrient intake of children with OA, thus future research in this area is warranted.

Dysphagia did not significantly correlate with growth in children with repaired OA in two studies[17,19]. However, this result may reflect the limitations of subjective symptom assessments in identifying the presence and severity of dysphagia. A recent cross-sectional Canadian study of 40 adult OA patients found that underweight patients more often reported severe difficulties swallowing dry solid foods compared to patients who were not underweight (50% *vs* 14.3%, $P = 0.045$), suggesting a possible relationship between dysphagia and nutritional status[40]. In fact, despite limited evidence, experts from the ESPGHAN-NASPGHAN Guidelines committee recommend that dysphagia be suspected in all OA patients who present with signs of malnutrition[60]. This highlights the need for further exploration of the relationship between dysphagia and undernutrition in children, as a more aggressive approach to identifying and managing the cause of dysphagia may be required in children who present with poor nutritional status.

Feeding difficulties

Studies have consistently found a high prevalence of feeding difficulties in OA, with a wide range of feeding issues identified (Table 2)[15,17,27,28,30,38,54,57,61-63]. These have been attributed to underlying dysphagia, aspiration, GORD, anastomotic strictures, oesophageal dysmotility, respiratory complications and behavioural disorders[11,48,60].

To our knowledge, the study by Baird *et al*[20] was the first to use a validated questionnaire to assess feeding problems in the OA cohort. Using the Montreal

Table 2 Feeding difficulties in children with oesophageal atresia

Feeding difficulty	Ref.
Challenging mealtime behaviour	[17]
Delayed introduction of solids	[28]
Selective eating	[15,17]
Food refusal	[28,30,38,61]
Slow eating/lengthy mealtimes	[17,28,38,61,62]
Regurgitation of food	[58]
Food impaction	[27,30,54,62,63]
Coughing/choking during meals	[28,30,34,54,61]
Vomiting during meals	[28,57,61]
Texture avoidance	[17,57]

Children's Hospital Feeding Scale, the authors reported that 17.5% of children with OA aged between 6 months-6 years were 1SD above the mean and 6.7% were > 2SDs above the mean for feeding difficulty score, suggesting a high prevalence of feeding issues.

The frequency and severity of feeding difficulties has been noted to decrease with age[17,27,28,34]. A recent study reported that 72% of children aged 0-2 years were not eating age-appropriate textures, compared to 30% of children > 5 years[17]. Gastrostomy tube feeds are frequently required in the neonatal period, or in early life if aversive feeding behaviours are present[37,48,64]. Tube feeding can delay the development of oral-motor skills, leading to later feeding difficulties[64,65].

To date, only two studies have investigated the direct relationship between feeding difficulties and growth in children with OA[17,28]. Puntis and colleagues[28] did not find a correlation between feeding scores calculated by a non-validated questionnaire, and HFA and WFA SD scores based on parent-reported growth measures. The lack of observed relationship between feeding and growth may be a result of non-validated questionnaire utilisation and inaccurate growth measurements. Almost three decades later, Menzies *et al*[17] similarly observed no association between specific feeding difficulties (lengthy mealtimes, not accepting appropriate textures, extreme food selectivity and challenging meal times) and accurate weight-for-length/BMI z scores. However, this may reflect the retrospective identification of feeding difficulties and lack of grading of severity. It would be worthwhile to validate feeding questionnaires in this cohort, to allow accurate identification of the presence and severity of feeding difficulties and their relationship with growth.

While it is evident that feeding problems, which are often caused by dysphagia, are frequent following operative repair of OA, no relationship has yet been identified between dysphagia or feeding difficulties with poor growth. This is likely to be due to the limitations of measurement tools. Nevertheless, the higher prevalence of these issues in the early years of life necessitates early involvement of a dietitian and speech pathologist in the care of children with OA.

INTESTINAL MICROBIOTA

Another possible reason for poor growth is impaired metabolism or absorption, resulting from an altered intestinal microbiota[66,67]. The microbiota refers to the complex and dynamic micro-organisms that inhabit the human gastrointestinal tract[68]. Unfortunately, research in this area is lacking in OA. The most recent study to investigate the intestinal microbiota in OA was published over 3 decades ago. Bayston *et al*[66] cultured faecal samples from 24 neonates with OA for their first 3 weeks of life, observing delayed intestinal colonisation, a dominance of the skin microbe *Staphylococcus Epidermidis* and lower abundance of *Bacteroides, Bifidobacteria* and *Escherichia coli* compared to healthy neonates. The authors proposed that the discontinuity in the oesophagus prevented organisms normally acquired *in utero* or during parturition from colonising the infant's gut. This resulted in an imbalance in the gut microbial community, which is commonly known as "dysbiosis"[68]. Other factors which may contribute to dysbiosis in childhood include frequent antibiotic use for respiratory infections, the early and prologed use of high-dose proton pump inhibitors for GORD, and dietary composition, all of which are relevant to OA[69,70]. The emerging link between intestinal dysbiosis and childhood malnutrition[67], as well

as several metabolic, inflammatory and immune diseases[71], raises the possibility that intestinal dysbiosis in children with OA is influencing their nutritional status and overall health.

Though the study by Bayston *et al*[66] was innovative and fundamental in establishing the significance of the microbiota, it remains a small study, limited to neonates and it used outdated techniques for microbial identification, which did not allow a complete exploration of microbial richness and diversity. The development of culture-independent high-throughput sequencing, such as 16s rRNA sequencing, has greatly expanded knowledge about the composition of intestinal microbial communities[72]. Analysis of faecal samples using this technique may offer novel insights into the intestinal microbiota of children with OA, and its relationship with nutrition and growth.

CONCLUSION

Overall, poor growth is a relatively common sequelae of OA repair, particularly in early life. The association between poor growth with younger age and fundoplication appears to have the most supportive evidence. However, insufficient evidence exists to reach conclusions about other factors which may negatively influence growth, due to the limited exploration of these factors in the literature, conflicting findings, inconsistent definitions and lack of validated tool utilisation. While swallowing and feeding difficulties are particularly frequent in younger children, their relationship with growth remains unclear. The microbiota is another unexplored area. Future high-quality research is required to confirm the contribution of the above factors to growth impairment, in order to implement appropriate interventions which optimise growth and developmental outcomes of children with repaired OA.

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