Respiratory Follow-up in a Cohort of Children with Congenital Malformations Affecting Lung Development: A Cohort Study

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Abstract: *Background;* Congenital malformations like oesophageal atresia (OA) and tracheo-esophageal fistula (TOF), congenital pulmonary airway malformations (CPAMs), congenital diaphragmatic hernia (CDH) and vascular rings (VRs) can influence lung development and respiratory function with significant impact on individuals, families, and health care system. This observational study outlines our multidisciplinary approach and respiratory follow-up for children with these congenital malformations.

Methods; We collected clinical data of children followed at the Pediatric Respiratory Unit of Parma University Hospital (Italy) between January 2015 and May 2023.

Results; Thirty-five patients have been included. The most common anomalies were AE (n = 12) and CHD (n = 9), followed by CPAMs (n = 9) and VRs (n = 5). In 50% of patients, the diagnosis was made through prenatal ultrasound, particularly in almost all patients with CPAMs (88.8%) and CDH (77.7%), contrary to OE, diagnosed postnatally in the majority of patients (83%). Children underwent their first respiratory visit at an average age of 2.5 years, follow-up was conducted on average every 6 months. More than half of patients (54%) was hospitalized for lower respiratory tract infections, particularly those with OA and those aged <3 years. Eight out of the 16 children capable of performing spirometry showed abnormalities in lung function.

Conclusions; Children with congenital malformations are at risk of short and long-term respiratory complications. A personalized follow-up with close collaboration between pediatric pulmonologist, surgeon, neonatologist, physiotherapist is essential to optimize their management and improve their respiratory function.

Keywords: Congenital malformation, Lung, Children, Respiratory infection, Lung development, Follow-up, Multidisciplinary, Oesophageal atresia, CPAM.

INTRODUCTION

Congenital malformations are structural defects present at the time of birth.

They affect about 3% of newborns and can contribute to long-term disability with significant impact on individuals, families and health care systems. Malformations like oesophageal atresia (OA) and tracheoesophageal fistula (TOF), congenital diaphragmatic hernia (CDH), congenital pulmonary airway malformations (CPAMs) and vascular rings (VRs) can influence lung development and respiratory function, leading to considerable morbidity during infancy and childhood [1].

OA is one of the most common malformations with a prevalence of 2.4 to 3.2 per 10.000 live births [2, 3]. It is characterized by discontinuity of the esophagus due to disruptions in foregut separation during embryological development [4]. There are five types of OA depending on the presence and location of TOF [5, 6]: type A (OA without TOF), type B (OA with proximal TOF) type C (OA with distal TOF), type D (OA with both proximal and distal TOF), type E (TOF without OA). Type C OA accounts for more than 80% of cases [5, 6]. Associated syndromes and other anomalies are present in more than 50% of patients [7-10].

CDH is a congenital defect of the diaphragm that leads to the protrusion of abdominal organs into the chest cavity, resulting in varying degrees of abnormal lung development and pulmonary underdevelopment. Typically, a left posterolateral hernia is observed [11]. It occurs in approximately 1 in 3.000 live births [11, 12]. Despite advancements in survival rates due to enhanced diagnostic techniques and improved medical and surgical care, the average mortality rate worldwide remains around 50% [13]. This is largely attributed to factors such as pulmonary hypoplasia, pulmonary hypertension, and heart failure [14, 15].

CPAMs are the most frequent congenital lung lesions with a prevalence between 1 out of 10,000 and 1 out of 35,000 births [16]. CPAMs are characterized by the presence of hamartomatous or dysplastic tissue within otherwise normal lung parenchyma [17]. Based

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on clinical and histological features, five distinct types of CPAMs, (from 0 up to 4) can be described [18]. Type 1 CPAM is the most prevalent form, accounting for 60-65% of cases, and typically is associated with a favorable outcome from the histological point of view, type 1 CPAM is characterized by the presence of single or multiple cysts ranging from 2 to 10 cm in diameter, originating from either distal bronchi or proximal bronchioles [19, 20].

VRs are congenital great arteries anomalies which lead to compression of the trachea and/or esophagus [21]. VRs are rare with an incidence of 2-10/10,000; the most common VR is double aortic arch [22]. Noisy breathing, barking cough, and dysphagia are the typical symptoms [23].

All these congenital malformations are considered both diagnostic and therapeutic challenges since fetal stage, as prenatal detection is not always straightforward. Some patients may necessitate corrective surgery within the first days or months of life and long-term follow-up with multiple specialists. Here we reviewed the series of patients born with congenital malformations and influencing lung development followed in our respiratory clinic.

METHODS

This study is a retrospective analysis of children diagnosed with TOF, CDH, CPAMs and VRs and followed in the Pediatric Respiratory Clinic of Parma University Hospital (Italy) between January 2015 and May 2024. From medical records we collected age at diagnosis, gender, surgical interventions, number of hospital admissions, antibiotic courses for respiratory exacerbations, pharmacological treatment, frequency of follow-up visits, and, when available, lung function test results. Parents provided their written informed consent for participation in the study and data publication.

Table 1: Characteristics of the Cohort

Malformation	n (%)	Prenatal diagnosis	n patients treated with surgery (%)	Age at first follow-up (years)	Age at last follow-up (years)	n patients able to perform spirometry (%) and results
Oesophageal atresia (OA)	12 (32.4%)	2	12 (100%)	4.2 (0.2-13.6)	7.9 (3.6-17.9)	7 (58.3%) normal: 4 (57.1%) restrictive: 1 (14.3%) obstructive: 2 (28.5 %) flattening of the expiratory curve: 1 (14.3%)
Congenital pulmonary airway malformations (CPAMs) • n 3 type 2 CPAM • n 1 type 1 CPAM • n 1 type 3 CPAM • n 1 sequestration • n 1 histological result not available	9 (24.3%)	8 (88.8%)	7 (77.7%)	0.8 (0.04-2)	6.2 (1.1-16.2)	3 (33.3%) normal: 1 (33.3%) obstructive: 2 (66.6%)
Congenital diaphragmatic hernia (CDH)	9 (24.3%)	6 (66.6%)	8 (88.8%)	4.0 (0.1-14.5)	7.2 (0.1-8.1)	3 (33.3%) normal: 1 (33.3%) mixed: 2 (66.6%)
Vascular malformations • double aortic arch • right aortic arch with mirror image branching • unilateral pulmonary artery agenesis • lusorial subclavian artery	5 (13.5%)	1 (20%)	1 (20%)	2.1 (1.2-3.6)	5.5 (3.0-8.2)	2 (40%) normal: 1 (50%) expiratory plateau: 1 (50%)

RESULTS

Thirty-five patients with congenital malformations affecting lung development were identified. The demographic characteristics are described in Table **1**.

Oesophageal Atresia (OA)

Twelve children (7 males) were followed-up in our outpatient clinic for type-C OA. All patients underwent corrective surgery by thoracotomy within the 5th day of life: most of them underwent primary repair by esophageal anastomosis and closure of the TOF; only one neonate underwent a two-step surgical approach due to a long-gap OA. Post-surgical complications were: anastomotic stricture (n=3), leakage of the anastomosis (n=2), ectasia of the oesophageal tract (n=1), pneumonia (n=2), leakage of the anastomosis (n=2) and recurrence of the fistula (n=1). Tracheomalacia was then found in six patients through fiber optic endoscopic examination because of “dying spells” acute episodes with oxygen desaturation (n=3), reduced exercise tolerance (n=1), barking cough (n=2), and respiratory distress (n=1). Regardless of the finding of tracheomalacia, patients with OA reported poor growth (n=2), gastroesophageal reflux (n=2) and dysphagia (n=2); one patient required Nissen fundoplication surgery. Moreover, almost all patients had a history of recurrent respiratory infections. The mean number of respiratory infections treated by antibiotic courses was 3.3 per year. Ten out of twelve patients were admitted to the hospital for pneumonia at least once (75% in the first 4 years of life) and 50% of patients showed 3 or more episodes of pneumonia in their lifetime. The mean number of hospitalizations was 2,2 per year, two patients (16%) required more than one admission in the intensive care unit (ICU) for severe respiratory distress. Five children (41.6%) showed preschool wheezing and two were diagnosed with bronchial asthma.): Children with wheezing were treated with short-acting beta-2 agonists (SABA) as needed and daily inhaled corticosteroids (ICS) and/or leukotriene receptor antagonists. Children with more persistent symptoms or asthma were treated with daily ICS/long-acting beta-2 agonist (LABA). Most of the patients (66.6%) regularly performed respiratory physiotherapy with positive expiratory pressure (PEP)-mask. Two children eventually required corrective surgery of tracheomalacia due to recurrent respiratory infections. Patients with OA were seen for the first time at a mean age of 4 years (standard deviation [SD] 4.66) and followed on average every 6 months.

Congenital Pulmonary Airway Malformations (CPAMs)

Among the 9 patients (5 males) with CPAMs, 8 had congenital cystic adenomatoid malformation (CCAMs) and one patient has left pulmonary sequestration. Thirty-three per cent of patients experienced respiratory distress at birth, including one girl born extremely preterm at 26 + 6 weeks of gestational age. Infants with a known prenatal diagnosis underwent chest X-rays on their first day of life to confirm the condition, while the patient without prenatal diagnosis received chest X-rays due to respiratory distress. To obtain a more detailed anatomical assessment of the pulmonary defect, 7 patients underwent chest high-resolution computed tomography (HRCT). Seven children (77.7%) underwent surgery at a median age of 15.4 months (0.3-22 months). The surgical procedures were performed using either video-assisted thoracoscopic (VATS) approach (in 4 cases) or thoracotomic approach; 6 underwent atypical lung resection and one lobectomy. Post-surgical complications included pleural effusion with subcutaneous emphysema in two cases, and residual diaphragm elevation in one case. Among the operated children, 3 had preschool wheezing and were given long-term maintenance treatment with ICS; only one required hospitalization.

The non-operated patient (M, 16 years) had on average two respiratory infections per year and CT scan revealed fibrotic septa and multiple bronchiectasis with decrease in the volume of the right lung.

Follow-up examinations started at one-month intervals post-birth for patients who received prenatal diagnosis in our hospital (n=5), while started between 12 and 24 months of age for the other patients (n=4). Follow-up visits were scheduled every six months. A total of six patients received palivizumab during the first year of life. Pulmonary function tests (PFTs) were available for only 3 children since most were too young to perform spirometry. In the patient with untreated bilateral CPAMs, PFTs performed at the age of 14 years showed a mixed ventilatory defect with obstruction and restriction (FEV_1 36%, FVC 64%, FEV_1/FVC 54%, FEV_{25-75} 17%).

Congenital Diaphragmatic Hernia (CDH)

The 9 patients (7 males) with CDH showed a postero-lateral defect (through the foramen of Bochdalek). Seven patients (77.7%) received prenatal

diagnosis and underwent surgical correction within 48 hours since birth. One patient developed recurrence around one month after the initial surgery, necessitating further corrective intervention along with intestinal resection. In one child, CDH was diagnosed at 20 months of age following a chest X-ray performed for recurrent respiratory infections and poor growth. Postoperative respiratory follow-up was initiated and maintained at 6-12 months intervals for the majority of patients.. Four patients were hospitalized: two children, aged 8 and 14 years, for asthma exacerbation, and two preschool-aged children for pneumonia. On average, patients with CDH required 0,4 (±0.74) courses of antibiotics per year. Three children were able to perform spirometry: two exhibited a mixed obstructive-restrictive respiratory pattern (FEV_1 64.65%±4.73, FVC 61.15±5.4, FEV_1/FVC 89.23±1.49, FEF_{25-75} 57.85%±7.28), and one an obstructive pattern with a positive bronchodilator test. Two patients have started continuous treatment with ICS/LABA and leukotriene receptor antagonist. Palivizumab has been administered to five patients.

Vascular Malformations

Of our 5 patients (3 males) with vascular malformations followed at our centre, 2 had a right aortic arch, 1 a double aortic arch, 1 a lusorial subclavian artery and 1 an unilateral pulmonary artery agenesis. In the first patient with right aortic arch, the diagnosis was made during the prenatal period and confirmed at birth with a cardiac echo-doppler; in the other patient, recurrent wheezing, stridor and poor weight gain, lead to a chest CT-angiography and barium-X-rays of upper gastrointestinal tract at the age of 3 years. The findings were right aortic arch with mirror image branching and left arterial ligament with posterior esophageal impression. The patient underwent corrective surgery with complete resolution of the respiratory symptoms.

In the other 3 patients, the diagnosis was made after birth by chest CT-angiography at the age of 4 months (unilateral pulmonary artery agenesis), 1 year (lusorial subclavian artery) and 4 years (double aortic arch) following examinations for recurrent wheezing. Only two patients were old enough to perform spirometry: one patient (unilateral pulmonary artery agenesis) showed a restrictive pattern (FEV_1 54%, FVC 59%, FEV_1/FVC 82.74) and the other one with right aortic arch showed a normal pattern with expiratory plateau. These patients continue the respiratory follow-up every 6 months.

DISCUSSION

Congenital malformations of the thorax can affect the development of the respiratory system and its function. The most commonly observed abnormalities were OA type III (n=12), CDH (n=9) and CPAMs (n=9).

Prenatal Diagnosis

Almost half of our patients (44.4%) received prenatal diagnosis of the malformation by morphologic ultrasound. Prenatal diagnosis is often possible for CPAMs (88.8% of our cases) as demonstrated by a 2017 meta-analysis in which more than 85% of patients were diagnosed with CPAMs by ultrasound performed between 21 and 24 weeks of gestation [24]. In contrast, prenatal diagnosis of OA remains difficult and only 50% of cases are identified prenatally. Hydramnios and/or absence or lack of stomach are the two most frequent ultrasound warning signs, but they are not specific [25]. Therefore, the majority of OA cases are diagnosed after birth when clinical signs such as spitting, sialorrhea, choking, and the inability to pass a feeding or suction catheter through the mouth or nose into the stomach are observed [26]. Vascular malformations, particularly VRs, can also be very difficult to diagnose prenatally with an incidence of prenatal diagnosis of 1 in 1000 patients [27]. Fetal echocardiography can diagnose VRs but only fetuses with high-risk factors undergo a specific fetal echocardiography able to detect VRs. Most fetuses receive only a basic cardiac examination and the success of detection relies on the operator's experience and knowledge of the condition [28]. Prenatal diagnosis could lead to timely treatment, thereby reducing ongoing compression from vascular structures and minimizing the impact of secondary tracheobronchomalacia [29]. In our experience, only 1 in 5 children had a prenatal diagnosis of right-posterior aortic arch while in all other cases, the diagnosis was made postnatally using chest CT- angiography and bronchoscopy and following recurrent respiratory symptoms.

Respiratory Morbidity

Our cohort of patients had an average of 4.9 lower respiratory tract infections in their lifetime and 59% was hospitalized for respiratory exacerbation at least once. Children with the highest respiratory morbidity were those with OA with a mean of 3.4 courses of antibiotic therapy per year, greater severity of the episodes and more frequent hospitalizations. Residual tracheomalacia is the most frequently described alteration in this group of patients, with an incidence of 80% [30, 31]. Tracheomalacia is secondary to the abnormal development of the tracheal wall at the origin

of the TOF; it is associated with impaired mucociliary clearance in the affected area that promotes the retention of respiratory secretions, thus representing a risk factor for respiratory infections and respiratory failure [32]. Sometimes, tracheomalacia is exacerbated by the presence of anomalies in the large vessels surrounding and compressing the trachea. The vessel most frequently involved is the innominate artery, as occurred in one of our patients [33]. For the more severe cases of tracheomalacia, surgical and endoscopic options include aortopexy, tracheopexy, or the placement of airway stents [34, 35].

In children with CPAM, recurrent respiratory infections can be present with 10% of patients experiencing more than three episodes per year of middle and/or lower airway infections [36]. In our cohort, most patients (7/9) were operated within the first year of life and only one was hospitalized for respiratory infection. None of the non-operated patients required hospitalization for respiratory exacerbations, only one child reported frequent episodes of respiratory infections complicated by wheezing and required numerous courses of oral antibiotics (about 3 per year). CPAM is the most prevalent type of congenital lung malformation, representing 25% of all congenital lung anomalies [37, 38]. In absence of prenatal diagnosis, some lesions are incidentally found during chest imaging in asymptomatic patients. However, when CPAM is diagnosed later in life, chronic inflammation from recurrent infections may alter its radiological and histological appearance as demonstrated by our non-operated adolescent patient. When CPAMs are not removed, malignancy is rare but possible [39]. Treatment strategy depends on clinical presentation (for example recurrent lung infections or respiratory distress) and severity of the malformation [40] but most are surgically removed depending on the experience of the centre [41].

Considering CDH, approximately 34-55% of patients candidates for surgery experience frequent respiratory infections [42, 43]. In our cohort, 6 out of 9 patients with CDH were hospitalized at least once for respiratory infection. In a French long-term prospective study, almost 60% of CDH survivors exhibited wheezing before 2 years of age, with 40% testing positive for respiratory syncytial virus (RSV) despite a 62% rate of prophylaxis with palivizumab [44]. In another study conducted in Poland involving 50 children who underwent surgery for CDH, 70% exhibited ipsilateral lung hypoplasia on scintigraphy, a condition that could elevate the likelihood of recurring lung infections and decreased respiratory function [42]. None of our patients performed scintigraphy, but lung hypoplasia was suspected in four cases: two baby boys had a radiological image shortly after surgery indicating residual lung hypoplasia, and two children exhibited a restrictive spirometry pattern suggestive of the condition. Postnatal risk factors for long-term pulmonary issues in CDH include prolonged mechanical ventilation, extended hospitalization, requirement for medical treatment including oxygen therapy and mechanical ventilation during or after hospitalization [45], and particularly the need for pulmonary assistance on day 30 of life, which can predich higher risk of morbidity and asthma at 1 and 5 years of age [46]. In addition, higher rates of inhaler use, ventilation/perfusion (V/Q) mismatch, lower spirometric values, worse physical performance, and asthma were reported in the years following the diagnosis in comparison to healthy individuals [46, 43].

Primary prevention of respiratory infections is a crucial strategy in patients with congenital malformations of the chest. Influenza vaccination must be encouraged in all infants aged at least 6 months, in addition to routine vaccinations. Furthermore, out of the 15 patients who came to our clinic before 2 years of age, 64% received immunoprophylaxis against RSV with palivizumab. This becomes very important considering that approximately 20% of all respiratory infections in children under 5 years of age are caused by RSV [47]. Patients at higher risk for severe RSV disease and hospitalization are infants younger than 6 months and those with certain comorbidities [48, 49]. Children with congenital airway abnormalities have about a two-fold greater risk of hospitalization for RSV respiratory infection compared to those who received prophylaxis with palivizumab for approved indications [50]. Of the three patients of our cohort who did not receive palivizumab, two experienced severe RSV infections with hospitalization. A recent review conducted by experts from Canada, Europe, and Israel suggested expanding the use of palivizumab to children with congenital pulmonary malformations up to 24 months of age [51]. The working group of Emilia Romagna region (Italy) recommends palivizumab to children with severe congenital tracheobronchial malformations, including CDH, in the first year of life [52].

Lung Function

Monitoring of lung function in patients with congenital malformations can reveal a certain impairment as demonstrated by the fact that more than one-third of our cohort exhibited an abnormal lung function pattern. Interestingly, both FVC and FEV_1 are

reported to decrease over time, suggesting a progressive worsening since early childhood [55]. In preschool children who underwent surgery for OA, bronchial hyperresponsiveness can persist into adulthood [53, 54] andasthma is frequently observed in these patients but whether an obstructive or restrictive pattern predominates is debated [30, 56-58]. Equally, there is no specific spirometric pattern associated with CPAMs. Most children with asymptomatic CPAMs have normal respiratory function values, while those who had extensive lung surgery may have reduced lung function compared to healthy children. This reduction seems to be due to the mass effect of the CPAM on the healthy adjacent lung tissue, rather than due to the loss of lung parenchyma from surgical resection [59, 60]. Spirometry in children who underwent thoracoscopic lobectomy for CPAM showed no difference between those operated before or after 5 months of age, indicating that the timing of surgery does not affect the clinical outcomes [61]. Studies on respiratory function of children operated for CDH indicated a decrease in FEV_1 since early age, particularly in those with severe CDH (*i.e* large defect size and/or oxygen dependence at birth). When children start adolescence and/or early adulthood, many have LFTs suggestive for pulmonary obstruction, which rarely respond to bronchodilation (therefore indicating fixed obstruction) [62]. Of the patients followed for CDH at our centre, only three could perform spirometry. Of these, two showed a mixed pattern, while one child had an obstructive pattern with a positive bronchodilator test. Regarding VRs, spirometry sometimes reveals a plateau in the expiratory phase of the flow-volume curve, indicative of central airway obstruction [63]. Early treatment of symptomatic patients experiencing dyspnea and/or dysphagia typically mitigates the long-term complications associated with tracheobronchial compression [64]. However, even successful surgical airway decompression can occasionally lead to residual tracheobronchomalacia, especially in children with double aortic arch [65].

Airway Clearance Technique

Most patients with OA and one with right aortic arch routinely performed respiratory physiotherapy. The goal of airway clearance techniques (ACTs) is to facilitate movement and expectoration of mucus from the lungspreventing infections and improving lung function [66]. As a specialized centre for cystic fibrosis, we always recommend chest physiotherapy in patients experiencing recurrent infections and/or in patients with structural abnormalities like bronchiectasis, lung hypoplasia, or tracheomalacia [35, 67, 68]. In clinical practice, the most commonly used ACT is a flow-regulated method called positive expiratory pressure (PEP) with a mask [69]. Positive pressure is achieved by augmenting expiratory flow against a resistance, which increases lung volume, reduces hyperinflation, and optimize airway clearance, thereby facilitating the removal of respiratory secretions [69, 70]. While a PEP value ranging from 5 to 10 cm H_2O appears to enhance peak expiratory flow and induce coughing in children with tracheobronchomalacia [71], it is still uncertain whether the utilization of this device effectively reduces lower respiratory tract infections [72, 35].

Limitations

Our study has several limitations such as the retrospective nature, the small size of the cohort, and the short duration of follow-up (less than five years in 65% of the children). Nonetheless, given that the majority of respiratory complications occurred within the first years of life, we may speculate that our cohort reflects the short-term clinical outcomes of patients with congenital malformations impacting lung development. Due to the young mean age of our cohort, only 40% (15/37) of patients underwent spirometry and no additional pulmonary function tests were conducted. Therefore, the residual lung function after surgery was not assessed in most of our patients

CONCLUSIONS

When possible, the care of children with congenital malformations of the thorax should start during gestation. Multidisciplinary counselling involving neonatologists, pediatric surgeons, and pediatric pulmonologists or gastroenterologists can provide parents with comprehensive information about management, necessity for prompt surgery if needed, potential issues, and expected outcomes. Prenatal diagnosis is often possible for CPAMs and some cardiac defects but less frequent for other malformations like OA or VRs. In these cases, persistent respiratory symptoms or signs at birth or in early life can make suspect the diagnosis. Similarly, management and follow-up of the child with congenital malformations affecting lung development and respiratory function must be multidisciplinary involving pediatric surgeons, pediatric radiologists, pediatric gastroenterologists, and physiotherapists. Since airway congenital malformations can cause both short- and long-term respiratory complications, respiratory follow-up is particularly essential. However, nutritional status and growth must always be assessed and, when needed, other specialists must be involved (Figure **1**).

The risk of respiratory infections is higher in early age as demonstrated by more than one third of our patients hospitalized within three years of age. Overall, OA is the malformation with the greatest increased risk of respiratory morbidity.

Further long-term studies are necessary to optimize the management of these patients and develop strategies to improve respiratory outcomes. In addition, a proper transition to adult care is needed when the patient reaches adulthood.

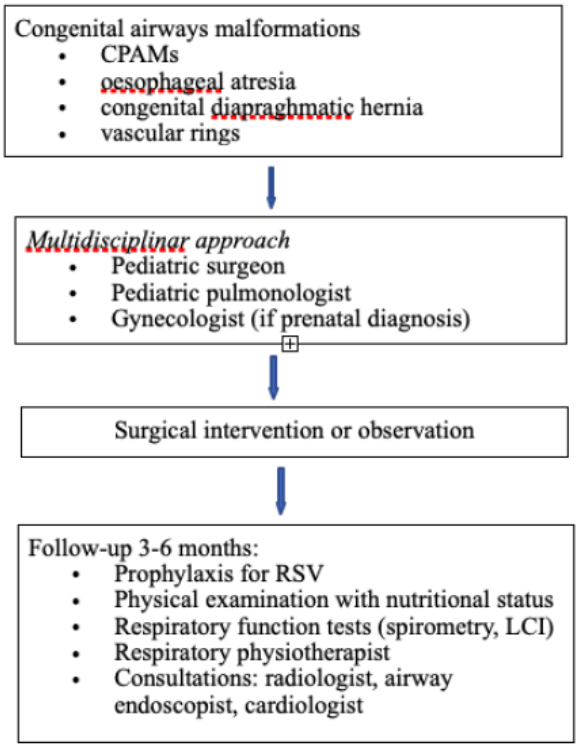

Figure 1: Flow-chart of a proposed multidisciplinary approach for children with congenital airways malformation affecting lung development.

CPAM, congenital pulmonary malformation; RSV, respiratory syncitial virus; LCI, lung clearance index; ENT, ear-nose-throath.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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