

# Antenatally diagnosed congenital cystic adenomatoid malformations (CCAM): Research Review

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## Summary

**Prenatal identification of lung abnormalities has increased with prenatal surveillance. With the advent of improved antenatal imaging over the past ten years, the diagnosis, assessment and management of congenital cystic lung abnormalities have changed. These were once considered the exclusive domain of the surgeon, who had the authority to operate on all congenital cystic lung abnormalities regardless of size or clinical signs in order to avoid the risk of cancer and improve lung growth in even asymptomatic infants. Clinicians are reconsidering this approach in the light of the spontaneous improvement and possible resolution that occurs over months to years with many of these lesions, thinking about the opportunity to take a more conservative approach in many minimally symptomatic or asymptomatic infants in the early months of life. The risks of subsequent cancer are poorly understood and probably overstated. Many centers advocate surgery only in cases of symptomatic or significant lesions, although there is little consensus as to what constitutes a significant lesion.**

**This article will review current knowledge (classification, pathogenesis, genetics, prenatal evaluation, clinical implications) on congenital cystic adenomatoid malformations (CCAM) and discuss management options for young children with these lung abnormalities.**

*Key words: fetal lung, CCAM, cystic adenomatoid malformations.*

## Introduction

Cystic adenomatoid malformations (CCAM) are relatively rare developmental abnormalities of the lung, first described as a separate entity in 1949 by Chin and Tang (1). They are generally characterized as benign hamartomatous or dysplastic lung tumors characterized by overgrowth of terminal bronchioles with a reduction in the number of alveoli. The incidence of CCAMS is reportedly between 1:11,000 (2) and 1:35,000 (3) live births, with males in most series being marginally more commonly affected (4). Given the operator-dependent nature of recognising antenatal abnormalities on ultrasound and limited access to this testing in some populations, the true prevalence may be even higher. CCAM is usually unilateral and usually involves only one lobe of the lung. A majority of antenatally diagnosed CCAMS is left-sided (5,6). As most series are small, there are few data on bilateral CCAMS (5-7). The significance of bilateral lesions may relate to a genetic predisposition to an underlying cell signalling problem and perhaps increase the likelihood of a predisposition to subsequent malignant change within the CCAM or elsewhere in the lung.

The reported perinatal mortality of antenatally diagnosed CCAMS has varied greatly, ranging from 9% to as high as 49% (2,5,8-14).

## Material and methods

In this work, we give an up-to-date of the main pathophysiological, clinical, diagnostic and therapeutic advances in CCAM. The literature search, based on the PubMed and the Cochrane database, was done from 2003 to 2011, focusing more on the latest research. We obtained additional articles from reference sections of the selected manuscripts. We paid special attention to systematic reviews, randomised clinical trials, consensus documents and review articles focused on the diagnostics and therapy of cystic adenomatoid malformations. Older articles were also included to draw attention to pathogenetic, clinical, and epidemiological issues.

## Classification of CCAM

The nomenclature of congenital cystic lung lesions has evolved over time, from 30 years ago.

The microscopic criteria for diagnosis of CCAM were first summarized as follows (15):

- Proliferation of polypoid glandular epithelium

- Proliferation of smooth muscle and elastic tissue in cyst walls
- Absence of cartilage
- Absence of inflammation
- Normal arterial and venous connections.

In order to determine the clinical and pathological spectrum of CCAM, Stocker et al. (16) were the first to propose three types of CCAM depending on cyst diameter and predominant cell types on histological examination, and suggested prognosis. (Tab. 1).

In a subsequent study Stocker expanded his classification to five types based on the site of origin of the malformation: tracheal, bronchial, bronchiolar, bronchiolar/alveolar duct and alveolar/distal acinar. Each subgroup was labeled '0' to '4', indicating the lesion's progression distally along the airway (20).

Although the Stocker system was the most widely used, some major drawbacks were recognized. First, it is based on histological criteria, which cannot be applied to prenatal ultrasound technology. Second, Stocker's prognoses and outcomes were derived from the clinical data and features of 38 neonates collected from 1917 to 1975, and are no longer pertinent.

In view of these disadvantages Adzick et al. (21) suggested abandoning Stocker's three types and dividing CCAM into two major groups based on gross anatomy

and ultrasound. This because the advent of better antenatal imaging has facilitated a deeper appreciation of the dynamic nature of cystic lung lesions in utero (5,6,22). The two categories were based on the predominant component of the lesion (cystic or solid): the macrocystic group contains single or multiple cysts  $\geq 5$  mm diameter, while the microcystic tumors are more solid and bulky with cysts  $< 5$  mm diameter. The variants are readily differentiated on prenatal ultrasound because the macrocystic type appears as fluid-filled lesions, whereas the microcystic lesions have innumerable interfaces that return the ultrasound beam and therefore appear solid. This simple classification into two types, either cystic or solid, has become the gold standard of in-utero CCAM diagnosis and prognosis (13,23,24). More recent attempts (4) have been made to update the classification.

The purpose of precise in-utero definition of fetal lung lesions is to extrapolate prognosis. In this regard, the main problem with the current classification system is to differentiate CCAM from BPS. Although the prenatal diagnosis of lung lesions is simple and Doppler studies have enhanced our ability to identify BPS, defining the exact nature of the anomaly may still prove difficult. These data make prenatal counseling very difficult and postnatal management uncertain (25), particularly since prognosis is related to lesion classification.

**Table 1. Classification of Cystic adenomatoid malformations (CCAM).**

***Stocker type I (Macrocystic adenomatoid malformation)***

It may manifest as a large cystic regions expanding through the development of air-trapping and mediastinal shift, giving rise to respiratory distress in the newborn (4). In extreme cases, such as those of diaphragmatic hernia, there may be associated pulmonary hypoplasia and pulmonary hypertension occurring as a consequence of the mass effect of the large cystic lesion (17). These lesions generally have an excellent prognosis as they are rarely associated with hydrops, pulmonary hypoplasia or fetal death (4). Type I CCAMs only usually affect a single lobe (4,18). The cysts are usually greater than 2 cm in diameter, although the term 'cysts' is inappropriate, because the walls have a layer of respiratory epithelium overlying fibroelastic tissue and small amounts of smooth muscle (4). They communicate with proximal airways and distal lung parenchyma (4). An associated systemic arterial supply may be found in up to 25% of cases (4).

***Stocker type II (Microcystic adenomatoid malformation)***

This condition occurs as a result of airway obstruction during development. The lesion contains multiple small cysts  $< 1$  cm diameter. These lesions demonstrate distal regional replacement of the lung parenchyma with microcystic maldevelopment (4). The solid parts of the lung are filled with distended respiratory bronchioles and alveolar material. Microcystic types are the predominant type reported in larger series (4,18). This group has a poor prognosis.

***Stocker type III (Solid cystic adenomatoid malformation)***

These solid lesions were originally more commonly reported in stillbirths and were thought to have a worse prognosis (4). They consist of a solid airless mass of tissue consisting almost entirely of bronchiolar elements lined by partly ciliated cuboidal epithelium and some alveolar elements (4,18,19). This mass affects an entire lobe or lobes and producing mediastinal shift.

## Pathogenesis

Various etiologies have been suggested to describe the pathogenesis of CCAM, among them overgrowth (1), hyperplasia (26) and hamartoma (27). However, all agreed that the defect occurred at the level of the bronchiole.

Stocker et al. (16) were the first to attempt classification of CCAM types based on embryogenesis, or the developmental stage at which the insult may have occurred. The development of the vertebrate lung, in fact, has been subdivided into five distinct periods based on the anatomical changes that occur in lung architecture: embryonic (3-7 weeks), pseudoglandular (7-17 weeks), canalicular (17-29 weeks), saccular (24-36 weeks), and alveolar (36 weeks to maturity). Most CCAM develops during the pseudoglandular period when there is a rapid expansion of the conducting airways and peripheral lung tubules, which continue to branch and bud to form acinar tubules. Arrest in this phase of lung development involves the bronchial type of epithelium causing CCAM pathology type I-III while a later arrest in weeks 22-36 results in an alveolar acinar type CCAM pathology (type IV) of epithelium.

Ostor and Fortune (28) viewed the embryogenesis of the disease differently. They stated that the presence of normal alveoli at the periphery of the lesion, with abnormal growth in the center, implies failure of canalization of the terminal bronchioles and subsequent inability to connect the conducting and respiratory elements. They conclude that the insult probably occurred later in gestation, at as late as 16-20 weeks (28).

Bronchography studies and serial microscopic examination showed that bronchial atresia is the primary defect leading to the development of CCAM. The morphology of the lesion, i.e. the type of malformation, is determined by the extent of dysplastic lung growth beyond the atretic segment (29). Modern pathological studies have suggested that CCAM may arise from failed interaction between mesenchyme and epithelium during development and a lack of maturation. This observation was confirmed by immunohistological studies. Thus the discordance between vascularity and proliferation in CCAM may represent an arrest in vascular development and a loss of synchrony between stroma and epithelium (30). It was suggested that in the developing lung the interaction between epithelial cells and interstitial cells is crucial to normal lung development (31). The imbalance between cell proliferation and programmed cell death or apoptosis has been demonstrated in CCAM. Investigation of other factors that down-regulate apoptosis or up-regulate proliferation in CCAM may further illuminate the pathogenesis of this entity.

CCAM and BPS appear to have similar causes, even if some authors attempted to view a distinct pathogenesis. The mechanism of their development has been described as a continuum of anomalous interactions among adjacent cells' excreted factors (32). The microscopic resemblance of BPS and CCAM, and the frequent appearance of CCAM receiving systemic arterial blood supply, indicates a common primary defect early during embryogenesis (33). The most prevalent theory states that during early development the laryngotracheal groove arises as

a ventral out-pouching of the primitive foregut and migrates caudally to give rise to the bronchial tree. It is possible that in the early stages of development, when the lung bud lies in close proximity to the primitive foregut from which it is derived, some insult or adhesion in an area where these two developing organ systems are adjacent will affect both structures, resulting in a lung lesion and foregut malformation (34).

## Genetics

Two recent review articles (35,36) have looked at the genetic and molecular basis influencing lung formation and abnormal lung development. CCAM is characterized by abnormal airway patterning during lung branching morphogenesis and is formed by abnormal branching of the immature bronchioles. One of the potential genes of influence for this development disorder is HOXB5, as its expression is maintained at a level typical for early lung development (37). Fetal CCAMs that grew rapidly, progressed to hydrops and required in utero resection showed increased platelet derived growth factor (PDGF-B) gene expression and PDGF-BB protein production compared with normal fetal lung or term CCAM specimens (38).

## Prenatal diagnosis and assessment

The accuracy of antenatal diagnosis is a central issue in the care of the fetus with a congenital cystic lung malformation. The advent of high-quality antenatal ultrasonography has dramatically changed the understanding of the evolution and involution of congenital cystic lung lesions such as CCAMs. For the vast majority, the outcome is far more favourable than previously reported (5). It is important that both the radiologist reporting the antenatal ultrasound and the obstetrician caring for the mother are fully informed about the outcome of congenital cystic lung lesions.

Antenatally, the use of repeat ultrasound with Doppler studies and fetal magnetic resonance imaging (MRI) is helpful in improving the accuracy of diagnosis (39-44). Ultrasound and MRI are used to identify the location of the lung abnormality, characterize the abnormality by its appearance, evaluate the blood supply and venous drainage by Doppler ultrasound, and determine any changes in thoracic position of other lung lobes, mediastinum, and the cardiac structures (40,45). MRI scanning is most helpful in distinguishing a CCAM from a diaphragmatic hernia (40). Although this investigation is expensive and limited to selected tertiary referral centres, this would be within the realm of normal practice for many women in whom the fetal ultrasound has detected a large cystic abnormality. Prenatal diagnosis of fetal lung lesions relies on the appearance of space-occupying lesions or the appearance of chest masses (46). The appearance of fetal CCAM varies from predominantly solid to purely cystic masses. Ultrasound will usually characterize the lesions as macrocystic or microcystic. The macrocystic category has large variable size cysts (2-10 cm) with thin intervening

echogenic areas. These multiple cysts are interconnected, but at times only a single cyst can be seen. The microcystic category has a defined echogenic area in the fetal lung with no cystic spaces being identified. A CCAM categorization between the macrocystic and microcystic 'definition' is sometimes used where the cyst spaces are present but small to moderate sized (<2 cm) with adjacent echogenic tissue areas. CCAM has both its arterial and venous blood flow from the pulmonary system.

The CCAM volume (cc) is sonographically measured by using the formula for an ellipse (length\*height\*width\*0.52) (47). A CVR is obtained by dividing the CCAM volume (cc) by the head circumference (cm) to correct for differences in the fetal gestational age. Surveillance of a CCAM is dictated by these features with high risk lung lesions being followed two to three times per week, while smaller lung lesions may be followed on a weekly basis (<1.2) or twice per week (1.2-1.6) depending on the gestational age and CVR ratio at initial evaluation (48-50). The CCAM is usually highly unpredictable in its growth potential between 18 and 26 weeks of gestation. The fastest growth in the CVR appears to occur between 20 and 25 weeks with a peak in the mean CVR occurring at 25 weeks gestation (51). There is a plateau in CCAM growth beginning at 25 weeks gestation with a decrease in the CVR after 25 weeks gestation reflecting continued fetal growth. Other ultrasound features that should be followed are cardiac function especially if there is a significant shift of the mediastinum and heart. Additional ultrasound evaluations should include amniotic fluid volume, umbilical artery Doppler flow patterns, ductus venosus Doppler flow patterns, and placental thickness. There is no known association of CCAM with chromosome abnormalities, but additional structural abnormalities in the renal (renal agenesis) and gastrointestinal (diaphragmatic hernia and bowel atresia) systems should be assessed (52).

Previous reports had commonly described a high incidence (up to 30%) of adverse features such as fetal death or hydrops (5,16). Generally, if hydrops develops secondarily to the CCAM location and growth, there is a high risk for fetal or neonatal death depending on gestation age at onset of hydrops. CCAM lesions that are predicted to be 'high-risk for hydrops' have a CVR greater than 1.6 or lesions with a significant macrocystic component. More recent experience has, however, suggested a far more favourable outcome (2,3,5,7). In particular, one recent ultrasound study reported an improved prediction of mortality or severe respiratory difficulty in fetuses with cystic lung abnormalities with the combination of the presence of polyhydramnios, fetal hydrops and a final normal lung-to-thorax transverse ratio (a marker of mass effect and pulmonary hypoplasia) of less than 0.25 (48,51,53).

Ultrasound in its routine obstetrical use in the second trimester, allows more fetuses with a lung malformation to be identified and the differential diagnosis includes CCAM, bronchopulmonary sequestration (BPS), bronchogenic or neuroenteric cysts, and diaphragmatic hernia (4,39,40,45,52,54). These lesions have different natural histories and prognosis so the correct diagnosis of the lung abnormality is very important (48). BPS may have a

sonographic appearance similar to that of CCAM, particularly in the microcystic subgroup; in fact it appears as a well-circumscribed, uniformly echogenic solid mass, but Doppler ultrasound technology can be very useful in distinguishing between CCAM and BPS: the latter is supplied by a supporting systemic artery arising from the abdominal aorta, while CCAM is supplied by the pulmonary artery (55). But some lung lesions show a 'hybrid status' with blood flow from both the pulmonary and aortic systems (45,56).

It seems to be an apparent tendency for natural resolution of such tumors with advancing gestation. Macrocystic (type I) disease tended to remain little changed by the end of pregnancy, whereas microcystic (type II) disease tended to shrink (5,7).

The antenatal ultrasound resolution of CCAMs or the finding of a normal chest X-ray at birth are not diagnostic of tumor regression as the majority of these infants will have CCAM when CT imaging is undertaken. Both antenatal ultrasound and neonatal chest X-ray appear to be unreliable investigations to diagnose complete resolution of CCAM lesions (2,3,5).

Diagnosis in fetal life is generally worse than diagnosis in postnatal life. Adverse prognosis, defined antenatally, continues to be associated with the development of non-immune hydrops and premature delivery, mediastinal shift with the cystic mass involving over 50% of the thoracic cavity, and pulmonary hypoplasia (2,5-7,41). Large series report a CCAM related perinatal mortality of around 10-15% (7,41,57).

## **Clinical implications**

The present state of our knowledge on fetal lung masses indicates that the traditional classification of CCAM is insufficient to provide definitive information regarding the pathogenesis and, specially, prognosis in each individual case. Clements and Warner (58) were the first to suggest a model based on a rational sequence of events in lung development, known as the 'wheel' theory. This model helped elucidate and simplify the classification of congenital lung anomalies. The authors based their theory on the assumption that any insult to the tip of a developing bronchus may lead to a different lesion depending on the timing and severity, rather than on the nature, of the insult. They were the first to suggest considering all anatomical components of the lung involved in the pathological lesion in each particular case. These components are the bronchial airways, the arterial supply and venous drainage, and the lung parenchyma.

With the advent of high-resolution ultrasound technology, coupled with sophisticated Doppler and power Doppler angiography, it is now possible to evaluate fetal arterial (59) and venous systems (60). So recently, Achiron et al. (61) adopted Clements and Warner's classification system with modifications, based on 2D and Doppler ultrasound, and applied it to fetal findings. The novelty of this new classification system is that it enables separate delineation of each fetal lung component involved in the anomaly: the parenchyma, arterial circulation and venous drainage. Further, it is based on prena-

tal sonographic identification and Doppler flow studies: the arterial supply and venous drainage of the lesions, as opposed to tissue consistency. Morphologic description of the lesion as solid or cystic does not affect fetal prognosis, since the natural course of the entity during gestation is probably influenced primarily by the vascular component of the malformation.

## Management

Presentation ranges from respiratory failure to a well infant (62). With the advent of improved antenatal imaging, recognition of the occurrence and dynamic nature of congenital cystic abnormalities has changed (39).

There is agreement that infants and older children with symptomatic CCAMs, require surgery (39,47). Most commonly, this occurs in a neonate presenting with tachypnoea, increased work of breathing, hypoxaemia, carbon dioxide retention, poor feeding or overt respiratory failure requiring invasive or non-invasive ventilatory support. Infants and young children with borderline symptoms may become overtly symptomatic or may persist with tachypnoea, feeding difficulties and failure to thrive. A chest radiograph may identify a localised lesion and they will proceed to surgery.

Infants with abnormal chest radiographs requiring prolonged mechanical because of a large CCAM, typically confirmed on a postnatal chest CT scan, generally undergo lobectomy, even if there is little clinical disagreement about this. A CCAM may become symptomatic if associated with an intercurrent chest infection with a pneumothorax or if affected by ball-valve hyperinflation (4,47,49). Such children are considered symptomatic and usually proceed to lobectomy.

Treatment in asymptomatic infants with a CCAM on imaging is controversial as there are two schools of thought. The first argues that any lesion, regardless of size, should be removed to minimise the risk of subsequent malignancy, facilitate optimal lung growth and minimise the risk of potential local morbidity, including infection and pneumothorax (39,47,63). The opposing view argues that the risk of malignancy is not well defined, a postnatal decrease in size is possible, the influence on lung growth is small and continued review is appropriate before considering surgery (64,65). Continued follow-up, even in infants who have had surgery, would seem appropriate to better quantitate the outcome, particularly with regard to later malignancy (66).

The arguments in favour of early surgery in asymptomatic infants are:

1. The risk of infection makes surgery more difficult. An infection is believed to be the most common presenting symptom in children after the neonatal period (39,67,68).
2. There is a risk of enlargement or pneumothorax leading to respiratory compromise. Rarely, pneumothorax may be the presenting feature of a CCAM (39,68).
3. Resection allows compensatory lung growth. It is unclear whether the timing of surgery influences the degree of lung growth achieved (39).
4. There is a risk of malignancy, either as a differential

diagnosis at presentation or with subsequent development.

5. A CCAM is not a 'normal variant' and is likely to become symptomatic at a later stage. The quantitation of how likely the lesion is to become symptomatic is unclear, but the main risk is that of infection or less commonly pneumothorax (2,3,18,39).
6. There is more rapid postoperative recovery in a younger child. This is not true for neonates, which has led one group to delay surgery until the second month of life (47).

About gestational age, although some argue in favour of operating in the neonatal period (11), others consider the risks of anaesthesia and the length of postoperative ventilation to be unjustified (47). Others suggest 6 months (39,69), whereas some wait until 2 years (70).

The arguments against surgery in asymptomatic infants are (39,71):

1. The natural history of CCAMs is still not well defined. This is because the clinical decision has been to resect them (39,66). Accurate postnatal diagnosis with modern imaging techniques now poses few problems (22). Only 10% of children with an asymptomatic CCAM developed an infection or pneumothorax over a 3-year period. The exception to this may be the rare issue of distinguishing a PPB from a CCAM (39).
2. There is morbidity from surgery. This is, however, no different whether the child with a CCAM presented symptomatically or underwent elective surgery (71).
3. The issue of a CCAM as a premalignant condition has provided the most emotive indication for surgery, but proponents of a conservative approach argue that the risk is extremely small and vastly overstated, and that the evidence for a link between CCAMs and cancer may be an association rather than a causal link (72). The greatest risk of malignancy may be in those with bilateral CCAMs (<5%) who have a probable genetic susceptibility to CCAMs and to malignancy. The conservative approach includes regular follow-up with serial chest CT scans (71). One may question the appropriateness of up to yearly chest CT scans, with their increased risk of an unrelated cerebral malignancy (73,74). The proponents of surgery for all CCAMs argue that 'the association between CCAM and malignancy is now more than anecdotal' (39). The most quoted associations are between CCAMs and PPBs in infants and young children and between CCAMs and bronchoalveolar carcinoma in older children and adults (39,68,71). There are some reports suggesting a link between CCAMs and rhabdomyosarcoma (39). Conversely, large reviews of childhood lung tumours have reported an association between CCAMs and tumours in 4% (75) and 9% (76) of cases. Bronchiolar carcinoma has been reported in older children and adults with previously unrecognised Stocker type I CCAMs or with incomplete resection of these malformations (4,77,78). The aetiology of malignant change is hypothesised to originate in the mucigenic epithelium, evident in type I CCAMs (39,77-80). The link between PPBs and CCAMs is less clear (39). It may be difficult to distinguish a cys-

- tic (type 1) PPB from a CCAM on imaging, an argument in favour of resecting all such lesions according to proponents for surgery (39).
4. There is a likelihood of further regression with increasing age. Interestingly, the size of the removed CCAM did not influence surgical morbidity in 29 children whether they presented with or without symptoms (71). If the regression in size of the CCAM during the third trimester continues postnatally, it may obviate the need for surgery (71).

### In utero therapy

In utero evaluation and treatment can vary from serial observation in utero with normal delivery and resection at 5-8 weeks of newborn life to in utero therapy in rare situations. There are no universal guidelines for fetal intervention with demonstrated large cystic lung lesions. Similarly, there is little published information on the indications for termination of pregnancy with severe CCAMs.

Open maternal-fetal therapy has been reviewed in a number of previous publications (47,81,82).

Fetal intervention can be based upon gestational age, the size of the lesion, the mother's health and the development of fetal hydrops (47). In utero techniques include open maternal-fetal therapy with fetal thoracotomy and lobectomy, thoracoamniotic shunting of macrocystic CCAM's and third trimester EXIT delivery with fetal thoracotomy, and lobectomy on maternal placental bypass (81).

The current approach to in utero management of large CCAM's requires evaluation by fetal ultrasound, fetal echocardiogram, ultrafast MRI, and fetal karyotype (50,81). When associated anomalies or chromosomal anomalies are identified, that fetus would not be a candidate for any in utero treatments. Counseling and expectant management of the pregnancy would be recommended. When a fetus with an isolated CCAM is complicated by hydrops, the next triage decision is dependent on gestational age. If the fetus is less than 32 weeks and no dominant cyst is available for drainage, an open maternal-fetal surgery is considered for fetal thoracotomy/lobectomy. Expectant management in this situation has a predicted 100% lethal outcome. If the fetus is less than 32 weeks gestation and has a single or multiple large CCAM cysts, a fetal thoracoamniotic shunting is an appropriate approach because fetal thoracocentesis alone is ineffective because of rapid reaccumulation of cyst fluid. Thoracoamniotic shunting has been used successfully to treat hydrops in 8 of 9 infants with large CCAMs with a large predominant cyst. The volume reduced by 60%, and the mean time between shunt insertion and delivery was 13 weeks. Thoracoamniotic shunting is not recommended for multicystic or predominantly solid CCAMs (47,81). If the fetus is greater than 32 weeks gestation, the plan would be for delivery with or without an EXIT procedure (ex-utero intrapartum treatment). One of the significant aspects of this triage decision is that fetuses need to be 34 weeks gestation or have a weight of 2,000 g to have additional pulmonary support by extracorporeal membrane oxygenation (ECMO) if required, due to

pulmonary hypertension or pulmonary hypoplasia. In the survivors, there is resolution of the hydrops in 1-2 weeks with movement of the mediastinum back to the midline in 3 weeks. There is rapid residual lung growth. The mean time to delivery following the in utero maternal-fetal surgery was 8 weeks. To date the follow-up of these children have shown normal developmental outcome. In the non-survivor group, some fetal losses have been intraoperative usually after developing profound bradycardia after delivery of the CCAM mass from the chest. It is hypothesized that the CCAM delivery from the thorax and abrupt removal of cardiac compression results in a pathophysiology response similar to correction of a pericardial tamponade with fetal hemodynamic collapse and reactive bradycardia. Fetal echocardiography is used on a routine continuous basis for all maternal-fetal surgery cases, but it has more significant value in the CCAM cases as direct monitoring of the fetal myocardial performance can be obtained and appropriate adjustments of fluid volumes and medications can be utilized. Other fetal losses have been secondary to preterm labor, intrauterine death at 24 hr, and 'maternal mirror' syndrome requiring early delivery with neonatal death. The EXIT delivery is considered using placental bypass during the fetal thoracotomy and lobectomy (83,84). At the time of the EXIT delivery, only head and neck are initially delivered through the hysterotomy. The intrauterine volume is maintained with lower fetal body and continuous amnio infusion of warmed Ringers lactate to prevent cord compression. Uterine relaxation is maintained by high concentration inhalational anesthetics with additional tocolysis, if necessary. These maneuvers preserve the utero-placental circulation and continue gas exchange between maternal, placental, and fetal compartments. The EXIT delivery allows for controlled resection of large fetal lung masses at delivery, avoiding acute respiratory decompensation related to mediastinal shift, air trapping, and compression of normal lung. The survival for in utero indicated treatments of open maternal-fetal therapy, thoracoamniotic shunting, and EXIT delivery are 50%, 75%, and 89%, respectively. In the appropriate situation, these maternal-fetal surgeries for CCAM pathology are life saving for the affected fetus at risk for hydrops or severe respiratory dysfunction while allowing acceptable maternal risk in the present and future pregnancies. This type of fetal therapy requires the energy, dedication, and expertise of a multi-disciplinary team with both maternal and fetal risk/benefit considerations (81). Realistically, fetal surgery is limited to only a few centres worldwide.

### Conclusion

The evolution of better antenatal imaging has been crucial in changing thinking about appropriate management of congenital cystic adenomatoid malformation (CCAM). The antenatal diagnosis of this pathology has become more frequent with increasing sonographer training and higher resolution ultrasound imaging platforms. The postnatal management of antenatally diagnosed fetal lung tumors has also changed more recently. The outcome of antenatally detected CCAM is much better than previously

reported, probably because of the high spontaneous regression rate of this tumor in the last trimester of pregnancy and in the early years of life. Despite the antenatal resolution of CCAMs on ultrasound, postnatal follow-up is recommended in view of the long-term complications of this malformation (52,85). Postnatal CT imaging is mandatory in all fetuses thought to have lung lesions because of the high false-negative rate of neonatal chest Xrays. The appropriateness of either expectant management or surgical intervention in asymptomatic infants with lung lesions remains to be established.

An improved understanding of the classification of CCAMs and their natural course has been prompted, and there is a recent move toward the generation of large-scale databases to more accurately define the natural history of CCAMs. With state-of-the-art ultrasound equipment and sophisticated Doppler capabilities, in utero evaluation of related vascular anomalies in fetuses with lung dysplasia is now feasible. In-utero mapping of significant intrapulmonary shunts and vascular connections may provide better understanding of the pathogenesis of these lesions and improve prenatal and postnatal management.

## References

1. Ch'in KY, Tang MY. Congenital adenomatoid malformation of one lobe of a lung with general anasarca. *Arch Pathol* 1949;48:221-229.
2. Laberge J-M, Flageole H, Pugash D et al. Outcome of the prenatally diagnosed congenital cystic adenomatoid malformation: a Canadian experience. *Fetal Diagn Ther* 2001;16:178-186.
3. Gornall AS, Budd JL, Draper ES et al. Congenital cystic adenomatoid malformation: accuracy of prenatal diagnosis, prevalence and outcome in a general population. *Prenatal Diagn* 2003;23:997-1002.
4. Langston C. New concepts in the pathology of congenital lung malformations. *Sem Pediatr Surg* 2003;12:17-37.
5. Davenport M, Warne SA, Cacciaguerra et al. Current outcome of antenatally diagnosed cystic lung disease. *J Pediatr Surg* 2004;39:549-556.
6. Calvert JK, Boyd PA, Chamberlain PC et al. Outcome of antenatally suspected congenital cystic adenomatoid malformation of the lung: 10 years experience 1991-2001. *Arch Dis Child fetal Neonatal Ed* 2006;91:26-28.
7. Ierullo AM, Ganapathy R, Crowley S et al. Neonatal outcome of antenatally diagnosed congenital cystic adenomatoid malformations. *Ultrasound Obstet Gynecol* 2005;26:150-153.
8. Thorpe-Beeston JG, Nicolaidis KH. Cystic adenomatoid malformation of the lung: prenatal diagnosis and outcome. *Prenat Diagn* 1994;14:677-688.
9. Cacciari A, Ceccarelli PL, Pilu GL et al. A series of 17 cases of congenital cystic adenomatoid malformation of the lung: management and outcome. *Eur J Pediatr Surg* 1997;7:84-89.
10. Sapin E, Lejeune V, Barbet JP et al. Congenital adenomatoid disease of the lung: prenatal diagnosis and perinatal management. *Pediatr Surg Int* 1997;12:126-129.
11. Waszak P, Claris O, Lapillonne A. Cystic adenomatoid malformation of the lung: neonatal management of 21 cases. *Pediatr Surg Int* 1999;15:326-331.
12. Roggin KK, Breuer CK, Carr SR et al. The unpredictable character of congenital cystic lung lesions. *J Pediatr Surg* 2000;35:801-805.
13. Bunduki V, Ruano R, Marques DaSilva M et al. Prognostic factors associated with congenital cystic adenomatoid malformation of the lung. *Prenat Diagn* 2000;20:459-464.
14. Monni G, Paladini R, Ibba RM et al. Prenatal ultrasound diagnosis of congenital cystic adenomatoid malformation of the lung: a report of 26 cases and review of the literature. *Ultrasound Obstet Gynecol* 2000;16:159-162.
15. Kwittken J, Reiner L. Congenital cystic adenomatoid malformation of the lung. *Pediatrics* 1962;30:759-763.
16. Stocker JT, Madewell JE, Drake RM. Congenital cystic adenomatoid malformation of the lung. Classification and morphologic spectrum. *Hum Pathol* 1977;8:155-171.
17. Njinimbam CG, Hebra A, Kicklighter SD et al. Persistent pulmonary hypertension in a neonate with cystic adenomatoid malformation of the lung following lobectomy: survival with prolonged extracorporeal membrane oxygenation therapy. *J Perinatol* 1999;19:64-67.
18. Clements BS. Congenital malformations of the lungs and airways. In: Taussig LM, Landau LI, eds: *Pediatric Respiratory Medicine*. St Louis: Mosby, 1999;1106-1136.
19. Alt B, Shikes FH, Stanford RE et al. Ultrastructure of congenital cystic adenomatoid malformation of the lung. *Ultrastruct Pathol* 1982;3:217-228.
20. Stocker JT. Congenital and developmental diseases. In *Pulmonary Pathology* (2nd edn), Dial DH, Hammer SP (eds). Springer: New York, NY, 1994;174-180.
21. Adzick NS, Harrison MR, Glick PL et al. Fetal cystic adenomatoid malformation: prenatal diagnosis and natural history. *J Pediatr Surg* 1985;20:483-488.
22. Van Leeuwen K, Teitelbaum DH, Hirschl RB et al. Prenatal diagnosis of congenital cystic adenomatoid malformation and its postnatal presentation, surgical conditions and natural history. *J Pediatr Surg* 1999;34:794-799.
23. Gilbert-Barness E. The respiratory system. In: Gilbert-Barness E, editor. *Potter's pathology of the fetus and infant*. St Louis: Mosby-Year Book. 1997;712.
24. Gilbert-Barness E, Debich-Spicer D. Respiratory system. In: Gilbert-Barness E, Debich-Spicer D, editors. *Embryo and fetal pathology*. Cambridge, UK: Cambridge University Press. 2004;470-489.
25. Case Records of Massachusetts General Hospital (case 36-1999). *N Engl J Med* 1999;341:1680-1685.
26. Craig JM, Kirkpatrick J, Neuhauser EBD. Congenital cystic adenomatoid malformation of the lung in infants. *Am J Radiol* 1956;76:516-526.
27. Dempster AG. Adenomatoid hamartoma of the lung in the neonate. *J Clin Pathol* 1969;22:401-406.

28. Ostor AG, Fortune DW. Congenital cystic adenomatoid malformation of the lung. *Am Clin Pathol* 1978;70:595-604.
29. Moreman P, Fryns JP, Vandenberghe K et al. Pathogenesis of CCAM of the lung. *Histopathology* 1992;21:315-321.
30. Cangiarella J, Greco MA, Askin F et al. Congenital cystic adenomatoid malformation of the lung: insights into the pathogenesis utilizing quantitative analysis of vascular marker CD34 (QBEND-10) and cell proliferation marker MIB-1. *Mod Pathol* 1995;8:913-918.
31. Sakamoto K, Nagai A, Ueno H et al. Cellular proliferation of pre and postnatal lung cells in the mouse (Abstract). *Am Rev Respir Dis* 1991;143:A500.
32. Kousseff BG, Gilbert-Barness E, Debich-Spicer D. Bronchopulmonary-foregut malformations: a continuum of paracrine hamartomas? *Am J Med Genet* 1997;68:12-17.
33. Hutchin P, Friedman PJ, Saltzstein SL. Congenital cystic adenomatoid malformation with anomalous blood supply. *J Thorac Cardiovasc Surg* 1974;62:220-225.
34. Stovin PGI. Early lung development. *Thorax* 1985;40:401-404.
35. Whitsett JA, Wert SE, Trapnell BC. Genetic disorders influencing lung formation and function at birth. *Human Mol Genet* 2004;13:207-215.
36. Groenman F, Unger S, Post M. The molecular basis for abnormal human lung development. *Biol Neonate* 2005;87:164-177.
37. Volpe MV, Pham L, Lessin M et al. Expression of Hoxb-5 during human lung development and in congenital lung malformations. *Birth Defects. Res Part A Clin Mol Teratol* 2003;67:550-556.
38. Liechty KW, Quinn TM, Cass DL et al. Elevated PDGF-B in congenital cystic adenomatoid malformations requiring fetal resection. *J Pediatr Surg* 1999;34:805-810.
39. Laberge J-M, Puligandla P, Flageole H. Asymptomatic congenital lung malformations. *Sem Pediatr Surg* 2005;14:16-33.
40. Hubbard AM, Adzick NS, Crombleholme TM et al. Congenital chest lesions: diagnosis and characterization with prenatal MR imaging. *Radiology* 1999;212:43-48.
41. Illanes S, Hunter A, Evans M et al. Prenatal diagnosis of echogenic lung: evolution and outcome. *Ultrasound Obstet Gynecol* 2005;26:145-149.
42. Matsuoka S, Takeuchi K, Yamanaka Y et al. Comparison of magnetic resonance imaging and ultrasonography in the prenatal diagnosis of congenital thoracic abnormalities. *Fetal Diagn Ther* 2003;18:447-453.
43. Breysem L, Bosmans H, Dymarkowski S et al. The value of fast MRI imaging as an adjunct to ultrasound in prenatal diagnosis. *Eur Radiol* 2003;13:1538-1548.
44. Quinn TM, Hubbard AM, Adzick NS. Prenatal magnetic resonance imaging enhances prenatal diagnosis. *J Pediatr Surg* 1998;33:312-316.
45. Goldstein RB. Ultrasound evaluation of the fetal thorax. In: Callen PW, editor. *Ultrasonography in obstetrics and gynecology*, 4th edn. Philadelphia: W.B. Saunders. 2000;426.
46. Hubbard AM, Crombleholme TM. Anomalies and malformations affecting the fetal/neonatal chest. *Sem Radiol* 1998;23:117-125.
47. Adzick NS, Flake AW, Crombleholme TM. Management of congenital lung lesions. *Sem Pediatr Surg* 2003;12:10-16.
48. Adzick NS. Management of fetal lung lesions. *Clin Perinatol* 2003;30:481-492.
49. Adzick NS, Harrison MR, Crombleholme TM et al. Fetal lung lesions: Management and outcome. *Am J Obstet Gynecol* 1998;10:884-889.
50. Adzick NS, Kitano Y. Fetal surgery for lung lesions, congenital diaphragmatic hernia, and sacrococcygeal teratoma. *Semin Pediatr Surg* 2003;12:154-167.
51. Crombleholme TM, Coleman B, Hedrick H et al. Cystic adenomatoid malformation volume ratio predicts outcome in prenatally diagnosed cystic adenomatoid malformation of the lung. *J Pediatr Surg* 2002;37:331-338.
52. Sanders RC. Cystic adenomatoid malformation of the lung (CCAM). In: Sanders RC, editor. *Structural fetal abnormalities the total picture*, 2nd edn. St. Louis: Mosby. 2002;181-182.
53. Usui N, Kamata S, Sawai T et al. Outcome predictors for infants with cystic lung disease. *J Pediatr Surg* 2004;39:603-606.
54. Sanders RC. Pulmonary Sequestration. In: Sanders RC, editor. *Structural fetal abnormalities the total picture*, 2nd edn. St. Louis: Mosby. 2002;193-195.
55. Sauerbrei E. Lung sequestration. Duplex Doppler diagnosis at 19 weeks' gestation. *J Ultrasound Med* 1991;10:101-105.
56. Cass DL, Crombleholme TM, Howell LJ et al. Cystic lung lesion with systemic arterial blood supply: A hybrid of congenital cystic adenomatoid malformations and bronchopulmonary sequestrations. *J Pediatr Surg* 1997;32:986-990.
57. Stocker JT. Congenital and developmental diseases. In: Dail OH, Hammar SP, eds: *Pulmonary Pathology*. New York: Springer, 1994;155.
58. Clements IS, Warner JO. Pulmonary sequestration and related congenital bronchopulmonary vascular malformations: nomenclature and classification based on anatomical and embryological considerations. *Thorax* 1987;42:401-408.
59. Sivan E, Rotstein Z, Lipitz S et al. Segmentary fetal branch pulmonary artery blood flow velocimetry: in utero Doppler study. *Ultrasound Obstet Gynecol* 2000;16:453-456.
60. Achiron R, Hegesh J, Yagel S et al. Abnormalities of the fetal central veins and umbilico-portal system: prenatal ultrasonographic diagnosis and proposed classification. *Ultrasound Obstet Gynecol* 2000;16:539-548.
61. Achiron R, Hegesh J and Yagel S. Fetal lung lesions: a spectrum of disease. New classification based on pathogenesis, two-dimensional and color Doppler ultrasound. *Ultrasound Obstet Gynecol* 2004;24:107-114.

62. Fitzgerald D.A. Congenital cyst adenomatoid malformations: resect some and observe all? *Paediatric Respiratory Reviews* 2007;8:67-76.
63. Shanmugam G, MacArthur K, Pollock JC. Congenital lung malformations – antenatal and postnatal evaluation and management. *Eur J Cardiothoracic Surg* 2005;27:45-52.
64. Butterworth SA, Blair GK. Postnatal spontaneous resolution of congenital cystic adenomatoid malformations. *J Pediatr Surg* 2005;40:832-834.
65. Hsieh CC, Chao AS, Chang YL et al. Outcome of congenital cystic adenomatoid malformation of the lung after antenatal diagnosis. *Int J Gynaecol Obstet* 2005;89:99-102.
66. Cloutier MM, Schaeffer DA, Hight D. Congenital cystic adenomatoid malformation. *Chest* 1993;103:761-764.
67. Takeda S, Miyoshi S, Inoue M et al. Clinical spectrum of congenital cystic disease of the lung in children. *Eur J Cardiothorac Surg* 1999;15:11-17.
68. Zach MS, Eber E. Adult outcome of congenital lower respiratory tract malformations. *Thorax* 2001;56:65-72.
69. Bagolan P, Nahom A, Giorlandino C et al. Cystic adenomatoid malformation of the lung: clinical evolution and management. *Eur J Pediatr* 1999;158:879-882.
70. Papagiannopoulos K, Hughes S, Nicholson AG et al. Cystic lung lesions in the paediatric and adult populations: surgical experience at the Brompton Hospital. *Ann Thorac Surg* 2002;73:1594-1598.
71. Aziz D, Langer JC, Tuuha SE et al. Perinatally diagnosed asymptomatic congenital cystic adenomatoid malformation: To resect or not? *J Pediatr Surg* 2004;39:329-334.
72. Thurlbeck WM. Postnatal growth and development of the lung. *Am Rev Respir Dis* 1975;111:803-844.
73. De Jong P, Mayo JR, Golmohammadi K et al. Estimation of cancer mortality associated with repetitive computed tomography scanning. *Am J Respir Crit Care Med* 2006;173:199-203.
74. Frush DP, Donnelly LF, Rosen NS. Computed tomography and radiation risks: what paediatric health care providers should know. *Pediatrics* 2003;112:951-957.
75. Hartman GE, Shochat SJ. Primary pulmonary neoplasms of childhood: a review. *Ann Thorac Surg* 1983;36:109-119.
76. Hancock BJ, Di Lorenzo M, Youssef S et al. Childhood primary neoplasms. *J Pediatr Surg* 1993;28:1133-1136.
77. Morresi A, Wockel W, Karg O. Adenomatoid cystic lung abnormality in adults with associated bronchoalveolar carcinoma. *Pathologie* 1995;16:292-298.
78. Granata C, Gambini C, Balducci T et al. Bronchoalveolar carcinoma arising in congenital cystic adenomatoid malformation in a child: a case report and review of malignancies originating in congenital cystic adenomatoid malformation. *Pediatr Pulmonol* 1998;25:62-66.
79. Ota H, Langston C, Honda T et al. Histochemical analysis of mucous cells of congenital adenomatoid malformation of the lung: insights into the carcinogenesis of pulmonary adenocarcinoma expressing gastric mucins. *Am J Clin Pathol* 1998;110:450-455.
80. Wang NS, Chen MF, Chen FF. The glandular component in congenital cystic adenomatoid malformation of the lung. *Respirology* 1999;4:147-153.
81. Wilson RD, Hedrick HL, Liechty KW et al. Cystic adenomatoid malformation of the lung: review of genetics, prenatal diagnosis and in utero treatment. *Am J Med Genet A* 2006;140:151-155.
82. Baxter JK, Johnson MP, Wilson RD et al. Thoracoamniotic shunts: pregnancy outcome for congenital cystic adenomatoid malformation and pleural effusion. *Am J Obstet Gynecol* 1998;185:S245.
83. Hedrick HL. Ex utero intrapartum therapy. *Sem Pediatr Surg* 2003;10(3):190-195.
84. Hedrick HL, Flake AW, Crombleholme TM et al. The ex utero intrapartum therapy procedure for high-risk fetal lung lesions. *J Pediatr Surg* 2005;40:1038-1043.
85. Bianchi DW, Crombleholme TM, D'Alton ME. Cystic adenomatoid malformation. In: Bianchi DW, Crombleholme TM, D'Alton ME, editors. *Fetology diagnosis & management of the fetal patient*. New York: McGraw-Hill. 2000;289-297.