

Antenatal Diagnosis of Congenital Fetal Lung Lesions and Postnatal Outcome — A Case Series and Review of the Literature

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Objectives: To review our local experience of prenatal diagnosis and management of congenital fetal lung lesions, and to compare the pregnancy outcomes with those published in the literature.

Methods: A retrospective study of all cases with antenatal diagnosis of congenital fetal lung malformations from January 2003 to December 2012 was performed. Outcomes of these pregnancies and neonatal records were reviewed to assess the antenatal course, management, and postnatal outcome.

Results: Of 48,619 deliveries, 15 cases of congenital lung lesions were diagnosed during this period, giving an incidence of 0.03%. All fetuses carried normal karyotype. Two fetuses had concurrent structural abnormalities. Two patients opted for termination of pregnancy, one because of macrocystic lesions and the other for concurrent structural abnormalities. The remaining 13 pregnancies were carried to term without specific antenatal intervention. Only one baby was symptomatic shortly after birth, while the others remained largely asymptomatic. Two babies underwent surgical excision of lung lesions. There was no antenatal fetal hydrops or perinatal mortality in this cohort.

Conclusion: Congenital fetal lung lesions were uncommon in our locality; most had good outcome and did not require any antenatal intervention. The spectrum of severity encountered was apparently milder than that reported in the literature. Postnatal paediatric assessment and further imaging of the lung lesions are essential.

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Introduction

Congenital fetal lung lesions are uncommon and are estimated to occur in 1 in 15,000 live births¹. The detection of these lung lesions has increased with the availability of sophisticated antenatal ultrasonography (USG). The most frequently diagnosed lesions are congenital cystic adenomatoid malformation (CCAM) and bronchopulmonary sequestration (BPS). CCAM is an overgrowth of terminal respiratory bronchioles in the form of cysts (Stocker type I and II) or solid parenchymal dysplasia (Stocker type III)². BPS is a non-functioning lung mass that arises from an aberrant systemic artery and does not connect to the native tracheobronchial tree. The natural history of these lung lesions varies as they may progress in size, remain the same volume, or regress in utero³. A progressing lesion may cause compression of the heart and major vessels, resulting in mediastinal shift, polyhydramnios, and hydrops which may be associated with poor prognosis. Other lesions may regress or even disappear with advancing gestation. Prenatal counselling for these lesions is often difficult due to their variable course in the antenatal period and uncertain perinatal outcome after birth. There are few local publications comparing the incidence and severity of such congenital fetal lung lesions

in Hong Kong with that reported in the literature.

This study aimed at reviewing our local experience of prenatal diagnosis and management of congenital fetal lung lesions over a period of 10 years. We evaluated the antenatal course and the postnatal outcome of these pregnancies complicated by congenital fetal lung malformations, and compared the findings with that reported in the literature.

Methods

A retrospective review of all cases with antenatal diagnosis of congenital fetal lung malformations over a 10-year period from January 2003 to December 2012 was performed, based on a comprehensive prenatal diagnosis statistics registry used in the Department of Obstetrics and Gynaecology, United Christian Hospital, as well as the obstetric database currently in use by all obstetric units in public sector in the territory. Our department is a regional service unit that provides general obstetric care to a population of around 0.8 million and manages an average

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of around 5000 deliveries per annum. The department has a well-established maternal fetal medicine team headed by subspecialist consultants, and is also a training centre for maternal fetal medicine subspecialty training. Specific diagnoses of CCAM, BPS, and lung cysts were searched for and reviewed. Cases diagnosed as congenital pleural effusion were also reviewed to evaluate whether there were any specific diagnoses of primary lung lesions. Those with oligohydramnios or anhydramnios with pulmonary hypoplasia, and those with pleural effusion either alone or in association with general hydropic changes without any diagnosis of primary lung parenchymal lesions were excluded from the current study.

All cases with suspected fetal lung lesions had a detailed anomaly scan by a subspecialist in maternal and fetal medicine for confirmation of the diagnosis. Karyotyping was offered to all. Detailed counselling was provided by the subspecialist, together with an integrated team of paediatricians and paediatric surgeons in our hospital. The cases were then followed up regularly every 2 to 4 weeks to assess the progress of the lesion till term.

The clinical notes, USG reports, and archived USG images of identified cases were carefully reviewed. The gestational age at diagnosis, the antenatal USG diagnosis and descriptive appearance of the lesions, presence or absence of mediastinal shift, polyhydramnios, pleural effusion or fetal hydrops, and identifiable feeding arteries were evaluated. The diagnoses were made by using 2-dimensional USG based on findings of focal increased echogenicity or cysts indicative of lung lesions. A finding of mediastinal shift was also suspicious of lung lesion and warranted further detailed evaluation of lung parenchymal texture for confirmation. As CCAM lesions were supplied by normal pulmonary vasculature, the diagnosis of BPS was made when an aberrant vessel from the aorta to the lung lesion was identified. Otherwise, a sonographic diagnosis of CCAM was made. The lung lesions were subclassified as microcystic if they were predominantly homogeneous, or macrocystic if there were significant cystic areas within the lesion.

The largest dimension of the lesions as measured in serial USG was then used to calculate a maximal CCAM volume ratio (CVR)¹. The CCAM volume was calculated as the volume of the lesion using the formula for a prolate ellipse, with measurement of the lung mass in three perpendicular planes. The CVR was obtained by dividing the CCAM volume by the concurrent head circumference to correct for differences in the overall fetal

size and gestational age. Thus, the equation for CVR would be $(\text{length} \times \text{height} \times \text{width}) \times 0.52 / \text{head circumference}$. As no fetal magnetic resonance imaging (MRI) was used in this cohort, all CVRs were calculated from USG data. A qualitative description of the antenatal progress of the lung lesion was also assigned depending on whether the size of the lesions was considered to be progressively enlarging, remained stationary, or regressing.

The outcome of the pregnancy, including any miscarriage, termination of pregnancy, gestational age at delivery, and mode of delivery were also recorded. For all live births, the neonatal records were reviewed to assess the presence or absence of respiratory symptoms of the neonate at birth, chest X-ray (CXR) or thoracic computed tomography (CT) findings, whether any surgery was performed, and the histological diagnosis if resection was done. Indications for referral included patient's preference of hospital for delivery, and the availability of cardiothoracic surgical unit for necessary postnatal operation as recommended by our paediatric surgeons. For patients who did not deliver in our hospital, the neonatal records of the corresponding paediatric unit were reviewed to retrieve the same parameters.

Results

Of a total of 48,619 deliveries, 15 cases of congenital lung lesions were diagnosed during the study period, giving an incidence of 0.03%. The mean gestational age at diagnosis was 21.9 weeks. Both genders were equally affected. There were nine left-sided lesions, five right-sided, and one in the subdiaphragmatic area. Among these 15 cases, 13 were CCAM, and two were BPS (feeding vessels were identified on Doppler USG). Only three of the 15 cases had macrocystic malformations on USG, and the rest had either microcysts or merely lung lesions with increased echogenicity. The median CVR was around 0.62 at the time of diagnosis (range, 0.17-1.70); two cases had CVR of 1.70 (cases 1 and 8; Table 1).

All cases were confirmed to have a normal karyotype: 13 by amniocentesis, one by chorionic villus sampling at 12 weeks before the diagnosis as the subject tested positive for Down syndrome (case 7), while the other had placental tissue karyotyping after termination of pregnancy (case 2). Two of the fetuses were found to have concurrent structural abnormalities, one with a major facial cleft diagnosed antenatally (case 2) and the other had multiple minor abnormalities including a small muscular ventricular septal defect, a hypoplastic thumb, and cervical hemivertebra at C8 level diagnosed postnatally (case 3).

Table 1. Antenatal ultrasound features of congenital lung lesions

	Gestational age at diagnosis (weeks)	Ultrasonography diagnosis	Location of lesion	Maximal CVR	Mediastinal shift / hydrops / effusion	Karyotype	Antenatal progress
1	21	Macrocytic CCAM	Left lung	1.70	Mediastinal shift	Normal	TOP
2	19	Microcystic CCAM	Left lower zone	0.80	Nil	Normal	TOP
		Right cleft lip					
3	31	Microcystic CCAM	Right lower zone	0.25	Nil	Normal	Stable
4	20	Microcystic CCAM	Left lower zone	0.17	Nil	Normal	Regressing Disappeared at 36 weeks
5	23	Microcystic CCAM	Right middle zone	0.18	Nil	Normal	Stable
6	28	Microcystic CCAM	Left lower zone	0.62	Nil	Normal	Stable
7	19	BPS	Left lower zone + sub-diaphragmatic	N/A	Nil	Normal	Regressing
8	19	Microcystic CCAM	Left lower zone	1.70	Nil	Normal	Stable
9	20	Microcystic CCAM	Right upper zone	1.20	Mediastinal shift	Normal	Regressing Not seen in third trimester
10	19	Microcystic CCAM	Right upper / middle zone	0.37	Nil	Normal	Stable
11	28	BPS	Left lower zone	N/A	Nil	Normal	Regressing
12	20	Macrocytic CCAM	Left upper / middle zone	1.50	Mediastinal shift; polyhydramnios	Normal	Progressive
13	20	Macrocytic CCAM	Left middle / lower zone	1.00	Mediastinal shift	Normal	Regressing
14	21	Microcystic CCAM	Right middle / upper zone	0.32	Nil	Normal	Regressing
15	20	Microcystic CCAM	Left upper / middle zone	0.39	Nil	Normal	Regressing

Abbreviations: BPS = bronchopulmonary sequestrations; CCAM = congenital cystic adenomatoid malformation; CVR = CCAM volume ratio; N/A = not available; TOP = termination of pregnancy

Two mothers opted for termination of pregnancy, one of them having gross macrocytic CCAM with mediastinal shift suggestive of poor prognosis at an early gestation age of 21 weeks (case 1), while the other one was diagnosed by antenatal ultrasound to have a fetus with concurrent facial cleft (case 2). In the latter case, joint counselling with paediatricians and paediatric surgeons of our Joint Facial Cleft Team on possible postnatal surgical repair of cleft was made before the couple's decision to terminate the pregnancy. Diagnoses of CCAM and associated structural abnormalities were confirmed on pathological examination of both fetuses after termination of pregnancy.

Serial USG assessments were available in all cases. Seven cases showed regression with advancing gestation; the lesion apparently disappeared on USG in the third

trimester in two cases, while five cases showed stable lesions that remained roughly the same dimensions with advancing gestation. Only one with macrocytic CCAM showed significant increase in size of the lesions in the third trimester (case 12). None of the fetuses had developed hydropic changes. No fetal intervention was required in the antenatal period for any of the ongoing pregnancies (Figure 1).

All of the 13 ongoing pregnancies were carried to term and delivered alive. There was no incidence of perinatal mortality in this series. Of the two fetal lung lesions that showed apparent complete resolution antenatally, case 9 had complete regression of lung lesion as evidenced by postnatal CT scan, while case 4 had BPS diagnosed on postnatal CT scan.

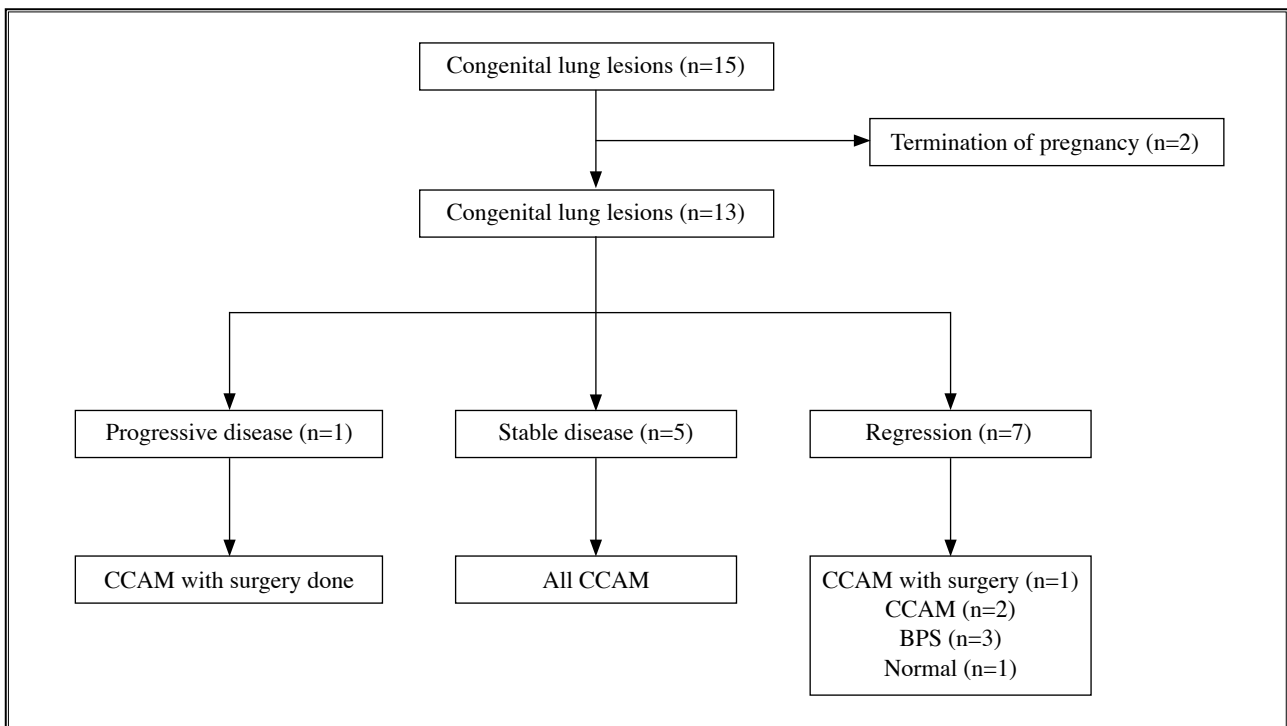


Figure 1. Antenatal course of congenital lung lesions

Abbreviations: BPS = bronchopulmonary sequestrations; CCAM = congenital cystic adenomatoid malformations

All neonates had CXR and CT scan after birth. The CXR was abnormal in eight cases; these also had confirmed abnormalities on CT scan; three cases with normal CXR were subsequently found to have abnormality on CT scan, while the remaining two had unremarkable CXR and CT scans. The sensitivity of CXR was 80%.

After delivery, the baby (case 12) with progressive macrocystic CCAM developed respiratory symptoms on day 4, and subsequently underwent an uneventful surgical excision at 3 weeks of life. Another case with asymptomatic macrocystic lesion had surgical treatment at around 6 weeks after birth (case 13). Both were confirmed to be CCAM on histological examination. All other babies remained asymptomatic after birth and were regularly followed up at the paediatric clinic. The duration of follow-up of these babies ranged from 3 months to 9 years in this cohort. Thus, until the time of this review, only two of the 13 live births had undergone surgery for excision of the lesions with good outcomes (Table 2).

Prenatal sonographic diagnosis of CCAM was made in 13 cases and BPS in two. Postnatally, CCAM was histologically confirmed in both cases of termination of pregnancies. In the remaining 13 pregnancies, two cases (cases 4 and 9) diagnosed as CCAM prenatally were found to be BPS on postnatal CT scans and another case diagnosed

BPS prenatally was found to be normal on postnatal CT scan (case 11). All other cases had consistent antenatal and postnatal diagnoses.

Discussion

From our data, the incidence of congenital lung lesions was estimated to be 0.03%, confirming that this was a rare congenital fetal malformation in Hong Kong. However, this could be an underestimation of the true incidence as data on subsequent postnatal diagnosis in infancy or later childhood of such lesions were not available and were, therefore, not included in this study. On the other hand, there was no good evidence in the literature that further extension of routine morphology scan would improve the detection rate of these lesions.

Antenatal Assessment and Progress

USG with Doppler not only detects lung lesions, but also provides important information about the diagnosis. USG can identify the anatomical location of the lesions and the extent of involvement of the lung lobules, characterise the abnormality, evaluate blood drainage, and determine the severity of changes in thoracic position of other lung lobes, the mediastinum, and cardiac structures. Characteristic USG features of CCAM include single or multiple hyperechoic areas within the thorax. It can be subclassified into micro- and / or macro-cystic types (Figures 2 and 3).

Table 2. Pregnancy outcome and postnatal progress

	Gestational age at delivery (weeks)	Mode of delivery	Symptoms at birth	Diagnosis confirmed after birth / TOP	Chest infection	Postnatal imaging	Surgery	Follow-up period
1	21	TOP	-	CCAM	-	-	-	-
2	20	TOP	-	Right cleft lip and palate CCAM	-	-	-	-
3	40	NSD	Nil	CCAM Hemivertebra Small VSD Hypoplastic right thumb	14 Months	CXR-X CT-X	-	18 Months
4	39	NSD	Nil	BPS	Nil	CXR-N CT-X	Nil	6 Months
5	39	NSD	Nil	CCAM	Nil	CXR-X CT-X	-	14 Months
6	38	LSCS	Nil	CCAM	Nil	CXR-X CT-X	-	6 Months
7	39	LSCS	Nil	BPS	Nil	CXR-N CT-X	Nil	4 Years
8	39	NSD	Nil	CCAM	Nil	CXR-X CT-X	-	6 Months
9	38	NSD	Nil	BPS	Nil	CXR-N CT-X	Nil	5 Years
10	38	NSD	Nil	CCAM	Nil	CXR-X CT-X	-	3 Months
11	41	LSCS	Nil	Normal	Nil	CXR-N CT-N	Nil	32 Months
12	38	LSCS	Yes	CCAM	Nil	CXR-X CT-X	Left upper lobectomy at 3 weeks Pathological CCAM type I	5 Years
13	38	LSCS	Nil	CCAM	Nil	CXR-X CT-X	Left upper lobectomy at 6 weeks Pathological CCAM type II/III	8 Months
14	39	NSD	Nil	CCAM	Nil	CXR-N CT-N	Nil	9 Years
15	39	NSD	Nil	CCAM	Nil	CXR-X CT-X	-	12 Months

Abbreviations: BPS = bronchopulmonary sequestrations; CCAM = congenital cystic adenomatoid malformations; CT = computed tomography; CXR = chest X-ray; LSCS = lower (uterine) segment Caesarean section; N = normal findings on imaging; NSD = normal spontaneous delivery; TOP = termination of pregnancy; VSD = ventricular septal defect; X = abnormal finding on imaging

BPS may appear similar to CCAM on USG, but it can be differentiated by its blood supply directly from the descending aorta using colour Doppler techniques. Different lesions may have variable natural history and prognosis. In general, it was found that microcystic lesion, bilateral lung involvement, and hydrops were each highly correlated with poor prognosis⁴. Hence, correct diagnosis is essential for

counselling and formulating management plan.

All cases were followed up at our department every 2 to 4 weeks to assess the progress of the lesion including measurement of CVR. The CVR was shown to correlate strongly with the development of fetal hydrops¹. Crombleholme et al⁵ reported that CVR of >1.6 predicted



Figure 2. Ultrasonographic findings of macrocystic congenital cystic adenomatoid malformations in the right middle and lower zones with mediastinal shift at 21 weeks with termination of pregnancy (case 1)



Figure 3. Ultrasonographic findings of microcystic congenital cystic adenomatoid malformations with mediastinal shift in right upper zone at 23 weeks of gestation (case 9)

an increased risk of hydrops and correlated with a poor outcome, with only 53% survival rate; whereas a ratio of <1.6 suggested $<3\%$ risk of hydrops, in the absence of a dominant cyst. In one fetus with CVR of >1.7 , the couple opted for termination of pregnancy due to the sonographic evidence of mediastinal compression and predicted high risk of hydrops (case 1; Figure 2). However, while the CVR could be used as a prognostic indicator, other clinical and USG features need to be taken into account. Thus, in our protocol, we refrained from using a specific cut-off for CVR above which termination of pregnancy would be offered.

Theoretically, 3-dimensional USG should aid the measurement of lung mass volume as it permits visualisation of a complex-shaped mass and calculation of its absolute volume. It can also measure contralateral lung

volume which correlates with clinical and postmortem findings⁶. However, skills and training are required before using it routinely in the obstetric department. In addition, prenatal MRI has been reported to be useful in identifying and refining the diagnosis of lung lesions. It can accurately differentiate congenital diaphragmatic hernia, CCAM, and BPS prenatally⁷. However, this relatively new imaging technique requires substantial cost and experienced radiologists for making diagnoses confidently. In the literature, in-utero regression was associated with isolated hyperechogenicity and improved gestational age at birth⁸. In our series, two (15%) of the lung lesions resolved on serial USG. In-utero regression was reported to be up to 18-19% in other retrospective studies^{9,10}.

While the incidence of chromosomal abnormalities associated with CCAM or BPS was low, associations with recombinant chromosome 18 and trisomy 13 have occasionally been reported^{11,12}. We, therefore, continued to offer karyotyping to all diagnosed cases. Associated structural anomalies were reported to be around 18%, and included deformations such as renal agenesis and cardiac anomalies². In our series, all 15 cases carried normal karyotype and there were two cases with concurrent structural abnormalities, amounting to around 13%.

Antenatal Treatment Modalities

The overall reported prognosis of fetal lung lesions was generally good. If the lung lesion remained small and there were no hydropic features, expectant management till spontaneous onset of labour and postnatal evaluation were advocated. Evidence of fetal hydrops usually necessitates fetal intervention as it is a predictor of fetal demise. In

a large retrospective study of 101 fetuses with CCAM followed up expectantly, all 25 hydropic fetuses died¹³. In another series of 180 fetuses with large cystic lung masses, 97% of the untreated hydropic fetuses died¹⁴.

There is no universal guideline for fetal intervention with congenital lung lesions. A number of interventions had been reported^{13,14}. In general, management depends upon the gestational age. If there are hydropic changes after 28 to 32 weeks of gestation, one might consider maternal betamethasone, early delivery, and possible ex-utero intrapartum therapy and immediate postnatal resection of the lung lesion. Prenatal maternal betamethasone is associated with resolution of the hydropic changes, thus allowing the pregnancy to progress to full term, and birth of babies free of respiratory symptoms, with overall improved survival¹⁵. Steroids were particularly effective in predominantly microcystic lesions and were associated with decrease in CVR in 61.5%, resolution of hydrops in 77.8%, and survival to discharge in 84.6% of the cases¹⁶. However, unexpected intrauterine death has been reported after resolution of hydrops following betamethasone therapy¹⁷.

If hydrops occurs before 28 to 32 weeks of gestation, different interventions are proposed. Large macrocystic CCAM responds favourably to placement of thoracoamniotic shunts^{3,18,19}. However, it may be complicated by chest deformity if shunting is performed at early gestational age²⁰. Open fetal surgery has been described for fetuses with predominantly solid or multicystic lung lesions. Fetal lobectomy can be performed through a thoracotomy wound which heals in utero without leaving a scar. However, this procedure is associated with high mortality and requires special expertise with in-utero fetal surgery²¹. Successful sclerotherapy of abnormal feeding vessels or laser ablation have also been reported as alternative treatments^{22,23}. However, while the lesion might shrink after laser ablation, hydrops might deteriorate and lead to fetal death²⁴. The overall survival rates of thoracoamniotic shunt are up to 68% in hydropic and 87.5% in non-hydropic fetuses²⁵. In this series, no specific antenatal treatment was offered as none of the ongoing pregnancies developed hydropic changes.

Postnatal Management

Antenatal resolution of CCAM is often incomplete, hence it is recommended that all babies undergo postnatal CT scan, irrespective of the degree of antenatal regression of the congenital lung lesions²⁶. Our data supported this recommendation, as postnatal CXR and CT abnormalities

persisted even in cases with resolution of the lesions on antenatal USG. Our data demonstrated that both antenatal USG and neonatal CXR were unreliable to confirm complete resolution of CCAM, and illustrated the importance of postnatal follow-up with CT scan.

The severity of congenital lung lesions was apparently milder than in the cases reported in the literature and our outcomes were comparable to those of other fetal centres. Limited by our small number of cases, none of our cases was complicated by hydrops or serious neonatal complication as yet. Retrospective studies^{4,9,10} reported a 2-10% risk of fetal hydrops. A large series reported perinatal mortality of around 10-15%, while symptoms at birth were reported in around 25-44% of the cases.

There is a general consensus that symptomatic CCAM requires surgery. Nonetheless, surgery for asymptomatic CCAM cases remains controversial. Elective excisional surgery is recommended because of the long-term risk of infection, pneumothorax, and malignancy²⁷. The natural course of this lesion into childhood / adulthood is uncertain, making precise risk prediction difficult. In our series, only one out of 12 asymptomatic cases had prophylactic surgery against subsequent infection. However, as many of the babies are still in their infancy, longer follow-up will be required to observe the progress of these lesions, and subsequent surgical treatment might still be necessary for some of these babies at an older age.

There were certain limitations to the current study. The paucity of clinically significant congenital lung lesions limited the sample size of this cohort to only 15 cases despite a study period of 10 years. Thus, it could be argued that the cases analysed do not represent the typical clinical progress and outcomes of these pregnancies. In addition, as all data were collected retrospectively, measurements from serial USG follow-up were not documented in full in a few cases, and follow-up intervals were not entirely regular in some patients. Nevertheless, we believe that the overall findings of this small cohort were compatible with those from the current literature.

Conclusion

Our local experience confirmed that congenital fetal lung lesions were uncommon; most cases had good outcome and did not require any antenatal intervention. The spectrum of severity encountered was apparently milder than what is reported in the literature. There was no single indication for offering termination to these pregnancies, though some sonographic findings might suggest poor prognosis,

such as high CVR, mediastinal shift, and hydrops. The final decision should be made after thorough counselling by an integrated obstetric-paediatric team. In the current cohort, most of the babies were born healthy, in whom an elective operation might be considered at a later stage for

prophylaxis against possible complications. If a neonate is symptomatic at birth, referral to a surgeon for intervention is clearly required. It is best for asymptomatic newborns to undergo a CT scan during the neonatal period, even if the lesions appeared to resolve completely on antenatal USG.

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