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Prediction of postnatal outcome in fetuses with congenital lung malformation: 2-year follow-up study

N. C. J. PETERS[1#], A. HIJKOOP[2#], S. M. HERMELIJN[2], M. M. VAN SCHOONHOVEN[2], A. J. EGGINK[1], J. VAN ROSMALEN[3], S. C. M. COCHIUS-DEN OTTER[2], D. TIBBOEL[2], H. IJSSELSTIJN[2], J. M. SCHNATER[2] and T. E. COHEN-OVERBEEK[1]

[1]*Department of Obstetrics and Gynecology, Division of Obstetrics and Fetal Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands;* [2]*Department of Pediatric Surgery and Intensive Care, Erasmus MC – Sophia Children's Hospital, Rotterdam, The Netherlands;* [3]*Department of Biostatistics, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands*

KEYWORDS: congenital lung malformation; congenital pulmonary airway malformation; CPAM; CVR; prenatal counseling; prenatal diagnosis; respiratory support; surgery

CONTRIBUTION

What are the novel findings of this work?
The congenital lung malformation (CLM) volume ratio can predict the need for respiratory support within 24 h after birth and for surgery within 2 years in infants with a prenatal diagnosis of CLM managed mostly conservatively. Prenatal regression of a CLM does not rule out respiratory problems after birth. Approximately 40% of fetuses with a microcystic congenital pulmonary airway malformation are diagnosed after birth with congenital lobar overinflation.

What are the clinical implications of this work?
We propose using a structured ultrasonography report to describe CLM. We present guidance for prenatal counseling on the possible need for surgical intervention, and recommend that fetuses diagnosed with CLM are delivered at a center with pediatric surgical expertise and observed for at least 24 h.

ABSTRACT

Objectives *To identify, in fetuses with a congenital lung malformation (CLM), prenatal predictors of the need for postnatal respiratory support and the need for surgery by calculating the CLM volume ratio (CVR), and to evaluate the concordance between the prenatal appearance and the postnatal type of CLM.*

Methods *This was an analysis of prenatal, perinatal and postnatal data from fetuses diagnosed with a CLM at the Erasmus University Medical Center – Sophia Children's Hospital in Rotterdam, The Netherlands, between January 2007 and December 2016. For all included fetuses, CVR was measured retrospectively on stored ultrasound images obtained at 18 + 1 to 24 + 6 weeks (US1), 25 + 0 to 29 + 6 weeks (US2) and/or 30 + 0 to 35 + 6 weeks' gestation (US3). Postnatal diagnosis of CLM was based on computed tomography or histology. Primary outcomes were the need for respiratory support within 24 h and surgery within 2 years after birth.*

Results *Of the 80 fetuses with a CLM included in this study, 14 (18%) required respiratory support on the first postnatal day, and 17 (21%) required surgery within 2 years. Only the CVR at US2 was predictive of the need for respiratory support, with a cut-off value of 0.39. Four of 16 (25%) fetuses which showed full regression of the CLM prenatally required respiratory support within 24 h after birth. The CVR at US1, US2 and US3 was predictive of surgery within 2 years. Overall, the prenatal appearance of the CLM showed low concordance with the postnatal type. Prenatally suspected microcystic congenital pulmonary airway malformation (CPAM) was shown on computed tomography after birth to be congenital lobar overinflation in 15/35 (43%) cases. Respiratory support within 24 h after birth and surgical resection within 28 days after birth were needed in all cases of macrocystic CPAM.*

Correspondence to: Dr N. C. J. Peters, Department of Obstetrics and Gynecology, Erasmus MC, Room NA-1609, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands (e-mail: n.peters@erasmusmc.nl)

#N.C.J.P. and A.H. contributed equally to this work.

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Conclusions *CVR can predict the need for respiratory support within 24 h after birth and for surgery within 2 years. Regression of a CLM prenatally does not rule out respiratory problems after birth.* © *2020 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Congenital lung malformations (CLMs) comprise a heterogeneous group of anomalies that includes congenital pulmonary airway malformation (CPAM), bronchogenic cyst (BC), bronchopulmonary sequestration (BPS) and congenital lobar overinflation (CLO; formerly known as congenital lobar emphysema)[1]. Since the introduction in The Netherlands, in 2007, of the 20-week fetal anomaly scan, increasingly, CLMs are being detected prenatally[2,3]. The current estimated incidence is 4.2 per 10 000 live births[2]. Multiple prenatal ultrasound parameters have been suggested to predict postnatal outcome of CLM[4–9]. Crombleholme *et al.*[4] found that fetuses with a CLM volume ratio (CVR) > 1.6 have an 80% probability of developing fetal hydrops. An increased CVR has been associated with increased prenatal intervention rates and adverse postnatal outcome[5,6,8,10–13].

The postnatal outcome of a prenatally diagnosed CLM is dependent on the prenatal course and type; a CPAM is asymptomatic after birth in most cases, while CLO is expected to cause more respiratory problems[14]. This information is relevant for perinatal planning (e.g. location of the delivery) and for counseling the parents. Prenatally, it is difficult to establish the type of CLM. As the fetal lungs are not yet aerated, different types of CLM may appear similar on prenatal ultrasound. Furthermore, the prenatal ultrasound classification of CPAM by Adzick *et al.* (i.e. microcystic or macrocystic)[11] differs from the histopathological Stocker classification[15] which is used after birth.

In this study of fetuses with a CLM, we assessed the association between prenatal ultrasound parameters, including the CVR as either a cross-sectional or a repeated measurement, and postnatal outcome. The primary aim was to identify prenatal predictors of the need, due to the CLM, for respiratory support within 24 h after birth, and the need for surgical intervention within 2 years after birth. Secondarily, we evaluated the concordance between the prenatal appearance and the postnatal type of CLM.

METHODS

Study population

This was an analysis of data from fetuses diagnosed with a CLM at the Erasmus University Medical Center – Sophia Children's Hospital in Rotterdam, The Netherlands, between January 2007 and December 2016. We excluded pregnancies that were terminated, fetuses with a bilateral lesion and/or major multiple congenital anomalies and infants who were either lost to follow-up or whose follow-up was incomplete (i.e. computed tomography (CT) scan or histological data not available). The medical ethics review board waived the need for ethical approval because data obtained during routine care were analyzed retrospectively (MEC-2018-1086).

Prenatal parameters

For each fetus, an experienced physician (N.C.J.P.), who was blinded to the postnatal diagnosis and outcome, measured the CVR (as described by Crombleholme *et al.*[4]) retrospectively using stored ultrasound images, when available, from up to three gestational-age (GA) periods, (US1, 18 + 1 to 24 + 6 weeks' gestation; US2, 25 + 0 to 29 + 6 weeks; US3, 30 + 0 to 35 + 6 weeks). We also recorded the type of CLM (i.e. CPAM, BPS or hybrid), presence of mediastinal shift, presence of fetal hydrops, presence of multiple congenital anomalies and whether there had been prenatal intervention (e.g. cyst drainage or polyhydramnios drainage) during these time periods. We determined the type of CLM from the prenatal ultrasound findings. CPAMs were classified as microcystic, macrocystic[11] or mixed-type (i.e. a lesion which was both microcystic and macrocystic). The CLM was classified as BPS when arterial blood supply directly from the systemic arteries (in most cases, the aorta) was visualized. The CLM was classified as hybrid when arterial blood supply from both a systemic artery and the pulmonary arteries was visualized. In cases with multiple measurements of the lesion throughout gestation, we evaluated any regression in the lesion size. Full regression was defined as a lesion not visible on ultrasound at the last prenatal examination (≥ 30 + 0 weeks' gestation). Partial regression was defined as an absolute decrease in lesion area (length × width × height) and/or a decrease of the CVR by at least 0.1, indicating a relative decrease in lesion size.

Perinatal characteristics

Data on delivery mode, GA at delivery, birth weight and 1-min and 5-min Apgar scores were retrieved from patient records. Infants born prior to 37 weeks' gestation were considered preterm. We recorded the need for, cause of and type of respiratory support during the first 24 h after birth (i.e. low flow supplemental oxygen, humidified high flow nasal cannula, continuous positive airway pressure, non-invasive positive pressure ventilation or mechanical ventilation). A pediatric intensivist (S.C.M.C.O.), who was blinded to the prenatal parameters, reviewed the charts and assessed whether the presence of the CLM had been an indication for the need for respiratory support < 24 h after birth.

Postnatal outcome

From patient records, we retrieved information regarding the length of initial hospital stay, duration of respiratory support on the initial hospital stay, presence of chronic lung disease and any surgery, including embolization of

an aberrant artery in case of BPS, within 2 years after birth. We included all outcome data of each infant until the age of 2 years. Chronic lung disease was defined by the administration of oxygen for at least 28 days[16]. During the study period, the hospital protocol was such that only infants who developed symptoms after birth, e.g. respiratory insufficiency, recurrent infection and/or volume overload, were recommended to undergo surgical resection followed by histological evaluation, in most cases after CT imaging. CT imaging in asymptomatic infants was scheduled approximately 6 months after birth. CT scans were carried out according to clinical imaging protocols at that time. We reviewed the scan with the least slice thickness. A trained observer (S.M.H.), experienced in systematic assessment of CT imaging in CLM, assessed all scans independently, blinded to patient data.

The types of CLM were defined as follows. CPAM was defined as cystic abnormality in the absence of systemic arterial blood supply; CPAM type 1 (CPAM-1) was an abnormality with a large dominant cyst, with or without surrounding multiple smaller cysts, and CPAM type 2 (CPAM-2) was a cluster of cysts. BPS was defined as a solid lesion with systemic arterial blood supply. Hybrid was defined as BPS accompanied by adjacent cystic abnormalities (i.e. CPAM/BPS). BC was defined as a (partial) fluid-filled cyst close to the mediastinum. CLO with or without atresia was defined as overinflated, hypodense lung lobes, occasionally exerting a mass effect on adjacent structures. We classified atresia under CLO as it produces the same CT-imaging abnormalities as does CLO, and it may be a component of these lung abnormalities rather than a separate abnormality[17]. CLM was defined as being in regression when there were small remnant lesions or no lesion visible.

If the assessment by S.M.H. conflicted with the radiology report, an independent pediatric radiologist, who was blinded to the patient data, evaluated the findings and consensus was reached by discussion.

Statistical analysis

Data are presented as *n* (%) or median (interquartile range (IQR)), as appropriate. We compared prenatal, perinatal and postnatal characteristics between neonates who received respiratory support within 24 h after birth and those who did not, using chi-square or Fisher's exact test (categorical variables) and the Mann–Whitney *U*-test (continuous variables). Considering the small number of fetuses with a CVR available at US2, we checked for selection bias.

Interobserver agreement was quantified using the intraclass correlation coefficient (ICC). A second senior prenatal physician (T.E.C.-O.) measured the CVR separately in 20 cases, selected randomly. The ICC was calculated in a two-way mixed model, with absolute agreement, and reported as single measures. ICC values between 0.75 and 0.90 were considered to indicate good agreement and values > 0.90 excellent agreement[18].

To calculate the predictive value and optimal cut-off point of CVR for predicting the need for respiratory support within 24 h after birth and the need for surgery within 2 years, we performed a receiver-operating-characteristics (ROC)-curve analysis for each GA period. These data are presented as area under the ROC curve (AUC) with 95% CI. AUC values of 0.7–0.8 were considered acceptable, 0.8–0.9 excellent and > 0.9 outstanding. The cut-off with the highest value of the Youden index (sensitivity + specificity − 1) was regarded as being the most suitable[19].

The trend in lesion size throughout gestation was assessed in terms of the change in absolute size of the lesion as well as the change in CVR between US1 and US3 and/or between US2 and US3, depending on the availability of data. We converted the change in lesion size into a categorical variable as follows: increase in size; stable in size compared with fetal growth; stable in absolute size; decrease in size (both in absolute measurement, independent of fetal growth, and in comparison to fetal growth); visible but not possible to measure in all planes; and not visible on prenatal ultrasound. Mann–Whitney *U*-tests were used to assess the association between the trend in lesion size and postnatal outcome (i.e. respiratory support within 24 h or surgery within 2 years after birth). The Kruskal–Wallis test was used to examine the association between the trend in lesion size and prenatal appearance and/or postnatal diagnosis. Univariable logistic regression analysis was used to examine the predictive value of the trend in lesion size for postnatal outcome (i.e. respiratory support within 24 h or surgery within 2 years after birth).

Multivariable lasso logistic regression analysis was performed using the 'glmnet' package in RStudio (version 1.0.153, RStudio, Inc., Boston, MA, USA). Lasso regression is a form of penalized regression, in which coefficients with unimportant terms are driven to zero[20]. This method was used as a variable selection tool to assess the predictive ability of prenatal ultrasound measurements when adjusting for all other parameters and to account for multicollinearity. The lasso logistic regression was performed to identify predictors for respiratory insufficiency within 24 h or surgery within 2 years after birth. The following prenatal parameters were included in the model: CVR at US1 and at US3, presence of mediastinal shift, location of CLM, type of CLM, presence of a systemic artery and prenatal regression of the lesion, measured as the difference in CVR and difference in lesion area between US1 and US3. The parameters at US2 were missing for a substantial number of cases and therefore were not added to the model. The penalization parameter lambda of the lasso regression was chosen using 10-fold cross-validation and the lambda with the minimum mean cross-validated error was used. Some coefficients were thus shrunk to be exactly zero, leaving a sparse subset of variables with non-zero regression coefficients. Statistical analysis was performed using SPSS (version 25, IBM Corp., Armonk, NY, USA) and RStudio.

RESULTS

Of 103 fetuses diagnosed with CLM between January 2007 and December 2016, there were 80 (78%) eligible for inclusion in this study (Figure S1). Their prenatal and postnatal characteristics are summarized in Figure 1 and Table 1. The postnatal type of CLM was based on CT imaging in 64 (80%) infants and on both CT imaging and histological examination in 16 (20%) infants. In 13 (16%) cases, there was a discrepancy between the assessment of the infant's CT scan by S.M.H. and the radiology report. In three cases, prenatal intervention was performed: in two cases with a macrocystic CPAM, one of which was complicated with hydrops, the cyst was drained; and one case with a microcystic CPAM and severe polyhydramnios underwent amniotic fluid drainage. The CVR was calculated for 70 fetuses at US1, 54 at US2 and 76 at US3. The bias analysis demonstrated that the primary outcomes for the fetuses with a measurement at US2 did not differ significantly from those in fetuses without a measurement at US2 (data not shown). Multiple (i.e. at least two) CVR measurements were available for 74 (93%) fetuses. The median GA at US3 was statistically significantly higher in fetuses which required respiratory support after birth compared with those that did not, which could be ascribed to late referral of cases with a possible need for extracorporeal membrane oxygenation. The median CVR of the six fetuses without multiple measurements (which had a CVR measurement only at US3) was significantly higher than the CVR at US3 of the fetuses with multiple measurements ($P < 0.001$). The median CVRs at US1 and at US2 both differed significantly from that at US3 ($P < 0.001$), showing an overall decrease after $30 + 0$ weeks' gestation. The

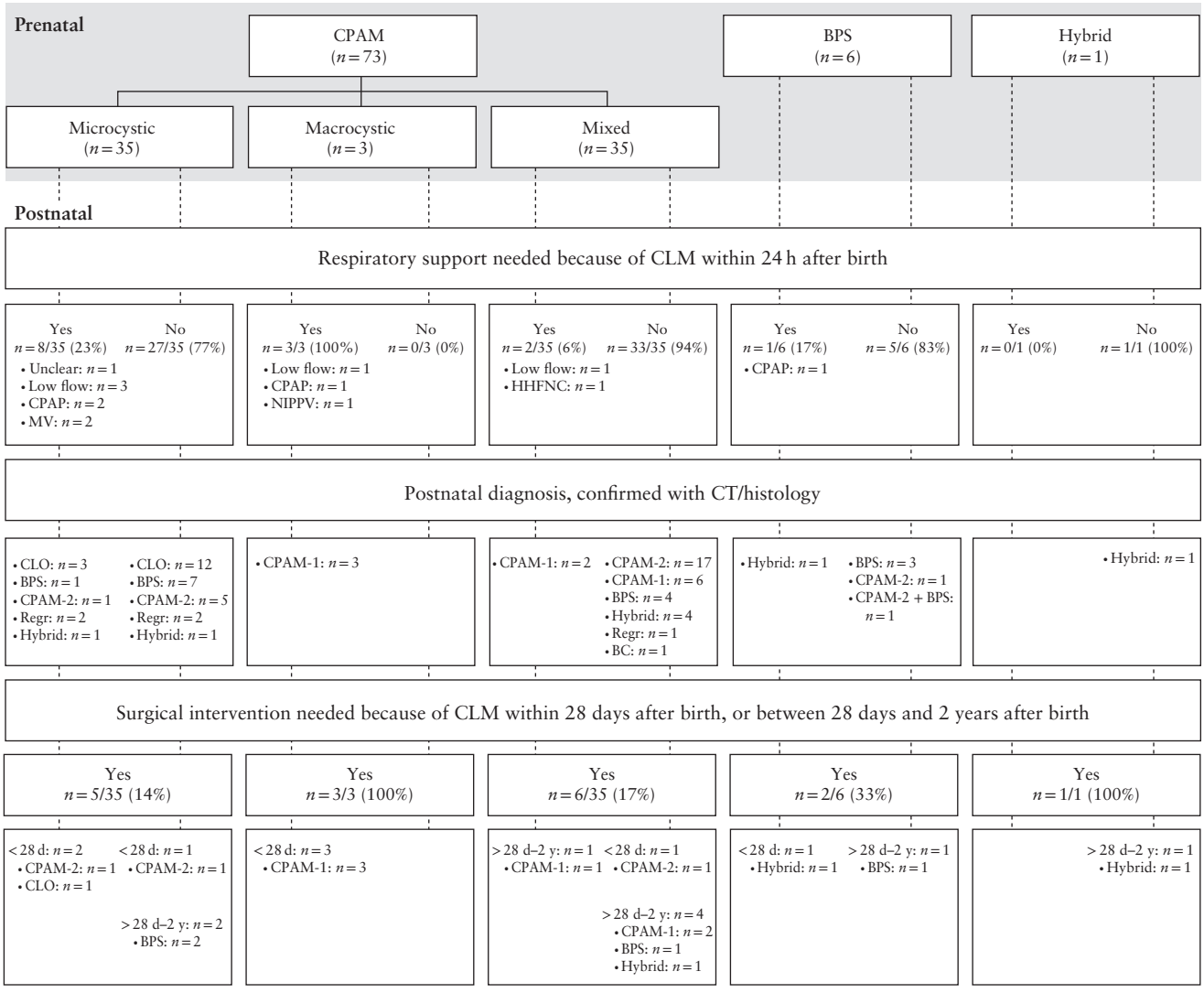

Figure 1 Flowchart presenting the need for respiratory support, postnatal diagnosis and need for surgery in 80 infants diagnosed prenatally with congenital lung malformation (CLM), stratified according to prenatal classification on prenatal ultrasound. BC, bronchogenic cyst; BPS, bronchopulmonary sequestration; CLO, congenital lobar overinflation; CPAM, congenital pulmonary airway malformation (prenatal classification according to Adzick *et al.*[11]; postnatal classification as follows: postnatal CPAM type 1: large dominant cyst, with or without surrounding multiple smaller cysts; postnatal CPAM type 2: cluster of cysts); CPAP, continuous positive airway pressure; CT, computed tomography; d, days; HHFNC, humidified high flow nasal cannula; MV, mechanical ventilation; NIPPV, non-invasive positive pressure ventilation; regr, regression; y, years.

Table 1 Pre- and postnatal characteristics of 80 infants diagnosed prenatally with congenital lung malformation (CLM), stratified according to need for respiratory support < 24 h after birth

	No respiratory support (n = 66)		*Respiratory support** (n = 14)		
Characteristic	n	*Value*	n	*Value*	P
Prenatal characteristics					
US1: 18 + 1 to 24 + 6 weeks (*n* = 70)					
GA (weeks)	60	21 + 2 (20 + 5 to 22 + 0)	10	21 + 4 (20 + 6 to 22 + 0)	0.76
CVR	60	0.40 (0.20–0.58)	10	0.57 (0.23–0.80)	0.31
Mediastinal shift	60	25 (42)	10	5 (50)	0.63
US2: 25 + 0 to 29 + 6 weeks (*n* = 55)					
GA (weeks)	46	26 + 4 (26 + 1 to 27 + 2)	9	28 + 0 (26 + 4 to 28 + 2)	0.16
CVR	45	0.34 (0.20–0.70)	9	0.81 (0.43–1.74)	0.04††
Mediastinal shift	46	17 (37)	9	6 (67)	0.14
US3: 30 + 0 to 35 + 6 weeks (*n* = 80)					
GA (weeks)	66	31 + 5 (30 + 5 to 32 + 2)	14	32 + 4 (31 + 6 to 33 + 6)	0.001††
CVR†	62	0.17 (0.03–0.33)	14	0.65 (0.00–1.34)‡‡	0.08
Mediastinal shift	66	8 (12)	14	4 (29)	0.21
Hydrops	66	0 (0)	14	2 (14)	0.03††
Isolated CLM‡	66	64 (97)	14	13 (93)	0.44
Prenatal diagnosis	66		14		0.90
CPAM		60 (91)		13 (93)	
Microcystic		27/60 (45)		8/13 (62)	
Mixed		33/60 (55)		2/13 (15)	
Macrocystic		0 (0)		3/13 (23)	
BPS		5 (8)		1 (7)	
Hybrid		1 (2)		0 (0)	
Side of lesion (left)	66	29 (44)	14	8 (57)	0.39
Multiple CVR measurements	66	63 (95)	14	11 (79)	0.06
CLM in regression	63	42 (67)	11	6 (55)	
Partial regression		30/63 (48)		2/11 (18)	0.17
Full regression		12/63 (19)		4/11 (36)	0.24
Postnatal characteristics					
GA at delivery (weeks)	66	39 + 2 (38 + 4 to 40 + 4)	14	39 + 1 (38 + 2 to 40 + 6)	0.85
SVD	66	58 (88)	14	11 (79)	0.23
5-min Apgar score	66	10 (9–10)	14	8 (7–9)	< 0.001††
Birth weight (g)	66	3340 (3133–3643)	14	3422 (2989–3958)	0.80
Female gender	66	32 (48)	14	6 (43)	0.84
Isolated CLM‡	66	61 (92)	14	12 (86)	0.60
Surgical intervention < 2 years of age	66	10 (15)	14	7 (50)	0.008††
Age at surgical intervention (days)	10	102 (25–271)	7	19 (7–29)	0.03††
Length of initial hospital stay (days)	66	2 (2–3)	12	7 (4–18)	< 0.001††
Chronic lung disease§	66	0 (0)	14	3 (21)	0.004††
Postnatal diagnosis	66		14		0.08
CPAM-1		6 (9)		5 (36)	
CPAM-2¶		23 (35)		1 (7)	
BPS**		14 (21)		1 (7)	
Hybrid		6 (9)		2 (14)	
CPAM-2 and BPS		1 (2)		0 (0)	
CLO		12 (18)		3 (21)	
Bronchogenic cyst		1 (2)		0 (0)	
In regression		3 (5)		2 (14)	

Data are presented as median (interquartile range (IQR)), *n* (%) or *n*/*N* (%). *Type of respiratory support: low flow supplemental oxygen (*n* = 5; 1 L; fraction of inspired oxygen (FiO_2), 21–60%), humidified high flow nasal cannula (*n* = 1; 4.5 L; FiO_2, 100%), continuous positive airway pressure (*n* = 4; positive end-expiratory pressure (PEEP), 5 or 6 cmH_2O; FiO_2, 21–40%), non-invasive positive pressure ventilation (*n* = 1; 5 above PEEP 6; FiO2, 40%), mechanical ventilation (*n* = 2; 16 or 19 above PEEP 6; FiO_2, 95% or 100%), unclear (*n* = 1; required respiratory support for only a few minutes during transportation (FiO_2, 30%)). †Cases with full regression had CVR = 0. ‡Non-isolated cases prenatally: Klinefelter mosaicism (*n* = 1), unilateral hydronephrosis (*n* = 2); postnatally: Klinefelter mosaicism (*n* = 1), unilateral hydronephrosis (*n* = 1), laryngeal cyst (*n* = 1), anorectal malformation (*n* = 1), atrial septal defect type 2 (*n* = 1), bicuspid aortic valve (*n* = 1), agenesis of the right middle lobe (*n* = 1). §Chronic lung disease was defined as oxygen dependency at day 28 postpartum[16]. ¶Including cases of CPAM-2 alone, not those which also had BPS. **Including cases of BPS alone, not those which also had CPAM-2. ††Statistically significant difference. ‡‡Lower value in IQR is zero as a result of rounding to two decimal places. BPS, bronchopulmonary sequestration; CLO, congenital lobar overinflation; CPAM, congenital pulmonary airway malformation (type 1: large dominant cyst, optionally surrounded by multiple smaller cysts; type 2: cluster of cysts); CVR, CLM volume ratio; GA, gestational age; SVD, spontaneous vaginal delivery; US, ultrasound.

interobserver agreement calculation gave an ICC of 0.891 (95% CI, 0.751–0.955), representing good agreement.

Need for respiratory support within 24 h after birth

Within 24 h after birth, in 14 (18%) infants, respiratory support was required that was most likely on account of the CLM (Table 1, Figure 1). The type of respiratory support was unclear for one infant, who required this for only a few minutes during transportation to the ward in the incubator. Details of the respiratory support are given in the footnote of Table 1. The median duration of respiratory support was 3 (IQR, 1–22; range, 1–387) days. No infant required extracorporeal membrane oxygenation. Only one (2%) infant who did not need respiratory support within 24 h developed respiratory distress within the first 28 days after birth due to the CLM. Of the 14 infants who needed respiratory support within 24 h after birth, 50% ($n = 7$) required surgery within 2 years, compared with 15% (10/66) of the infants without need of respiratory support ($P = 0.008$).

The CVR at US2 in the group of infants who required respiratory support within 24 h after birth was significantly higher than that in those who did not ($P = 0.04$, Table 1, Figure 2), while, at US1 and US3, the difference in CVR between these two groups did not reach significance ($P = 0.31$ and $P = 0.08$, respectively). Univariable logistic regression analysis revealed a positive association between the CVR at US2 and respiratory support within 24 h after birth (odds ratio (OR), 4.06 (95% CI, 1.21–13.61), $P = 0.02$) as well as between the CVR at US3 and respiratory support within 24 h after birth (OR, 3.51 (95% CI, 1.23–10.02), $P = 0.02$).

ROC-curve analyses demonstrated acceptable accuracy (AUC, 0.72) for CVR at US2 in the prediction of the need for respiratory support within 24 h after birth, with an optimal cut-off value of 0.39 (sensitivity, 89%; specificity, 58%). At US1 and US3, the ROC-curve analyses demonstrated low accuracy for CVR in prediction of the need for respiratory support (Table S1, Figure S2).

Of the 74 fetuses with multiple CVR measurements, 48 (65%) showed regression in size of the CLM. In 15 of the 16 (94%) fetuses which showed full regression on prenatal ultrasound from 30 + 0 weeks' gestation onwards, the CLM was visible on CT imaging after birth. In 11 of these 16 cases, the lesion was either BPS ($n = 6$) or CLO ($n = 5$) (Figure S3). Prenatal regression of the CLM, either partial or full, was not associated significantly with the need for respiratory support (OR, 0.60 (95% CI, 0.16–2.20), $P = 0.44$); four of the 16 (25%) fetuses which showed full regression of the lesion on prenatal ultrasound required respiratory support, two because of a bilateral pneumothorax (postnatal diagnosis: BPS in one and CLO in the other). Seven fetuses showed an increase in lesion size as gestation progressed; two (29%) of these, one with a mixed-type and one with a macrocystic CPAM, required respiratory support after birth. None of these seven cases had prenatal intervention. In these seven cases, no significant difference was found in CVR at US1, US2 or US3 between those which required respiratory support and those which did not ($P = 0.27$, $P = 0.80$ and $P = 1.00$, respectively). In the other 19 cases, the CLM remained stable in absolute or relative size.

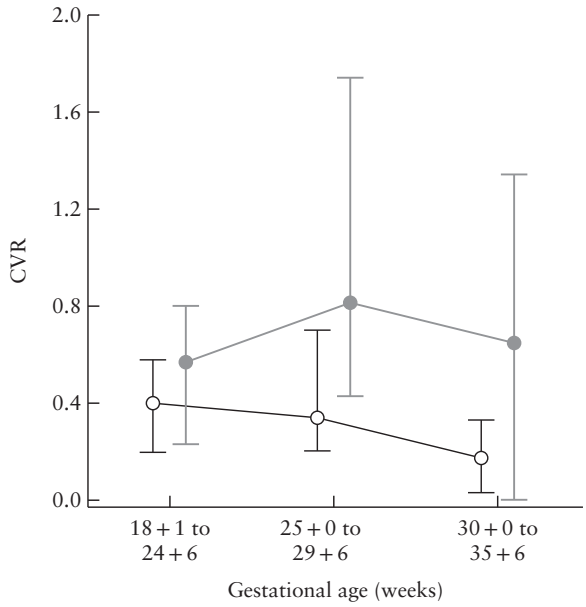

Figure 2 Plots of congenital lung malformation volume ratio (CVR) at three periods in gestation, in fetuses which required respiratory support within 24 h after birth (—●—) and in those which did not (—○—). Median and interquartile range are plotted.

The multivariable lasso regression analysis revealed that only CVR measured at US3 predicted the need for respiratory support within 24 h after birth. Other prenatal parameters, including CVR at US1, presence of mediastinal shift, location of CLM, type of CLM, presence of a systemic artery and prenatal regression of the lesion, were not found to be good predictors for this outcome.

Surgical intervention within 2 years after birth

Seventeen (21%) infants required surgical intervention within 2 years after birth, eight of these requiring it within 28 days (Figure 1). Histological data were available for 16 of the 17 (94%) infants whose CLM was resected. One infant with an intralobar BPS underwent embolization of the aberrant artery at the age of 6 months because of cardiac failure. Features of malignancy (i.e. adenocarcinoma) were found in one case. Histological data from this case were consistent with CPAM-2; semiannual follow-up of this infant is ongoing. At the last follow-up visit, 2 years after the resection, the infant showed neither symptoms nor signs of malignant recurrence on magnetic resonance imaging. Some of the infants required surgery after the 2-year follow-up period for this study; to date, the upper age limit for this is 6 years (data not shown).

ROC-curve analysis at US3 showed that the CVR predicted with excellent reliability the need for surgical intervention within 2 years after birth, with an optimal

cut-off value of 0.46 (AUC, 0.86; sensitivity, 71%; specificity, 90% (Table S1, Figure S4)). ROC-curve analysis at US1 and US2 showed that the CVR predicted only acceptably the need for surgical intervention, at an optimal cut-off value of 0.64 at US1 (AUC, 0.72; sensitivity, 60%; specificity, 83%) and 0.80 at US2 (AUC, 0.77; sensitivity, 70%; specificity, 82%). We designed a counseling flowchart (Figure 3) for prediction of the need for surgery within 28 days after birth, based on the prenatal appearance of the CLM and the CVR at US3 in the 76 fetuses with this measurement. Cut-offs for the CVR at US3 were based on ROC-curve analysis (AUC, 0.98 (95% CI, 0.93–1.00), $P < 0.001$). Eight infants underwent surgery within 28 days, all due to respiratory insufficiency. These included all seven infants with either a macrocystic CPAM or a CVR > 1.46. The remaining infant, with a CVR of 0.57, showed a hybrid lesion both on prenatal ultrasound and postnatal CT imaging. None of the infants with a CVR < 0.57 ($n = 60$) required surgery within 28 days after birth; these all had different types of CLM. Nine of the 68 (13%) infants who did not require surgery within 28 days after birth underwent surgery after this point but within 2 years (range, 42–433 days). Three of these had respiratory insufficiency due to CPAM-1 ($n = 2$) or a hybrid lesion ($n = 1$). Three other infants had cardiac failure because of a BPS, and one underwent surgery because of increasing size of a CPAM-1. In two cases (one hybrid and one BPS), the indication for surgery was unclear from the patient records.

Regression of the CLM on prenatal ultrasound, either partial or full, was not significantly associated with the need for surgery (OR, 0.48 (95% CI, 0.14–1.66), $P = 0.25$). One of 16 (6%) infants whose CLM was not visible at US3 required surgical resection of an extralobar BPS. Of the seven fetuses with increasing lesion size, four (57%) underwent surgery within 2 years after birth. In these seven cases, the CVR at each of US1, US2 and US3 did not differ significantly between the four who underwent surgery and the three who did not (data not shown).

The multivariable lasso regression analysis found the CVR measured at US3 and the presence of mediastinal shift at both US1 and US3 to be predictors of the need for surgery within 2 years after birth (OR, 1.19 and 2.12, respectively). Other prenatal parameters, including CVR at US1, location of CLM, type of CLM, presence of a systemic artery and prenatal regression of the lesion, were not found to be good predictors for this outcome.

Concordance between prenatal appearance and postnatal type of CLM

Concordance between prenatal appearance and postnatal type of CLM is presented in Figures 1 and S3,

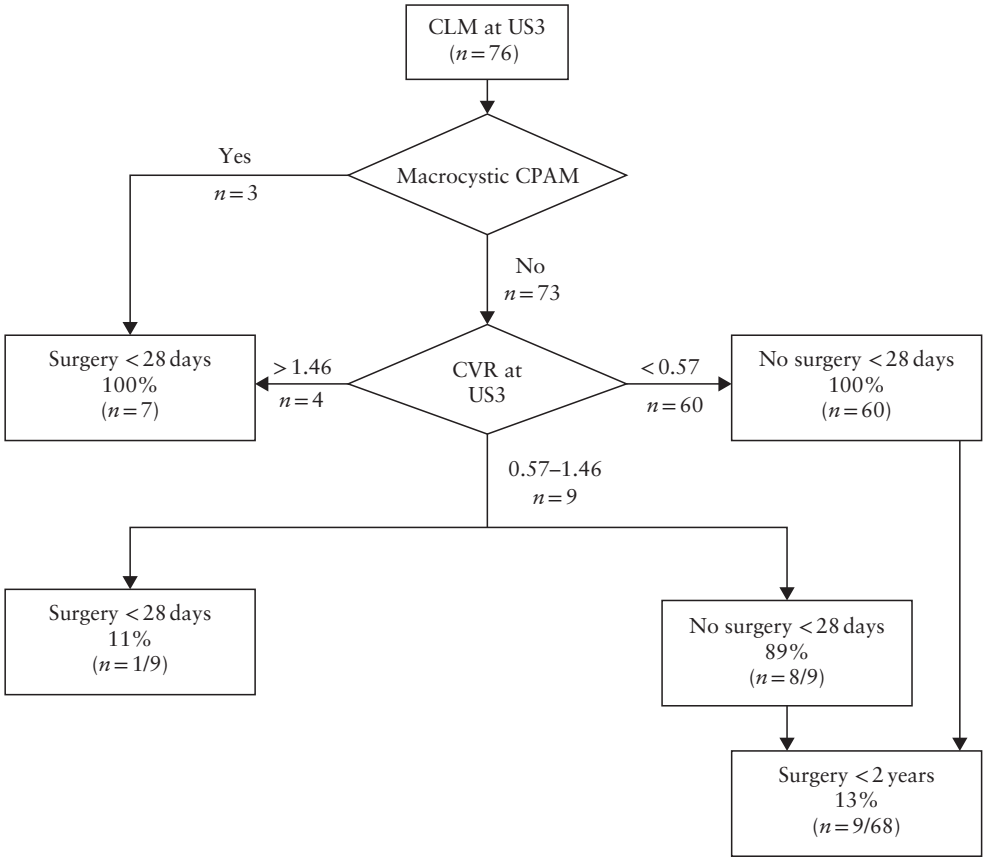

Figure 3 Counseling flowchart for the need for surgery after birth, according to prenatal type of congenital lung malformation (CLM) and CLM volume ratio (CVR) at 30 + 0 to 35 + 6 weeks' gestation (US3). Cut-offs are based on receiver-operating-characteristics-curve analysis. CPAM, congenital pulmonary airway malformation.

Structured ultrasonography report for Congenital Lung Malformations

Gestational age: **weeks** **days**

Isolated finding

☐ Yes ☐ No: Invasive testing? ☐ Yes ☐ No

Result invasive testing:

Fetal growth parameters

☐ <p10 ☐ p10-90 ☐ >p90

Head circumference: cm

Presence of hydrops

☐ Yes ☐ No

A. Description of fetal thorax

Location

☐ Left ☐ Right ☐ Bilateral ☐ Mediastinum

	RUL	RML	RLL	LUL	LLL
Extent					

RUL: Right Upper Lobe *LUL: Left Upper Lobe*

RML: Right Middle Lobe *LLL: Left Lower Lobe*

RLL: Right Lower Lobe

Normal lung tissue visible

☐ Only contralateral

☐ Both ipsilateral as well as contralateral

☐ None

Mediastinal shift

☐ Yes ☐ No

B. Description of CLM

Appearance

☐ Microcystic ☐ Macrocystic ☐ Mixed

Presence of a dominant cyst?

☐ No ☐ Yes

Size of largest cyst: x x mm

Size

AP cm

T cm

H cm

CVR:

$$\text{CLM Volume Ratio (CVR)} = \frac{\text{Volume CLM (AP} \times \text{T} \times \text{H)} \times 0.52}{\text{Head circumference (HC)}}$$

C. Border

☐ Well-defined ☐ Ill-defined

D. Vascularization

Arterial

☐ From pulmonary artery

☐ From systemic artery:

Venous

☐ Normal pulmonary

☐ Aberrant:

Remarks:

Figure 4 Our structured ultrasonography report for prenatal assessment of congenital lung malformations (CLM). AP, anteroposterior diameter; H, height; p, percentile; T, transverse diameter. See full-size, downloadable version online (Appendix S1).

and examples of prenatal appearance at ultrasound and corresponding postnatal CT images are given in Figure S5.

In five of the six (83%) fetuses identified as having BPS on prenatal ultrasound, postnatal CT imaging showed arterial blood supply from the aorta. Three (60%) of these five infants were subsequently diagnosed with BPS, one (20%) with a hybrid lesion and one (20%) with a BPS in one lung and CPAM-2 in the other lung; in this case, the CPAM was not visible on prenatal ultrasound. The sixth infant with BPS on prenatal ultrasound was diagnosed with CPAM-2; no systemic arterial blood supply was seen on CT imaging. The one case diagnosed prenatally with a hybrid lesion was confirmed after birth.

Prenatal description of the CLMs varied between ultrasonographers. To prevent variation in future, we devised a structured ultrasonography report for prenatal assessment of CLM, according to the Adzick criteria (Figure 4 and Appendix S1).

DISCUSSION

In this cohort of fetuses with CLM, a CVR > 0.39 at US2 (25 + 0 to 29 + 6 weeks) predicted the need for respiratory support within 24 h after birth. A CVR > 0.64 at US1 (18 + 1 to 24 + 6 weeks), > 0.80 at US2 (25 + 0 to 29 + 6 weeks) or > 0.46 at US3 (30 + 0 to 35 + 6 weeks) and a persisting mediastinal shift beyond 30 weeks' gestation were associated with the need for surgery within 2 years after birth. There was low concordance between the prenatal appearance at ultrasound and the postnatal diagnosis of a CLM, especially in cases with a prenatal mixed-type or microcystic CPAM.

In agreement with previous research[21], we found that in some cases with a lesion that seemingly regressed fully prenatally, it was still visible on postnatal CT imaging. In fact, two of the fetuses in our study whose CLM had apparently regressed fully prenatally presented with bilateral pneumothorax after birth. We hypothesize that this may have been caused by air trapped in the aberrant bronchial tree, potentially due to increased vulnerability of the lungs following air entry after birth. It is recommended, however, to explore this supposition further.

Previous research has suggested that a CVR > 0.84[22] or > 1.0[23] is a reliable predictor of the risk of respiratory morbidity and the need for surgical intervention. The authors, therefore, recommended delivering these fetuses at a tertiary care center with pediatric surgical expertise[22–24]. Similarly, we found a higher CVR in infants who required respiratory support or surgical intervention compared with those who did not. However, since the risk of respiratory morbidity after birth could not be predicted reliably by prenatal parameters (i.e. lesion size, CVR and/or lesion type), we recommend that all fetuses with a CLM are delivered at a center with pediatric surgical expertise and admitted for observation for at least 24 h after birth.

Approximately 80% of infants in our study did not require a surgical resection; therefore, their prenatal ultrasound findings were compared with postnatal CT imaging instead of histological evaluation. A previous study in 103 infants whose CLM was surgically resected showed that CT imaging had a concordance rate of 84% with the histological diagnosis of CPAM, and a concordance rate of 90% for the detection of a feeding vessel[25]. Diagnosis on postnatal CT is considered to be the gold standard in the absence of histological findings. However, no conclusions can be drawn regarding the risk of malignant transformation.

Previous studies[9,25,26] have attempted to classify CLMs prenatally according to postnatal classification guidelines, such as the Stocker criteria[15,27]. In our study, the type of CLM could not be determined based on prenatal assessment of the lesion. In particular, in the prenatal microcystic or mixed-type CPAM cases, various diagnoses were established after birth. This could have been due to the retrospective nature of the prenatal assessment of the lesion and to the fact that small systemic vessels and/or small lesions may be missed[28]. We therefore propose using a standardized description of lung lesions according to their ultrasound characteristics (Figure 4 and Appendix S1), i.e. describing them as hyperechogenic, hypoechogenic or mixed, and noting whether the arterial blood supply derives from the systemic or the pulmonary arteries. The type of CLM should then be determined after postnatal CT imaging and the timing of follow-up based on clinical symptoms and CT-scan findings. The timing of CT imaging is dependent on the chosen management modality, but is preferably performed after the neonatal stage, in order to improve resolution and eliminate possible artifacts caused by retained fetal lung fluid. Since some infants required surgery after the formal 2-year follow-up period, we recommend offering prolonged follow-up by a specialized team to all newborns presenting with a CLM; this is already standard practice in our center.

CLO is associated with a higher incidence of respiratory problems than are other CLM types, but is diagnosed more rarely than the other CLMs, both before and after birth[14,29]. In a previous multicenter consortium study, 10% of infants born with a CLM were diagnosed postnatally with CLO. Although 40% of these infants were asymptomatic after birth, they were almost three times as likely to present with respiratory distress as compared with infants with other types of CLM[29]. In our study, 19% of cases had a postnatal diagnosis of CLO, and 80% of these infants remained asymptomatic. We hypothesize that this discrepancy between our findings and those of previous studies may be explained by our inclusion of only prenatal cases rather than prenatal as well as postnatal cases. As CLO is easily distinguishable from other types of CLM on postnatal CT imaging, this discrepancy is likely not the result of inaccurate postnatal diagnosis. CLO may, however, be missed more easily on prenatal ultrasound than are other types of CLM, due to the subtlety of the increase in echogenicity[29,30]. Therefore,

with more being undetected prenatally, the proportion of symptomatic infants diagnosed with CLO only after birth may be relatively high compared with other types of CLM, and the proportion of asymptomatic infants with CLO may appear relatively low, as these asymptomatic infants remain undetected. As a result, CLO is regarded as being rare, with a high incidence of respiratory problems. When counseling parents following a prenatal diagnosis of any type of CLM, clinicians should focus on findings in the corresponding group diagnosed prenatally and not on such cases diagnosed solely postnatally. In line with our findings, Kunisaki *et al.*[29] reported that infants diagnosed prenatally with CLO were no more likely to be symptomatic at birth than were those with other types of CLM.

Conclusion

A CVR ≤ 0.39 at US2 ($25+0$ to $29+6$ weeks) predicts a low probability of the need for respiratory support within 24 h after birth, but does not rule out respiratory problems after birth. We therefore recommend that all fetuses with a CLM diagnosed prenatally are delivered at a center with pediatric surgical expertise and admitted for observation for at least 24 h. Newborns who do not show respiratory distress within 24 h can be discharged home safely, as the possibility of their developing acute respiratory distress after this period seems low. The need for surgery within 2 years after birth can be counseled according to the flowchart in Figure 3; in addition, a CVR < 0.57 without mediastinal shift at US3 predicts a low probability of the need for surgery within 2 years after birth. Low concordance was found between prenatal appearance at ultrasound and postnatal diagnosis of type of CLM. Yet, all three infants with a macrocystic CPAM on prenatal ultrasound showed a CPAM-1 on CT imaging and needed respiratory support within 24 h after birth and surgical resection within 28 days after birth. Microcystic CPAM on prenatal ultrasound proved to be CLO after birth in almost half of the cases. We propose prenatal description of CLMs according to their ultrasound characteristics. All infants with a prenatal diagnosis of a CLM should be offered postnatal CT imaging and prolonged follow-up by a specialized team, regardless of the lesion size or appearance on prenatal ultrasound.

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P. Ciet, an independent pediatric radiologist, evaluated discrepancies between the assessments of S.M.H. and the radiology report in the patient records in order to achieve consensus. K. Hagoort provided editorial advice. G. Eggenhuizen edited the images for publication.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Appendix S1 Downloadable version of our ultrasonography report for prenatal assessment of congenital lung malformations (CLM). AP, anteroposterior diameter; H, height; p, percentile; T, transverse diameter.

Figure S1 Flowchart summarizing inclusion in this study of fetuses with congenital lung malformation (CLM).

Figure S2 Receiver-operating-characteristics-curve analysis of congenital lung malformation (CLM) volume ratio (CVR) at different gestational-age periods in prediction of the need for respiratory support within 24 h after birth in infants diagnosed prenatally with CLM.

Figure S3 Prenatal type of congenital lung malformation (CLM), postnatal diagnosis and need for respiratory support within 24 h after birth in 74 cases with multiple CLM volume ratio (CVR) measurements available. Prenatal type of CLM is shown, stratified for gradient of regression (partial: absolute decrease in lesion area and/or decrease of at least 0.1 in CVR; full: not visible on last prenatal ultrasound exam) and need for respiratory support.

Figure S4 Receiver-operating-characteristics-curve analysis of congenital lung malformation (CLM) volume ratio (CVR) at different gestational-age periods in prediction of the need for surgical intervention within 2 years after birth in infants diagnosed prenatally with CLM.

Figure S5 Examples of prenatal appearance of congenital lung malformations (CLM) on ultrasound and corresponding postnatal appearance on computed tomography (CT) at *c.* 6 months postpartum. The position of ultrasound images was adjusted by rotating them in order to match the orientation on the postnatal CT. Descriptions are according to the suggested structured ultrasonography report for CLM (Figure 4). BPS, bronchopulmonary sequestration; Ca, caudal; CPAM, congenital pulmonary airway malformation; Cr, cranial; CVR, CLM volume ratio; L, left; R, right; US, ultrasound.

Table S1 Receiver-operating-characteristics-curve parameters for predictive value and optimal cut-off point of congenital lung malformation (CLM) volume ratio (CVR) in predicting the need for respiratory support within 24 h after birth and the need for surgery within 2 years in infants diagnosed prenatally with CLM